Public Summary

Summary for ARTG Entry: 198854 Istodax (romidepsin) 10mg powder for injection vial, and solvent for reconstitution vial

ARTG entry for	Medicine Registered
Sponsor	Celgene Pty Ltd
Postal Address	Level 7 607 St Kilda Road, MELBOURNE, VIC, 3004 Australia
ARTG Start Date	7/08/2013
Product category	Medicine
Status	Active
Approval area	Drug Safety Evaluation Branch

Conditions

Conditions applicable to all therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Conditions applicable to the relevant category and class of therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Products

1. Istodax (romidepsin) 10mg powder for injection vial, and solvent for reconstitution vial

Product Type Composite Pack **Effective date** 22/06/2016

Warnings

See Product Information and Consumer Medicine Information for this product

Standard Indications

Specific Indications

Istodax is indicated for the treatment of peripheral T-cell lymphoma in patients who have received at least one prior systemic therapy.

Additional Product information

Container information

Type	Material	Life Time	Temperature	Closure	Conditions
Vial	Glass Type I Clear	48 Months	Store below 25 degrees Celsius	Not recorded	Store in Original Container

Pack Size/Poison information

Pack Size

single-use powder for injection vial, with solvent vial

Poison Schedule

(S4) Prescription Only Medicine

Components

1. solvent for reconstitution vial

Dosage Form	Diluent, not applicable
Route of Administration	Intravenous Infusion
Visual Identification	clear colourless solution,

2. Istodax (romidepsin) 10mg powder for injection vial

Dosage Form	Injection, powder for
Route of Administration	Intravenous Infusion
Visual Identification	Romidepsin is a white to off-white lyophilised sterile powder for concentrate for solution for infusion.

Active Ingredients

Romidepsin	**10 mg**

This is not an ARTG Certificate document.

The onus is on the reader to verify the current accuracy of the information on the document subsequent to the date shown.

Visit www.tga.gov.au for contact information

Australian Government
Australian Institute of Health and Welfare

cancer IN AUSTRALIA *an overview* 2014

AACR
Australasian Association of Cancer Registries

Australian Government
Australian Institute of Health and Welfare

Authoritative information and statistics to promote better health and wellbeing

CANCER SERIES
Number 90

Cancer in Australia

An overview 2014

Australian Institute of Health and Welfare
Canberra
Cat. no. CAN 88

The Australian Institute of Health and Welfare is a major national agency which provides reliable, regular and relevant information and statistics on Australia's health and welfare. The Institute's mission is *authoritative information and statistics to promote better health and wellbeing*.

This publication is part of the Australian Institute of Health and Welfare's Cancer series. A complete list of the Institute's publications is available from the Institute's website <www.aihw.gov.au>.

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Please note that there is the potential for minor revisions of data in this report. Please check the online version at <www.aihw.gov.au> for any amendments.

Contents

Acknowledgments

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The support of the Australasian Association of Cancer Registries in producing this report is gratefully acknowledged.

Abbreviations

ABS	Australian Bureau of Statistics
ACD	Australian Cancer Database
ACHI	Australian Classification of Health Interventions
ACT	Australian Capital Territory
AIHW	Australian Institute of Health and Welfare
ALL	acute lymphoblastic leukaemia
ALOS	average length of stay
AML	acute myeloid leukaemia
ASGC	Australian Standard Geographical Classification
ASGS	Australian Statistical Geography Standard
ASR	age-standardised rate
CA	Cancer Australia
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CML	chronic myelogenous leukaemia
DCIS	ductal carcinoma in situ
DCO	death-certificate-only
FOBT	faecal occult blood test
GBD	Global Burden of Diseases
GHE	Global Health Estimates
IARC	International Agency for Research on Cancer
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICD-O	International Classification of Diseases for Oncology
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IRSD	Index of Relative Socio-economic Disadvantage
MBS	Medicare Benefits Schedule
MDS	Myelodysplastic syndromes

MIR	mortality-to-incidence ratio
NCCH	National Centre for Classification in Health
NDI	National Death Index
NHL	Non-Hodgkin lymphoma
NHMD	National Hospital Morbidity Database
NMD	National Mortality Database
No.	number
NSW	New South Wales
NT	Northern Territory
OLS	ordinary least squares
Pap test	Papanicolaou smear (cervical smear test)
PSA	prostate-specific antigen
Qld	Queensland
SA	South Australia
Tas	Tasmania
Vic	Victoria
WA	Western Australia
WHO	World Health Organization

Symbols

$	Australian dollars, unless otherwise specified
%	per cent
+	and over
. .	not applicable
n.p.	not published (data cannot be released due to quality issues)

Summary

Cancer in Australia: an overview 2014 was prepared by the Australian Institute of Health and Welfare with support from state and territory members of the Australasian Association of Cancer Registries. It provides comprehensive national information and statistics on cancer, including the latest available data and projections, as well as trends over time. Information by Aboriginal and Torres Strait Islander status, state and territory, remoteness area, life stages and socioeconomic disadvantage are also presented.

Cancer is a major cause of illness in Australia

In 2014, it is estimated that 123,920 Australians will be diagnosed with cancer (excluding basal and squamous cell carcinoma of the skin, as these cancers are not notifiable diseases in Australia). More than half (55%) of the cancer cases diagnosed in Australia are expected to be for males. The most commonly reported cancers in 2014 are expected to be prostate cancer, followed by colorectal (bowel) cancer, breast cancer in females, melanoma of the skin, and lung cancer.

Between 1982 and 2014, the number of new cancer cases diagnosed more than doubled—from 47,417 to 123,920. This increase can be largely attributed to the rise in the incidence of prostate cancer, colorectal cancer, breast cancer in females and lung cancer. The increase can also be partly explained by the ageing and increasing size of the population, improved diagnoses through population health screening programs, and improvements in technologies and techniques used to identify and diagnose cancer.

Mortality rate due to cancer has fallen

In 2014, it is estimated that nearly 45,780 Australians will die from cancer. Cancer accounted for about 3 in 10 deaths in Australia. For all cancers combined, the age-standardised mortality rate is estimated to decrease by 20%, from 209 per 100,000 in 1982 to 168 per 100,000 in 2014.

Survival improved over time, but not consistent across all cancers

Five-year survival from all cancers combined increased from 46% in 1982–1986 to 67% in 2007–2011. The cancers with the largest survival gains over this time were prostate cancer, kidney cancer and non-Hodgkin lymphoma.

People living in Australia who were diagnosed with cancer generally had better survival prospects compared with people living in other countries and regions who were diagnosed with cancer.

Cancer outcomes differ across population groups

Cancer outcomes differ by Aboriginal and Torres Strait Islander status and remoteness area. In 2008–2012, for all cancers combined, Indigenous Australians experienced higher mortality rates than non-Indigenous Australians. In 2005–2009, incidence rates were highest for those living in *Inner regional* areas of Australia; in 2008–2012, mortality rates were highest for those living in *Very remote* areas.

Data at a glance

Estimated incidence of cancer in 2014

Table 1: Estimated 20 most commonly diagnosed cancers, Australia, 2014[a]

Males			Females		
Site/type (ICD-10 codes)	**Cases**	**ASR[b]**	**Site/type (ICD-10 codes)**	**Cases**	**ASR[b]**
Prostate (C61)	17,050	128.7	Breast (C50)	15,270	114.5
Colorectal (C18–C20)	9,290	73.9	Colorectal (C18–C20)	7,340	51.5
Melanoma of the skin (C43)	7,440	59.7	Melanoma of the skin (C43)	5,210	39.4
Lung (C33–C34)	6,860	54.8	Lung (C33–C34)	4,720	33.2
Head and neck (C00–C14, C30–C32)	3,260	25.9	Uterus (C54–C55)	2,490	17.9
Lymphoma (C81–C85)	3,110	25.2	Lymphoma (C81–C85)	2,430	17.9
Leukaemia (C91–C95)	2,110	17.0	Thyroid (C73)	1,890	15.4
Bladder (C67)	2,060	16.7	Leukaemia (C91–C95)	1,440	10.4
Kidney (C64)	2,000	15.9	Ovary (C56)	1,430	10.5
Pancreas (C25)	1,530	12.2	Pancreas (C25)	1,410	9.7
Stomach (C16)	1,460	11.7	Unknown primary site (C80)	1,210	7.8
Unknown primary site (C80)	1,430	11.7	Head and neck (C00–C14, C30–C32)	1,160	8.4
Liver (C22)	1,260	10.1	Kidney (C64)	1,060	7.8
Oesophagus (C15)	1,070	8.5	Cervix (C53)	865	7.0
Brain (C71)	1,060	8.6	Stomach (C16)	785	5.4
Myeloma (C90)	975	7.8	Brain (C71)	740	5.6
Myelodysplastic syndromes (D46)	910	7.5	Myeloma (C90)	700	4.9
Testis (C62)	770	6.7	Bladder (C67)	675	4.5
Mesothelioma (C45)	640	5.1	Myelodysplastic syndromes (D46)	490	3.3
Thyroid (C73)	630	5.2	Oesophagus (C15)	455	3.1
All cancers combined[c]	**68,260**	**540.4**	**All cancers combined[c]**	**55,660**	**406.2**

(a) The 2014 estimates are based on 2002–2011 incidence data (see Appendix G). The estimates are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5.

(b) The rates were standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

(c) Includes cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.

Source: AIHW Australian Cancer Database 2011.

Estimated mortality from cancer in 2014

Table 2: Estimated 20 most common causes of death from cancers, Australia, 2014[(a)]

Males			Females		
Site/type (ICD-10 codes)	**Deaths**	**ASR**[(b)]	**Site/type (ICD-10 codes)**	**Deaths**	**ASR**[(b)]
Lung (C33–C34)	5,150	41.5	Lung (C33–C34)	3,480	24.1
Prostate (C61)	3,390	28.2	Breast (C50)	3,000	20.9
Colorectal (C18–C20)	2,210	17.9	Colorectal (C18–C20)	1,910	12.6
Pancreas (C25)	1,360	10.9	Pancreas (C25)	1,280	8.6
Unknown primary site (C80)	1,160	9.4	Unknown primary site (C80)	1,180	7.6
Melanoma of the skin (C43)	1,120	9.1	Ovary (C56)	1,000	6.9
Liver (C22)	1,080	8.7	Leukaemia (C91–C95)	695	4.6
Leukaemia (C91–C95)	1,040	8.5	Other digestive organs (C26)	680	4.3
Oesophagus (C15)	975	7.7	Lymphoma (C81–C85)	640	4.2
Lymphoma (C81–C85)	855	7.0	Brain (C71)	540	4.0
Brain (C71)	790	6.3	Liver (C22)	535	3.7
Bladder (C67)	780	6.5	Melanoma of the skin (C43)	505	3.5
Other digestive organs (C26)	740	6.0	Stomach (C16)	415	2.8
Stomach (C16)	700	5.7	Uterus (C54–C55)	405	2.8
Kidney (C64)	625	5.0	Myeloma (C90)	405	2.7
Mesothelioma (C45)	575	4.7	Oesophagus (C15)	380	2.5
Myeloma (C90)	535	4.3	Kidney (C64)	355	2.4
Multiple primary cancers (C97)	415	3.4	Bladder (C67)	335	2.1
Non-Melanoma skin cancer (C44)	345	2.8	Cervix (C53)	245	1.8
Myelodysplastic syndromes (D46)	275	2.3	Multiple primary cancers (C97)	230	1.5
All cancers combined[(c)]	**26,010**	**211.5**	**All cancers combined**[(c)]	**19,770**	**133.7**

(a) The 2014 estimates are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5.

(b) The rates were standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

(c) Includes cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.

Source: AIHW National Mortality Database.

1 Introduction

Cancer is a major cause of illness in Australia and has a substantial social and economic impact on individuals, families and the community. In 2014, it is estimated that 123,920 people will be diagnosed with cancer and 45,780 people will die from cancer. Findings from recent global burden of disease studies (World Health Organization [WHO] Global Health Estimates [GHE] 2012 and Global Burden of Diseases [GBD] 2010) show that cancer contributed between 16% and 19% of the total disease burden in Australia (The Lancet 2012; WHO 2014). In 2008–09, it was estimated that the total health system expenditure in Australia on cancer and non-cancerous tumours (neoplasms) was $4,526 million (AIHW 2013b).

Box 1.1: Defining cancer

Cancer, also called malignancy, is a term used for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer:

Carcinoma—is a cancer that begins in the skin or in tissues that line or cover internal organs

Sarcoma—is a cancer that begins in bone, cartilage, fat, muscle, blood vessels or other connective or supportive tissue

Leukaemia—is a cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood

Lymphoma and multiple myeloma—are cancers that begin in the cells of the immune system

Central nervous system cancers—are cancers that begin in the tissues of the brain and spinal cord.

Source: National Cancer Institute 2014.

Purpose and structure of this report

Cancer in Australia: an overview 2014 is the seventeenth in a series and provides a comprehensive overview of national statistics on cancer (see Box 1.1 for a list of terminology in this report). The report presents estimates for 2014 for all cancers combined, as well as for individual cancer sites/types (location of the body in which the cancer began). Estimates for 2014 provide the most up-to-date and current statistics and information possible. Actual cancer incidence data are presented for the period 1982–2011—except for New South Wales and the Australian Capital Territory, where data were available to 2009 and estimated for 2010 and 2011. Further information on data availability is in the Data sources section (page 3) and at Appendix I.

Information and statistics are presented on national population screening programs, cancer incidence, hospitalisations, survival, prevalence and mortality. The report is targeted at a wide audience, including health professionals, policy makers, health planners, educators, researchers, consumers and the general public.

The report is structured according to the general chronological 'journey through the health system' of people diagnosed with cancer. It is acknowledged, however, that this chronological order can vary widely for individuals diagnosed with cancer.

Box 1.2 Breast cancer in females

Both males and females can develop breast cancer. However, the proportion of females who develop breast cancer is much greater than the proportion of males who do so. To present the proportion across the entire population (males and females) would not accurately reflect the burden of breast cancer in females. For this reason, breast cancer data presented in this report refers to breast cancer in females, unless otherwise stated.

Supplementary data for each chapter are available as online Excel tables at <www.aihw.gov.au>. Throughout the report, these online tables are referred to with the prefix 'D'; for example, see online Table D2.1.

Data interpretation

A number of different classifications are referred to in this report, such as the International Statistical Classification of Disease and Related Health Problems (ICD) and the International Classification of Disease for Oncology (ICD-O). Information about these classifications is at Appendix E.

The report includes information on the number of cancer cases and deaths, as well as age-specific and age-standardised rates (ASRs).

Age-specific rates

Age-specific rates provide information on the incidence of a particular event in an age group relative to the total number of people at risk of that event in the same age group (see Appendix H for further information on age-specific rates).

Age-standardised rates

The use of ASRs is important when making comparisons between and within groups over time in order to take account of differences in the age structure and size of the population. This is especially important for cancer, since the risk of many cancers increases with age. Rates have been standardised to the Australian population as at 30 June 2001 and are generally expressed per 100,000 population (see Appendix H for further information on age-standardisation).

International comparisons

International comparisons are provided for cancer incidence, mortality and survival. Take care when comparing cancer data from different countries as observed differences may be influenced not only by the underlying number of cancer cases (or number of cancer deaths when considering mortality data), but by differences in age distribution and composition of populations, cancer detection and screening, types of treatment provided and access to treatment services, characteristics of the cancer (such as stage at diagnosis and histology type), coding practices and cancer registration methods, as well as the accuracy and completeness of recording of cancer cases.

Care must be exercised when interpreting differences in rates based on small counts and/or population groups as such rates may be volatile.

Data sources

The primary data sets used to produce this report are the Australian Cancer Database (ACD) and the National Mortality Database (NMD).

Australian Cancer Database

The ACD contains information on all new cases of primary invasive cancer (excluding basal cell and squamous cell carcinoma of the skin) diagnosed in Australia since 1982. Data are collected by state and territory cancer registries from a number of sources and are supplied annually to the Australian Institute of Health and Welfare (AIHW). The AIHW is responsible for compiling the ACD through the National Cancer Statistics Clearing House—a collaboration with the Australasian Association of Cancer Registries. The ACD includes actual data for the period 1982–2011—except for New South Wales and the Australian Capital Territory, where data were available to 2009 and estimated for 2010 and 2011 (see Appendix F).

National Mortality Database

The NMD is a national collection of information for all deaths in Australia from 1968 to 2012 and is maintained by the AIHW. Information on the characteristics and causes of death of the deceased is provided by the Registrars of Births, Deaths and Marriages and coded nationally by the Australian Bureau of Statistics (ABS).

In the NMD, both the *year of occurrence* of the death and the year in which the death was *registered* are provided. In this report, actual mortality data are shown based on the *year of occurrence* of the death, except for the most recent year (namely 2012) where the number of people whose death was *registered* is used. Previous investigation has shown that, due to a lag in processing of deaths, year of death information for the latest available year generally underestimates the true number of deaths, whereas the number of deaths registered in that year is closer to the true value. Note that deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS.

Several other data sources—including the National Death Index (NDI), the National Hospital Morbidity Database (NHMD) and the 2012 GLOBOCAN database—have also been used to present a broad picture of cancer statistics in Australia.

Additional information about each of the data sources used in this report is at Appendix I.

What is missing from the picture?

Detailed reliable data are not available on many aspects of cancer, so have not been included in this report. Reasons include difficulty in collecting some data and the associated resource implications.

Staging data

Cancer stage at diagnosis refers to the extent or spread of cancer at the time of diagnosis. The stage at cancer diagnosis and subsequent treatment outcomes are important determinants of cancer survival. They can also reflect the extent to which improvements in survival are a result of earlier detection or better treatment.

Although some cancer registries collect information on the stage of cancer at diagnosis, these data are not currently collected nationally. Further, no information is available on the treatments applied to cancers, complications with cancer treatment, or the frequency of recurrence of cancer after treatment. However, there are comprehensive national data on treatments provided through admitted patient hospitalisations—for example, surgery and non-surgical care.

Work is currently underway to enable the collection of national cancer staging data.

Primary health-care information

The primary health-care sector in Australia includes a wide range of professionals, such as general practitioners, pharmacists, ambulance officers, many different types of allied health professionals, community health workers, practice nurses, midwives, Aboriginal health workers and dentists, just to name a few.

The Australian health system collects vast amounts of clinical and administrative data that can yield valuable information that is useful for health policy development and evaluation. These data can also lead to enhanced clinical care and subsequently health outcomes through evidence-based practice, and to safety and quality monitoring (O'Keefe & Connolly 2010).

These data are often collected by individual clinicians for the purpose of recording the encounter with the patient; however, they are often not collected in a standardised format.

In effect, there is very little information publicly available on why an individual attended a primary health-care professional, what intervention the health professional provided to the individual, or the outcome of the visit. This situation causes inefficiencies for those reporting and collecting data. It also severely hampers evidence-based decision making and limits the self-improving capacity of the health system.

For more information on primary health care in Australia, see the feature article in *Australia's health 2014* at <http://www.aihw.gov.au/publication-detail/?id=60129547205>.

Burden of disease due to cancer

To ensure that a health system is aligned to a country's health challenges, policy makers must be able to compare the effects of different conditions that cause ill-health and premature death. Burden of disease analysis simultaneously compares the non-fatal burden (impact of ill-health) and fatal burden (impact of premature death) of a comprehensive list of diseases and injuries. This list, which includes cancers, quantifies the contribution of various risk factors to the total burden as well as to individual diseases and injuries.

The most recent global estimates come from the GBD 2010 and the WHO GHE for 2000–2012. The GBD 2010 covered 241 diseases and injuries and 57 risk factors for 187 countries for 1990, 2005 and 2010 (The Lancet 2012). The WHO GHE for 2000–2012 (WHO 2014) draw on many aspects of GBD 2010, but with different data and methods for some components (WHO 2013).

The last Australian national burden of disease report was published in 2007, based on 2003 data. The AIHW is updating these estimates using the GBD 2010 methodology where possible, with some enhancements to better suit the Australian contexts, and using more recent and detailed Australian data. The revised estimates are expected to be finalised in 2015.

Non-hospital palliative care

This report does not cover palliative care provided in settings other than in admitted patient care. The importance of having a comprehensive national data collection on community-based palliative care services is well recognised (AIHW 2004), but such a collection does not currently exist. Thus, the data in this report describe a subset of all palliative care services delivered in Australia. The relative balance between providing palliative care services in the admitted patient setting and in other settings is unknown, and is likely to vary across the jurisdictions. However, available data suggest that a substantial proportion of palliative care provided in Australia occurs within the admitted patient setting (PCOC 2010).

Health system expenditure on cancer

The most recent data on health system expenditure on cancer are for 2008–09. The AIHW is currently updating disease expenditure estimates to better reflect the current health system environment.

For more information on health system expenditure on cancer in Australia, see *Health system expenditure on cancer and other neoplasms in Australia 2008–09* at <http://www.aihw.gov.au/publication-detail/?id=60129545611>.

2 Risk factors, early detection and prevention

Known risk factors for cancer

A risk factor is any factor associated with an increased likelihood of a person developing a health disorder or health condition, such as cancer. Understanding what causes cancer is essential in setting processes and policies designed to successfully prevent, detect and treat the disease. For most cancers the causes are not fully understood. However, some factors that place individuals at a greater risk for cancer are well recognised and are outlined below. These risk factors were sourced from *World cancer report 2014* (IARC 2014) and *Food, nutrition, physical activity and the prevention of cancer: a global perspective* (WCRF & AICR 2007).

There has been increasing interest in the life course approach to reducing the incidence of chronic diseases, such as cancer. Studies suggest that exposure to risks during childhood, adolescence and early adult life influence the risk of adult incidence and mortality due to chronic disease (Uauy & Solomons 2005). Preventing death from cancer has often focused on early detection and treatment rather than on modifying long-term behaviour and exposure to risk factors.

It should be noted that exposure to a risk factor does not mean that a person will develop cancer. Many people are exposed to at least one cancer risk factor but will never get cancer.

Smoking/passive smoking, and smokeless tobacco use

Smoking is the major cause of cancer in humans. Evidence suggests that active and, for some cases, passive smoking can cause cancers of the:

- bladder
- bone marrow (myeloid leukaemia)
- cervix
- kidney
- larynx
- liver
- lung
- nasal cavity and nasal sinuses
- oral cavity (lip, mouth, tongue)
- oesophagus
- pancreas
- pharynx
- stomach.

Alcohol consumption

Alcohol consumption is an important risk factor for cancer. The risk of cancer increases with the amount of alcohol consumed. Cancers associated with alcohol consumption include those of the:

- breast (females)
- colon and rectum
- larynx
- liver
- oesophagus
- oral cavity (lip, mouth, tongue)
- pharynx.

Diet

Evidence suggests that high intake of particular foods (such as processed meat, and foods that are high in fat) may be associated with an increased risk of cancers of the:

- breast
- colon and rectum
- kidney
- oesophagus
- pancreas
- prostate
- stomach
- uterus.

Obesity and physical inactivity

Obesity is defined as abnormal or excessive fat accumulations that may impair health, and a body mass index of 30 and over.

Physical activity is an important part of a healthy lifestyle. Doing little or no physical activity increases an individual's risk of being overweight or obese, and is associated with a higher risk of developing cancer. Obesity and lack of physical activity increase the risk of cancers of the:

- breast (females)
- colon and rectum
- endometrium
- gallbladder
- kidney
- oesophagus
- ovary
- pancreas.

Chronic infections

Cancer associated with chronic infections (such as viruses, bacteria and parasites) include those of the:

- bladder
- blood or bone marrow (leukaemias)
- cervix
- gallbladder
- liver
- lung
- lymphatic system (lymphomas)
- nasopharynx and oropharynx
- oral cavity (lip, month, tongue)
- stomach.

Family history and genetic susceptibility

Some gene mutations increase the risk of cancer being passed from parent to child. Genetic inheritance increases the risk of cancers of the:

- bladder
- blood or bone marrow (leukaemias)
- breast
- colon and rectum
- gallbladder
- ovary
- pancreas
- prostate
- testis
- thyroid.

Occupational exposures

Occupational exposures include exposures to chemicals, dust, radiation and industrial processes. Cancers that have been found to be caused by occupational exposures include those of the:

- bladder
- blood or bone marrow (leukaemias)
- kidney
- liver
- lung
- lymphatic system (lymphomas)
- mesothelium
- nasal cavity
- nasopharynx
- non-melanoma of the skin
- oesophagus
- oral cavity (lip, mouth, tongue)
- pharynx
- stomach.

Sunlight

Excessive exposure to the ultraviolet rays of the sun is a risk factor for some cancers. The risk of cancer due to excessive exposure to sunlight is highest for people who have fair skin, blond or red hair, freckles, and/or a tendency to burn easily. Sunlight is a risk factor for:

- melanoma of the skin
- non-melanoma skin cancer.

Radiation

Ionising radiation from natural sources, from nuclear accidents and explosions, and from diagnostic X-rays can be risk factors for cancer. The most common source of radiation for the average person is diagnostic X-rays; however, the risk of developing a cancer after an X-ray is minimal and the benefits nearly always outweigh the risk. Ionising radiation can increase the risk of cancers of the:

- blood or bone marrow (leukaemias)
- breast
- lung
- thyroid.

Medical and iatrogenic factors

Medical and iatrogenic factors relate to the inadvertent adverse effect of, or complication resulting from, medical treatment or advice. For example, drugs or treatment used for one disease can potentially lead to the development of a secondary condition. Cancers relating to medical and iatrogenic factors include those of the:

- bladder
- colon and rectum
- kidney
- liver
- lung
- mesothelium
- oesophagus
- pancreas.

Reproductive and hormonal factors

Reproductive hormones are thought to influence the risk of developing some cancers. For women, the risk can be related to reproductive history, endogenous and exogenous hormone exposures and child-bearing. Cancers associated with reproductive and hormonal factors include those of the:

- breast
- endometrium
- ovary
- testis.

Environmental pollution

There are many pollutants in the environment that may cause cancer. People are exposed to these pollutants through the air, drinking water, food, soil, sediments, surface waters and groundwater. Pollution can contribute to cancers of the:

- bladder
- kidney
- liver
- lung
- skin
- stomach.

Early detection through organised population screening

Population-based cancer screening is an organised, systematic and integrated process of testing for signs of cancer or pre-cancerous conditions in asymptomatic populations. In Australia, there are three national population-based screening programs: for breast, cervical and bowel cancers. The three programs—BreastScreen Australia, the National Cervical Screening Program and the National Bowel Cancer Screening Program—are run through partnerships between the Australian Government and state and territory governments. These programs aim to reduce illness and death from these cancers through early detection of cancer and pre-cancerous abnormalities and through effective follow-up treatment.

The programs target specific populations and age groups where evidence shows screening is most effective at reducing cancer-related morbidity and mortality.

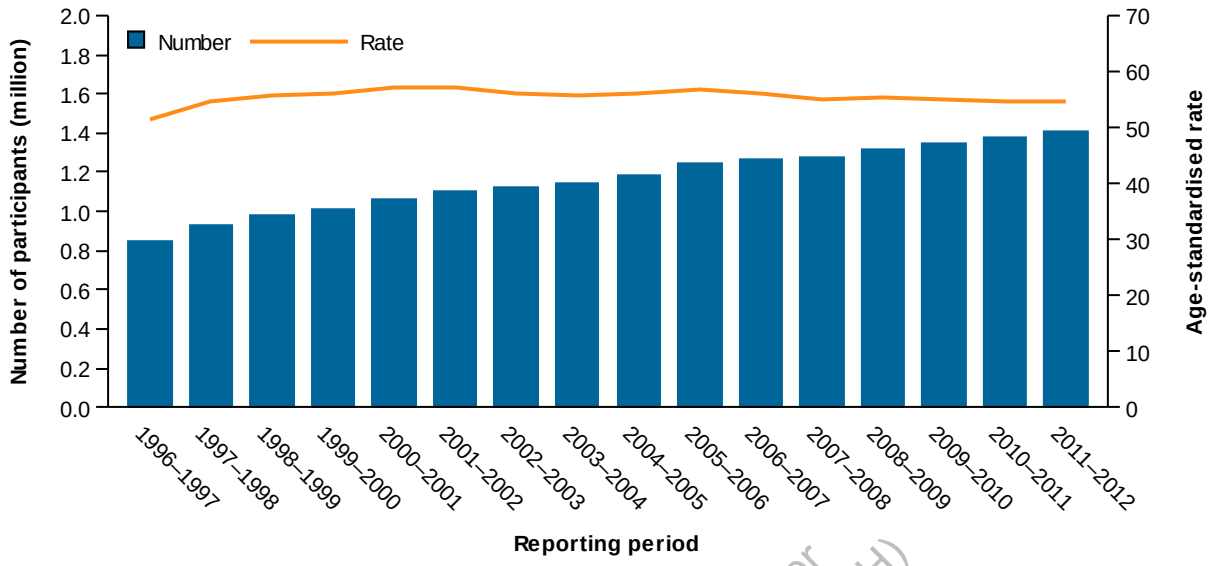
BreastScreen Australia

BreastScreen Australia, established in 1991, led to a rapid increase in the number of breast cancers diagnosed in women. This was due largely to increased detection of breast cancers that were too small to be felt. Screening led to increases in the incidence rate as a result of these cancers being diagnosed earlier than they would have been had they continued to grow until symptoms developed. The mortality rate for breast cancer decreased after BreastScreen Australia was introduced as detection of breast cancer at an earlier stage—when the tumour is often smaller—is associated with increased treatment options and improved treatment outcomes (AIHW 2013a). Additional mortality reductions are attributed to independent treatment advances, including the advent of new systemic therapies.

The program provides free 2-yearly screening mammograms to women aged 40 and over, and actively invites women aged 50–69 to participate.

Key statistics

- In the 2-year period 2011–2012, more than 1.4 million women aged 50–69 had a screening mammogram—a participation rate of 55%. Participation rates were highest for women aged 60–64 (60%) and lowest for those aged 50–54 (49%).
- Participation rates were lower among:
  - Aboriginal and Torres Strait Islander women (38%) than non-Indigenous women (54%)
  - women living in *Very remote* areas (46%) than women living in other regions
  - women who reported speaking a language other than English at home (50%) than women who spoke English at home (55%).
- The ASR of participation for women aged 50–69 was 52% in 1996–1997 when reporting began. This increased to a peak of 57% in 2001–2002 and thereafter remained steady at 55–57%, although the total number of women participating in screening increased (Figure 2.1).
- In 2012, there were 104 invasive breast cancers and 23 ductal carcinomas in situ detected for every 10,000 women screened for the first time. The detection rate was lower among women attending a subsequent screening, with 44 invasive breast cancers and 11 DCISs per 10,000.



Notes:

1. The ASR is the number of women aged 50–69 screened in each reporting period as a percentage of the ABS estimated resident population for women aged 50–69, and age-standardised to the Australian population as at 30 June 2001.
2. Data for this figure are in online Table D2.1.

Source: AIHW analysis of BreastScreen Australia data.

Figure 2.1: Participation number and age-standardised participation rate, BreastScreen Australia, Australia, 1996–1997 to 2011–2012

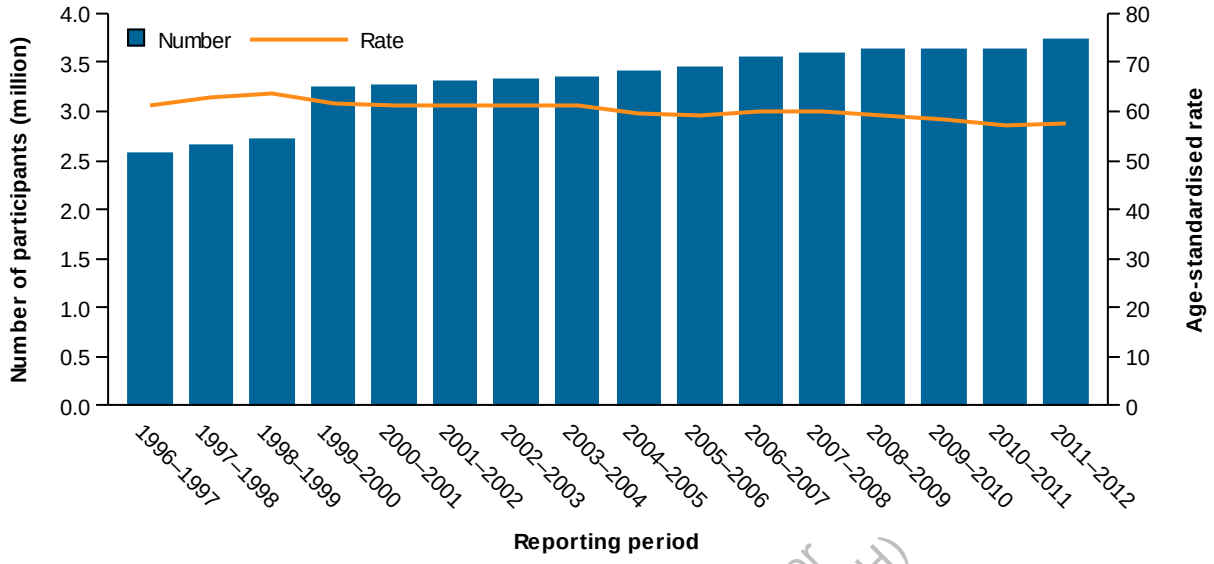
National Cervical Screening Program

The National Cervical Screening Program was established in 1991. It has led to falls in both cervical cancer incidence and mortality due to its ability to detect pre-cancerous abnormalities that may, if left, progress to cancer. With opportunistic cervical screening occurring in Australia since 1960, falls in incidence and mortality of cervical cancer were also evident before this program was introduced (in 1991).

The program targets women aged 20–69 for a 2-yearly Papanicolau (Pap) smear, or 'Pap test'.

Key statistics

- In the 2-year period 2011–2012, more than 3.7 million women aged 20–69 had a screening Pap test—a participation rate of 58% of women in the target population. Participation was highest for women aged 45–49 (64%) and lowest for those aged 20–24 (43%).
- Participation was lower among women living in *Very remote* areas than in other regions, and rose with increasing socioeconomic status—from 52% in areas of lowest socioeconomic status to 64% in areas of highest status.
- The participation rate was 58% in 2011–2012. This has remained relatively stable over time, although the total number of women participating in screening has increased (Figure 2.2).
- In 2012, a high-grade abnormality (pre-cancerous condition) was detected in 16,808 women aged 20–69, at a rate of 8 per 1,000 women screened. Detection presents an opportunity for treatment before possible progression to cancer.



Notes:

1. The ASR is the number of women aged 20–69 screened in each reporting period as a percentage of the ABS estimated resident population for women aged 20–69, adjusted to include only women with an intact cervix, and age-standardised to the Australian population as at 30 June 2001.
2. Data for this figure are in online Table D3.2.

Source: AIHW analysis of state and territory cervical cytology register data.

Figure 2.2: Participation number and age-standardised participation rate, National Cervical Screening Program, Australia, 1996–1997 to 2011–2012

National Bowel Cancer Screening Program

The National Bowel Cancer Screening Program was established in 2006. It is expected to lead to decreases in both cancer incidence and mortality as it has the ability to detect pre-cancerous abnormalities. However, it is likely to take some time for the effect of the program on incidence and mortality to become apparent. The bowel cancer screening program currently offers free screening, using a faecal occult blood test (FOBT), to people turning 50, 55, 60 and 65 years of age. The program is scheduled to be expanded from July 2015, with the phasing in of biennial screening for those aged 50 to 74 by 2020.

Key statistics

Of those people invited to participate in the National Bowel Cancer Screening Program in 2012–13:

- 321,413 returned a completed bowel cancer screening kit for analysis—a participation rate of 33.4%. Participation was higher among women (35.7%) than men (31.1%)
- 23,671 (7.5%) returned a valid screening test and had a positive screening result and 70.4% of those (16,670) had a follow-up colonoscopy recorded
- 404 participants (1 in 32) who underwent a colonoscopy were diagnosed with a confirmed or suspected bowel cancer, and 728 (1 in 17) were diagnosed with an advanced adenoma (pre-cancerous tumour).

What is missing from the picture?

National cancer data do not include whether a new case of cancer was identified through screening, or if cancers identified through screening are diagnosed at an earlier stage than for those that present naturally.

There is no national mechanism for reporting Aboriginal or Torres Strait Islander identification on pathology forms. As a result, state and territory cervical cytology (Pap test) registers are unable to report Indigenous status. Hence, the reporting of cervical screening indicators is not possible nationally for Indigenous women.

Outcome data for the National Bowel Cancer Screening Program—such as follow-up of a positive FOBT result by a primary practitioner, colonoscopy follow-up, histopathology follow-up, and bowel abnormality detected at colonoscopy—are under-reported. The Department of Health is working on a number of steps to improve reporting of outcomes.

3 Incidence of cancer

Key findings

In 2014 in Australia, it is estimated that:

- 123,920 new cases of cancer will be diagnosed
- more than half (55%) of all cancers will be diagnosed in males
- 75% of new cancer cases in males and 65% in females will be diagnosed among those aged 60 and over
- the most commonly diagnosed cancers in males will be prostate cancer (17,050 cases), colorectal cancer (9,290), melanoma of the skin (7,440), lung cancer (6,860) and head and neck cancers (3,260)
- the most commonly diagnosed cancers in females will be breast cancer (15,270 cases), colorectal cancer (7,340), melanoma of the skin (5,210), lung cancer (4,720) and uterine cancer (2,490)
- the age-standardised incidence rate will be 467 per 100,000
- the risk of being diagnosed with cancer before the age of 85 will be 1 in 2 for males and 1 in 3 for females.

About incidence

Incidence data refer to the *number of new cases* of cancers diagnosed in 1 year. It does not refer to the *number of people* newly diagnosed (because one person can be diagnosed with more than one cancer in a year), although the two numbers are likely to be similar.

Cancer incidence data come from the AIHW Australian Cancer Database (ACD) 2011, which contains information on Australians diagnosed since 1982 with primary invasive cancer (excluding basal cell and squamous cell carcinomas of the skin) (see Box 3.1 and Appendix F).

This chapter focuses on the estimated cancer incidence for 2014 and cancer trends from 1982 to 2014. Actual incidence data cover the period 1982–2011—except for New South Wales and the Australian Capital Territory, where data were available to 2009 and estimated for 2010 and 2011 (see Appendix F). Incidence data for 2012–2016 were estimated based on 2002–2011 national cancer incidence data (see Appendix G). The 2012–2016 estimates are only indicative of future trends and the actual incidence may be different from these estimates. They are not forecasts and do not attempt to allow for future changes in cancer detection methods, changes in cancer risk factors or for non-demographic factors (such as government policy changes and economic differences) that may affect future cancer incidence rates.

Summary pages for selected cancers on latest incidence data (2011) and estimates for 2014–2016 are at Appendix B. An overview of incidence statistics for all cancers is at Appendix C.

Box 3.1: Cancer registration in Australia

Registration of all cancers, excluding basal and squamous cell carcinomas of the skin, is required by law in each state and territory. Information on newly diagnosed cancers is collected by each state and territory cancer registry and provided to the AIHW annually to be compiled to form the ACD. Since basal and squamous cell carcinomas of the skin are not notifiable, data on these cancers are not included in the ACD and therefore not in this report. However, past research has shown that basal and squamous cell carcinomas of the skin are by far the most frequently diagnosed cancers in Australia (AIHW & CA 2008).

Estimated number of cases diagnosed

It is estimated that 123,920 new cases of cancer will be diagnosed in Australia in 2014 (excluding basal and squamous cell carcinoma of the skin, as these cancers are not notifiable diseases and hence are not reported to cancer registries). More than half (55%) of these cases are expected to be diagnosed in males (Table 3.1).

Table 3.1: Estimated incidence of all cancers combined[a], Australia, 2014[b]

	Males	Females	Persons
Number of cases	68,260	55,660	123,920
Crude rate	582.9	471.1	526.8
ASR[c]	540.4	406.2	467.3
Per cent (%) of all cancer cases	55.1	44.9	100.0

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.

(b) The 2014 estimates are based on 2002–2011 incidence data (see Appendix G). The estimated numbers of cancer cases diagnosed are rounded to the nearest 10. The estimates for males and females may not add up to the estimates for persons due to rounding.

(c) The rates were standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

Source: AIHW ACD 2011.

Most commonly diagnosed cancers

In 2014 (excluding basal and squamous cell carcinoma of the skin), prostate cancer is estimated to be the most commonly diagnosed cancer in Australia (17,050 cases), followed by colorectal cancer (16,640), breast cancer (15,410), melanoma of the skin (12,640) and lung cancer (11,580). These cancers are expected to account for about 60% of all cancers estimated to be diagnosed in 2014.

Males

Prostate cancer is estimated to be the most commonly diagnosed cancer (17,050 cases), followed by colorectal cancer (9,290), melanoma of the skin (7,440), lung cancer (6,860) and head and neck cancers (3,260) (Table 3.2). Head and neck cancers incorporate cancer of the lip, tongue, mouth, salivary glands, pharynx, nasal cavity sinuses and larynx. These 5 most commonly diagnosed cancers account for around 64% of all cancers estimated to be diagnosed in males in 2014.

Females

Breast cancer is estimated to be the most commonly diagnosed cancer (15,270 cases). This is followed by colorectal cancer (7,340), melanoma of the skin (5,210), lung cancer (4,720) and uterine cancer (2,490) (Table 3.2). These 5 cancers account for around 63% of all cancers estimated to be diagnosed in females in 2014.

Table 3.2: Estimated 10 most commonly diagnosed cancers, Australia, 2014[a]

Males				Females			
Cancer site/type (ICD-10 codes)	**Cases**	**Crude rate**	**ASR**[b]	**Cancer site/type (ICD-10 codes)**	**Cases**	**Crude rate**	**ASR**[b]
Prostate (C61)	17,050	145.6	128.7	Breast (C50)	15,270	129.2	114.5
Colorectal (C18–C20)	9,290	79.4	73.9	Colorectal (C18–C20)	7,340	62.1	51.5
Melanoma of the skin (C43)	7,440	63.5	59.7	Melanoma of the skin (C43)	5,210	44.1	39.4
Lung (C33–C34)	6,860	58.5	54.8	Lung (C33–C34)	4,720	40.0	33.2
Head and neck (C00–C14, C30–C32)	3,260	27.9	25.9	Uterus (C54–C55)	2,490	21.0	17.9
Lymphoma (C81–C85)	3,110	26.6	25.2	Lymphoma (C81–C85)	2,430	20.6	17.9
Leukaemia (C91–C95)	2,110	18.0	17.0	Thyroid (C73)	1,890	16.0	15.4
Bladder (C67)	2,060	17.6	16.7	Leukaemia (C91–C95)	1,440	12.2	10.4
Kidney (C64)	2,000	17.1	15.9	Ovary (C56)	1,430	12.1	10.5
Pancreas (C25)	1,530	13.1	12.2	Pancreas (C25)	1,410	12.0	9.7
All cancers combined[c]	**68,260**	**582.9**	**540.4**	**All cancers combined**[c]	**55,660**	**471.1**	**406.2**

(a) The 2014 estimates are based on 2002–2011 incidence data (see Appendix G). The estimated numbers of cancer cases diagnosed are rounded to the nearest 10. The estimates for males and females may not add up to the estimates for persons due to rounding.

(b) The rates were standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

(c) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.

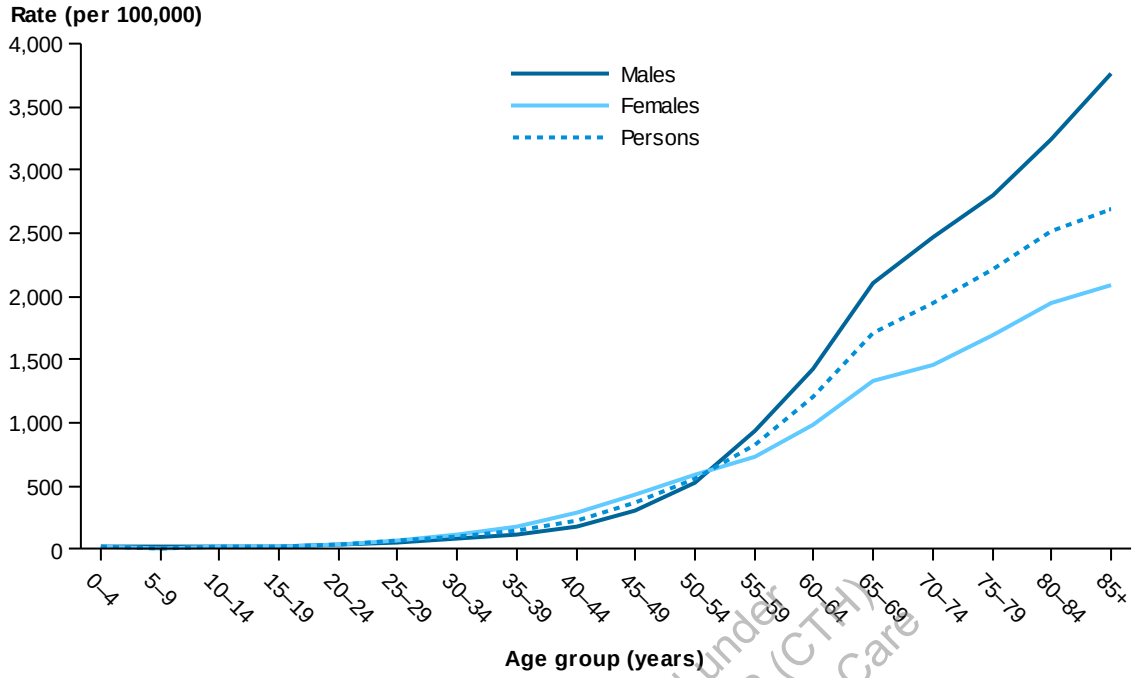
Source: AIHW ACD 2011.

Differences by age

The incidence of cancer increases with age (Figure 3.1). In 2014, it is estimated that 75% of new cancer cases diagnosed in males and 65% in females will occur in those aged 60 and over.

For those aged under 30, the estimated age-specific incidence rate is expected to be similar in males and females. For those aged 30–54, females have a higher estimated age-specific incidence rate than males.

The high incidence of cancer in females in this age group could be partly attributed to the estimated high incidence of breast cancer. After the age of 55, the age-specific incidence rate is then higher for males. Incidence of prostate cancer, colorectal cancer, melanoma of the skin and lung cancer contributes to the high incidence rate in males aged over 55.



Notes

1. The 2014 estimates are based on 2002–2011 incidence data (see Appendix G).
2. Data pertain to cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.
3. Data for this figure are in online Table D3.1.

Source: AIHW ACD 2011.

Figure 3.1: Estimated incidence rates of all cancers combined by age at diagnosis, Australia, 2014

Risk of being diagnosed with cancer

In 2014, it is estimated that 1 in 3 males and 1 in 4 females will be diagnosed with cancer by the age of 75. By the age of 85, the risk is estimated to increase to 1 in 2 for males and 1 in 3 for females (see Appendix H for an explanation of how these risks are calculated).

Table 3.3: Estimated risk of being diagnosed with cancer[(a)], by sex, Australia, 2014

Sex	Risk to age 75	Risk to age 85
Males	1 in 3	1 in 2
Females	1 in 4	1 in 3
Persons	**1 in 3**	**1 in 2**

(a) The 2014 estimates are based on 2002–2011 incidence data (see Appendix G).

Source: AIHW ACD 2011.

Males

For males, the risk of being diagnosed with cancer is estimated to be highest for prostate cancer, at 1 in 9 before the age of 75 and 1 in 6 before the age of 85. The risk is also expected to be high for colorectal cancer at 1 in 19 before the age of 75 and 1 in 10 before the age of 85. For lung cancer, the risk is expected to be at 1 in 28 before the age of 75 and 1 in 13 before the age of 85.

Females

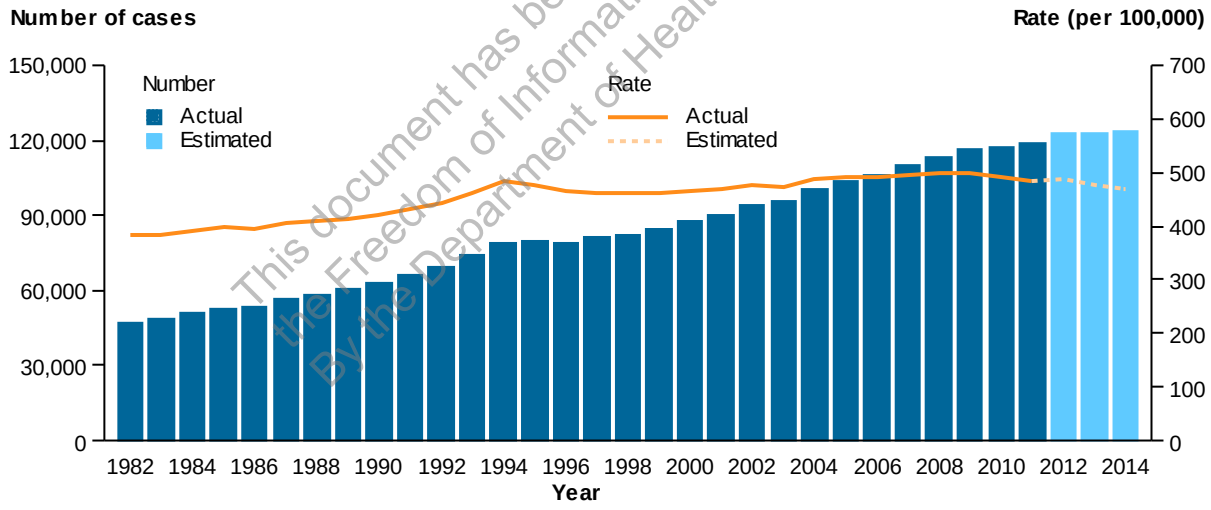
For females, the risk of being diagnosed with cancer is estimated to be highest for breast cancer with a risk of 1 in 11 before the age of 75 and 1 in 8 before the age of 85. In comparison, the risk of a female being diagnosed with colorectal cancer is estimated to be 1 in 28 before the age of 75 and 1 in 15 before the age of 85. For lung cancer, the risk is expected to be 1 in 38 before the age of 75 and 1 in 22 before the age of 85.

Change over time

In this section, trends in incidence for all cancers combined and selected cancer sites are presented for actual data for 1982–2011 and estimated data for 2012–2014.

Trends for all cancers combined

The number of new cancer cases expected to be diagnosed in 2014 is 2.6 times as high as in 1982—from 47,417 in 1982 to 123,920 in 2014. The age-standardised incidence rate of all cancers combined is expected to increase by 22%, from 383 per 100,000 in 1982 to 467 per 100,000 in 2014 (Figure 3.2). This suggests that the increase in the absolute number of cancer cases over the years can only be partly explained by the ageing and increasing size of the population. This increasing trend can be largely attributed to the rise in the number of prostate cancers, breast cancers in females and colorectal cancers diagnosed, as well as to improved diagnoses through population health screening programs and improvements in technologies and techniques used to identify and diagnose cancer.



Notes

1. The graph presents actual data for 1982–2011 and estimates for 2012–2014. Estimates for 2015 and 2016 are also available at Appendix B.
2. The 2012–2014 estimates are based on 2002–2011 incidence data (see Appendix G). Estimates are displayed on the graph as a dotted line or as bars in a lighter shade.
3. Data pertain to cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.
4. The rates were age-standardised to the Australian population as at 30 June 2001.
5. The data for this figure are in online Table D3.2.

Source: AIHW ACD 2011.

Figure 3.2: Trends in incidence of all cancers combined, Australia, 1982 to 2014

The trend in the incidence rate of all cancers combined was markedly different for males and females (online Table D3.2). For males, it increased steadily until 1994, where it peaked at 613 per 100,000. This was followed by a decline until the late 1990s when it began to increase again, reaching a rate of 612 per 100,000 in 2008. It then fell gradually to 580 per 100,000 in 2011.

It is expected to continue to fall to 540 per 100,000 in 2014. The trend in the rate for males is strongly influenced by changes in the incidence rate of prostate cancer—the most common cancer in males—as a result of initiatives such as Prostate-specific Antigen (PSA) testing.

For females, the incidence rate of all cancers combined rose steadily during the early 1990s, reaching 398 per 100,000 in 1995. Since then, it has been fairly stable, ranging from 390 to 410 per 100,000.

The incidence rate for all cancers in females is estimated to be 406 per 100,000 in 2014. The rate for females has been strongly influenced by the trend in the incidence rate of breast cancer. The development of new technologies, such as Magnetic Resonance Imaging (MRI), and the introduction of population screening programs, including BreastScreen Australia, contribute to the increased diagnosis of breast cancer.

Trends for specific cancers

Between 1982 and 2014, there were increases in the age-standardised incidence rates for some cancers, including:

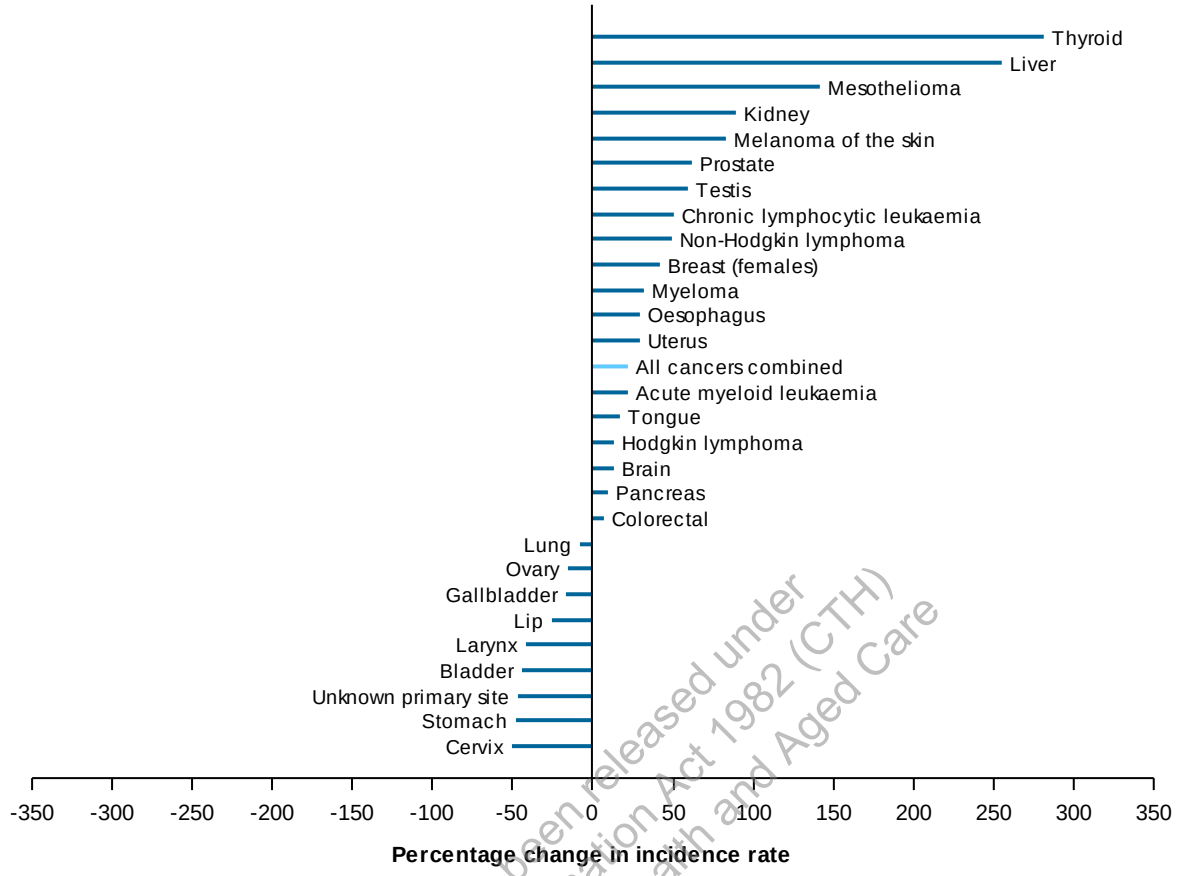
- thyroid cancer (from 2.7 to 10.3 per 100,000 persons)
- liver cancer (from 1.8 to 6.4 per 100,000)
- mesothelioma (from 1.2 to 2.9 per 100,000)
- kidney cancer (from 6.2 to 11.7 per 100,000)
- melanoma of the skin (from 26.7 to 48.8 per 100,000)
- prostate cancer (from 79.5 to 128.7 per 100,000).

Of these cancers, thyroid cancer had the greatest increase of 281% between 1982 and 2014.

The cancers that show the greatest percentage-point decreases between 1982 and 2014 are:

- cervical cancer (from 14.2 to 7.0 per 100,000)
- stomach cancer (from 15.8 to 8.3 per 100,000)
- cancer of unknown primary site (from 18.0 to 9.6 per 100,000)
- bladder cancer (from 17.8 to 10.0 per 100,000)
- larynx cancer (from 4.3 to 2.5 per 100,000) (Figure 3.3).

The incidence rate of each of these cancers decreased by at least 40 per cent.



Notes

1. The bars indicate the percentage change in incidence rates between1982 and 2014.
2. The 2014 estimates are based on 2002–2011 incidence data (see Appendix G).
3. The percentage change between 1982 and 2014 is a summary measure that allows the use of a single number to describe the change over a period of multiple years. However, it is not always reasonable to expect that a single measure can accurately describe the trend over the entire period.
4. The rates were age-standardised to the Australian population as at 30 June 2001.
5. The data for this figure are in online Table D3.3.

Source: AIHW ACD 2011.

Figure 3.3: Estimated percentage change in age-standardised incidence rates between 1982 and 2014, Australia

4 Hospitalisations and admitted patient palliative care for cancer

Key findings

In 2012–13 in Australia:

- cancer was the main reason (principal diagnosis) for 1 in 10 hospitalisations, accounting for 2.31 million bed days
- about three-quarters (76%) of cancer-related hospitalisations were for same-day care
- the average length of stay (ALOS) for all cancer-related hospitalisations was 2.5 days. When same-day hospitalisations were excluded, the ALOS was 7.3 days
- non-melanoma skin cancer was the most common cancer type recorded as principal diagnosis, with about 99,000 hospitalisations
- chemotherapy was the most common cancer-related treatment or service recorded as the principal diagnosis, with about 370,000 hospitalisations
- of all hospitalisations that involved palliative care, 56% (34,379) were cancer-related.

From 2001–02 to 2012–13:

- the number of cancer-related hospitalisations increased by 41% from 649,353 to 914,993
- the age-standardised cancer-related hospitalisation rate increased by 9%, from 337 per 10,000 to 367 per 10,000.

About hospitalisations

Hospitalisation data include information on admitted patient services provided for people with cancer in Australian hospitals.

This chapter presents the total number of cancer-related hospitalisations and provides information on cancer-related palliative care hospitalisations. The data source for this chapter was the NHMD, which contains data on admitted patient hospitalisations (Box 4.1).

Box 4.1: Interpreting cancer hospitalisations

National Hospital Morbidity Database

The NHMD 2012–13 is a comprehensive data set containing records for all episodes of admitted patient care from public and private hospitals in Australia during 2012–13. Admitted patients are those who undergo a hospital's formal admission process (AIHW 2014e).

A hospitalisation (also known as a 'separation') is an episode of care either that starts with admission and ends with discharge, transfer or death, or that is defined by a change in care type, such as from *acute care* to *rehabilitation*. Hospitalisations (or separations) refer to admitted patients only.

As the NHMD is episode based, the data presented in this chapter do not refer to individuals. An individual may be counted in the database multiple times in a reference year for each episode of care they receive as an admitted patient.

Diagnosis information recorded in the NHMD is coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) (NCCH 2010).

In this report, cancer-related hospitalisations are defined as those where:

- the principal diagnosis (the diagnosis chiefly responsible for the episode of care) is cancer (ICD-10-AM codes C00-C97, D45, D46, D47.1 and D47.3)
- the principal diagnosis is related to the treatment or management of cancer
- the principal diagnosis is a non-cancer-specific treatment or service and cancer is recorded as an additional diagnosis (a diagnosis that coexists with the principal diagnosis or arises during the episode of care) for that hospitalisation.

Data of cancer-related hospitalisations include those where palliative care was provided.

Chemotherapy

Not all cancer-related chemotherapy is provided on an admitted patient basis. Some jurisdictions provide a substantial amount of chemotherapy on a non-admitted basis, and this activity is therefore not reported to the NHMD.

For more information on the NHMD, see *Australian hospital statistics* at <http://www.aihw.gov.au/publication-detail/?id=60129546922>

and

National Hospital Morbidity Database Data Quality Statement: 2012–13 at <http://meteor.aihw.gov.au/content/index.phtml/itemId/568730>.

Box 4.2 Summary of terms used in the hospitalisation chapter

A **same-day** hospitalisation occurs when a patient is admitted to and separated from the hospital on the same date. An **overnight** hospitalisation occurs when a patient is admitted to and separated from the hospital on different dates.

Additional diagnosis is a condition or complaint that either co-exists with the principal diagnosis or arises during the episode of care. An additional diagnosis is reported if the condition affects patient management.

Average length of stay is the average number of patient days for admitted patient episodes. A same-day patient is allocated a length of stay of 1 day.

Care type defines the overall nature of a clinical service provided to an admitted patient during an admitted care, or the type of service provided by the hospital for boarders or posthumous organ procurement (care other than admitted care). Admitted patient care consists of *acute care*, *rehabilitation care*, *palliative care*, *geriatric evaluation and management*, *psychogeriatric care*, *maintenance care*, *newborn care* and *other admitted patient care*.

Palliative care hospitalisations in this report are defined as those where the care type is *palliative care*, and/or *palliative care* is recorded as an additional diagnosis, for admitted patients only (ICD-10-AM code Z51.5).

Principal diagnosis is the diagnosis established after study to be chiefly responsible for occasioning the patient's episode of admitted patient care.

Hospitalisations in 2012–13

In 2012–13, there were 914,993 cancer-related hospitalisations, accounting for 1 in 10 hospitalisations in Australia. Less than half (45%) of all cancer-related hospitalisations had a principal diagnosis of cancer (Table 4.1). The remainder had a principal diagnosis related to the treatment or management of cancer.

Table 4.1: Cancer-related hospitalisations[a], persons, Australia, 2012–13

	Number	Per cent	ASR[b]
Principal diagnosis of cancer[c]	415,130	45.4	165.1
Principal diagnosis of a cancer-related treatment or service[d]	499,863	54.6	201.9
Cancer specific treatment or services	491,947	53.8	198.7
Non-cancer specific treatment or services with an additional diagnosis of cancer	7,916	0.9	3.2
All cancer-related hospitalisations	**914,993**	**100.0**	**367.0**

(a) Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) The rates were age-standardised to the Australian population as at 30 June 2001 and are expressed per 10,000 population.

(c) Hospitalisations in which the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3).

(d) Hospitalisations in which the principal diagnosis is a health service or treatment that may be related to the treatment of cancer (see Appendix J).

Source: AIHW NHMD.

Length of stay

In 2012–13, cancer-related hospitalisations totalled 2.31 million bed days; 76% were same-day hospitalisations and 24% were overnight hospitalisations.

The average length of stay (ALOS) for overnight cancer-related hospitalisations was 7.3 days (Table 4.2). This is longer than the overnight ALOS for all hospitalisations (5.6 days).

More than half (52%) of hospitalisations in which the principal diagnosis was cancer were overnight, with an ALOS of 7.5 days. In contrast, the majority (99%) of hospitalisations with a principal diagnosis related to the treatment or management of cancer were same-day (Table 4.2).

Table 4.2: Average length of stay (days) for cancer-related hospitalisations[(a)], Australia, 2012–13

	Same-day		Overnight			Total	
	Number	Per cent of total	Number	Per cent of total	ALOS	Number	ALOS
Principal diagnosis of cancer[(b)]	199,837	48.1	215,293	51.9	7.5	415,130	4.3
Principal diagnosis of a cancer-related treatment or service[(c)]	494,364	98.9	5,499	1.1	2.2	499,863	1.0
Cancer specific treatment or services	486,916	99.0	5,031	1.0	2.1	491,947	1.0
Non-cancer specific treatment or services with an additional diagnosis of cancer	7,448	94.1	468	5.9	3.0	7,916	1.1
All cancer-related hospitalisations	**694,201**	**75.9**	**220,792**	**24.1**	**7.3**	**914,993**	**2.5**

(a) Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) Hospitalisations in which the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3),

(c) Hospitalisations in which the principal diagnosis is a health service or treatment that may be related to the treatment of cancer (see Appendix J).

Source: AIHW NHMD.

In 2012–13, for hospitalisations where the principal diagnosis was cancer, the five cancer types with the longest ALOS (excluding same-day hospitalisations) were acute myeloid leukaemia (16.8 days), Kaposi sarcoma (13.5 days), hypopharyngeal cancer (13.0 days), anal cancer (11.5 days) and cancer of the small intestine (11.3 days).

Hospitalisations for cancers and for cancer-related treatments

Data on hospitalisations include cancer as a principal diagnosis and cancer-related treatments and services (see Appendix J for more information). Note that some treatments and services (such as Z51.0 'Radiotherapy session') included in the data are not entirely cancer specific; that is, they may be provided to a small number of non-cancer patients. However, the proportion of these over counts is less than 0.01% of the data presented in this report.

Cancer as a principal diagnosis

In 2012–13, there were 415,130 hospitalisations where the principal diagnosis was cancer. Non-melanoma skin cancer was the most common principal diagnosis in this group (24%),

followed by cancer of secondary site (10%), prostate cancer (9%), colorectal cancer (7%) and breast cancer (6%).

The 10 most common cancers as a principal diagnosis accounted for 77% of all hospitalisations with a principal diagnosis of cancer (Table 4.3).

Table 4.3: Ten most common cancers as principal diagnosis[(a)], Australia, 2012–13

Principal diagnosis (ICD-10-AM codes)	Number	Per cent
Cancer site/type		
Non-melanoma of the skin (C44)	99,300	23.9
Secondary site (C77–C79)	41,080	9.9
Prostate (C61)	35,740	8.6
Colorectal (C18–C20)	28,213	6.8
Breast (C50)	25,117	6.1
Leukaemia (C91–C95)	21,782	5.2
Lymphoma (C81–C85)	20,496	4.9
Lung (C33–C34)	18,878	4.5
Bladder (C67)	14,051	3.4
Myelodysplastic syndromes (D46)	13,829	3.3
Total 10 most common cancers as a principal diagnosis	*318,486*	*76.7*
Total hospitalisations with a principal diagnosis of cancer[(b)]	**415,130**	**100.0**

(a) Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) Hospitalisations in which the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3 (see Appendix J).

Source: AIHW NHMD.

In 2012–13, non-melanoma skin cancer was the most common cancer type recorded as principal diagnosis for both males (25%) and females (23%).

The second most common cancer types recorded as principal diagnosis was prostate cancer in males (15%) and breast cancer in females (14%). These were followed by cancer of secondary site (9% males, 11% females), colorectal cancer (7% males, 7% females) and leukaemia (5% males, 5% females) (Table 4.4).

The 10 most common cancer types accounted for around 80% of all cancers recorded as principal diagnoses in both males and females.

Table 4.4: Ten most common cancers as principal diagnosis[a], by sex, Australia, 2012–13

Males		Females	
Principal diagnosis (ICD-10-AM codes)	**Number**	**Principal diagnosis (ICD-10-AM codes)**	**Number**
Cancer site/type		**Cancer site/type**	
Non-melanoma of the skin (C44)	59,119	Non-melanoma of the skin (C44)	40,180
Prostate (C61)	35,740	Breast (C50)	24,940
Secondary site (C77–C79)	21,166	Secondary site (C77–C79)	19,914
Colorectal (C18–C20)	15,617	Colorectal (C18–C20)	12,596
Leukaemia (C91–C95)	12,846	Leukaemia (C91–C95)	8,936
Lymphoma (C81–C85)	12,308	Lymphoma (C81–C85)	8,188
Lung (C33–C34)	11,089	Lung (C33–C34)	7,789
Bladder (C67)	10,794	Myelodysplastic syndromes (D46)	5,367
Myelodysplastic syndromes (D46)	8,462	Melanoma of the skin (C43)	4,608
Melanoma of the skin (C43)	6,344	Myeloma (C90)	4,391
Total 10 most common cancers as a principal diagnosis	*193,485*	*Total 10 most common cancers as a principal diagnosis*	*136,909*
Total hospitalisations with a principal diagnosis of cancer[b]	**239,518**	**Total hospitalisations with a principal diagnosis of cancer[b]**	**175,611**

(a) Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) Hospitalisations in which the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3 (see Appendix J).

Source: AIHW NHMD.

Cancer-related treatments and services

In 2012–13, there were 499,863 hospitalisations where the principal diagnosis was a cancer-related treatment or service. The 5 most common principal diagnoses were:

- pharmacotherapy session for neoplasm (Z51.1 'Chemotherapy') was the most common principal diagnosis in this group (75%)
- special screening examination for neoplasm of intestinal tract (11%)
- follow-up after surgery for cancer (8%)
- adjustment and management of vascular access device (1%)
- follow-up examination after combined treatment for malignant neoplasm (1%) (Table 4.5).

These 5 most common reasons for hospitalisation when the principal diagnosis was a cancer-related treatment or service accounted for 96% of all hospitalisations with a principal diagnosis of a cancer-related treatment or service.

Table 4.5: Five most common reasons for hospitalisation[a], when the principal diagnosis is a cancer-related treatment or service, Australia, 2012–13

Principal diagnosis (ICD-10-AM codes)	Number	Per cent
Pharmacotherapy session for neoplasm (Chemotherapy [Z51.1])	374,824	75.0
Special screening examination for neoplasm of intestinal tract (Z12.1)	54,480	10.9
Follow-up after surgery for cancer (Z08.0)	42,110	8.4
Adjustment and management of vascular access device (Z45.2)	5,838	1.2
Follow-up examination after combined treatment for malignant neoplasm (Z08.7)	4,758	1.0
Total 5 most common reasons for hospitalisation when the principal diagnosis was a cancer-related treatment or service	*482,010*	*96.4*
Total hospitalisations with a principal diagnosis of a cancer-related treatment or service[b]	**499,863**	**100.0**

(a) Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) Hospitalisations in which the principal diagnosis is a health service or treatment that may be related to treatment of cancer (see Appendix J).

Source: AIHW NHMD.

In 2012–13, the most common reasons by sex for hospitalisation when the principal diagnosis was a cancer-related treatment or service were:

- pharmacotherapy session for neoplasm in both males (72%) and females (78%)
- follow-up after surgery for cancer in males (12%) and special screening examination for neoplasm of intestinal tract in females (12%) (Table 4.6).

Table 4.6: Five most common reasons for hospitalisation[a], when the principal diagnosis is a cancer-related treatment or service, by sex, Australia, 2012–13

Males		Females	
Principal diagnosis (ICD-10-AM codes)	**Number**	**Principal diagnosis (ICD-10-AM codes)**	**Number**
Pharmacotherapy session for neoplasm (Chemotherapy [Z51.1])	170,926	Pharmacotherapy session for neoplasm (Chemotherapy [Z51.1])	203,898
Follow-up after surgery for cancer (Z08.0)	27,738	Special screening examination for neoplasm of intestinal tract (Z12.1)	30,313
Special screening examination for neoplasm of intestinal tract (Z12.1)	24,167	Follow-up after surgery for cancer (Z08.0)	14,372
Follow-up examination after combined treatment for malignant neoplasm (Z08.7)	3,426	Adjustment and management of vascular access device (Z45.2)	3,831
Follow-up examination after unspecified treatment for malignant neoplasm (Z08.9)	2,416	Family history of malignant neoplasm of digestive organs (Z80.0)	1,436
Total 5 most common reasons for hospitalisation when the principal diagnosis was a cancer-related treatment or service	*228,673*	*Total 5 most common reasons for hospitalisation when the principal diagnosis was a cancer-related treatment or service*	*253,850*
Total hospitalisations with a principal diagnosis of a cancer-related treatment or service[b]	**237,285**	**Total hospitalisations with a principal diagnosis of a cancer-related treatment or service[b]**	**262,578**

(a) Hospitalisation for which the care type was reported as Newborn with no qualified days and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) Hospitalisations in which the principal diagnosis is a health service or treatment that may be related to treatment of cancer (see Appendix J).

Source: AIHW NHMD.

Most hospitalisations where the principal diagnosis was a cancer-related treatment or service were for same-day services (99%). The 5 leading treatments, as detailed in Table 4.6,

accounted for the majority (97%) of all same-day hospitalisations for cancer-related treatments and services in 2012–13.

Hospitalisations by age

In 2012–13, people were more likely to be hospitalised for a cancer-related condition with increasing age (Figure 4.1).

The hospitalisation rates for patients with cancer were low for those aged under 30, at 42 per 10,000 persons or below. The hospitalisation rate then increased for each age group, peaking for those aged 75–79, at 1,741 per 10,000. The hospitalisation rate then decreased to 1,352 per 10,000 for those aged 85 and over.

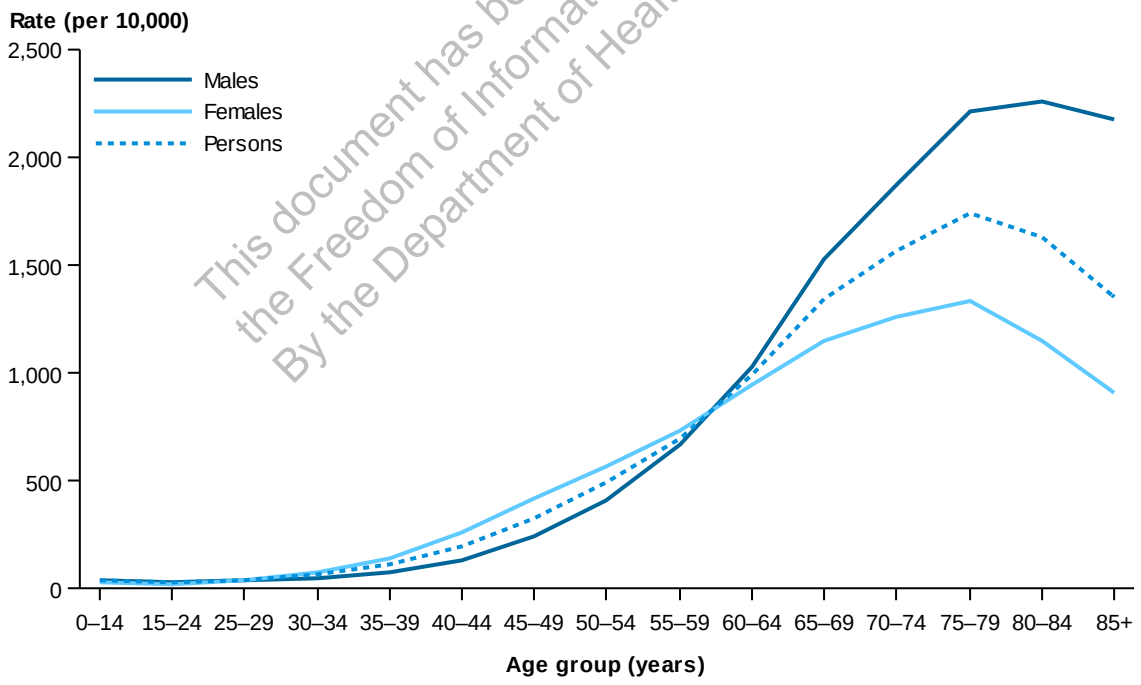
The cancer-related hospitalisation rate was similar for males and females aged under 30.

Females

Females aged 30–59 had a higher rate of hospitalisation than males of the same age. In particular, the hospitalisation rate for females aged 40–44 was 1.9 times as high as that for males (261 compared with 135, respectively, per 10,000). This may be partly attributed to the high number of breast cancer hospitalisations in females within this age group.

Males

Males aged 60 and over had a higher hospitalisation rate than females of the same age. In particular, the hospitalisation rate for males aged 85 and over was 2.4 times as high as that for females (2,177 compared with 909, respectively, per 10,000). This may be partly attributed to the high number of prostate cancer hospitalisations among males within this age group.



Notes

1. Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.
2. Hospitalisations in which (i) the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3) or (ii) the principal diagnosis is a health service or treatment that may be related to treatment of cancer (see Appendix J).
3. Data for this figure are in online Table D4.1.

Source: AIHW NHMD.

Figure 4.1: Age-specific rates for all cancer-related hospitalisations, Australia, 2012–13

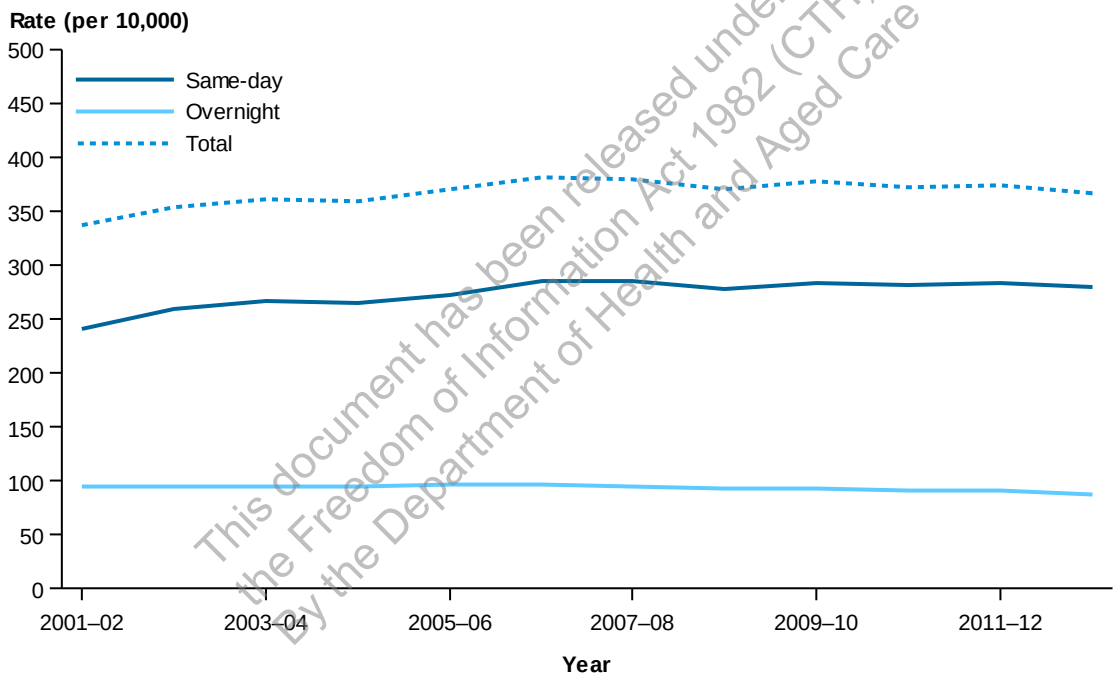
Cancer-related hospitalisations over time

Between 2001–02 and 2012–13, the total number of cancer-related hospitalisations increased by 41% from 649,353 to 914,993 hospitalisations. Much of this can be attributed to a 49% increase in the number of same-day hospitalisations, from 465,440 in 2001–02 to 694,201 in 2012–13.

In the same period, the age-standardised cancer-related hospitalisation rate increased slightly from 337 per 10,000 to 367 per 10,000.

Between 2001–02 and 2012–13, there was a slight increase in the hospitalisation rate for same-day hospitalisation, from 241 per 10,000 to 279 per 10,000. Over the same period, the hospitalisation rate for overnight hospitalisation fell from 96 per 10,000 to 88 per 10,000 (Figure 4.2).

The trend in the rate of all cancer-related hospitalisations is mostly due to changes in the rate of same-day hospitalisations, which is affected by changes in admission practices in some jurisdictions.



Notes

1. Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.
2. Hospitalisations in which (i) the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3) or (ii) the principal diagnosis is a health service or treatment that may be related to treatment of cancer (see Appendix J).
3. Rates were age-standardised to the Australian population as at 30 June 2001 and expressed per 10,000 population.
4. Data for this figure are in online Table D4.2.

Source: AIHW NHMD.

Figure 4.2: All cancer-related hospitalisations by same-day and overnight status, Australia, 2001–02 to 2012–13

Palliative care for cancer in the hospital setting

Admitted hospital care commonly focuses on the treatment and care of disease. Palliative care, sometimes referred to as 'hospice' or 'end-of-life' care, is care in which the clinical intent or treatment goal is primarily quality of life for a patient with an active, progressive disease with little or no prospect of cure. It is usually evidenced by an interdisciplinary assessment and/or management of the physical, psychological, emotional and spiritual needs of the patient; and a grief and bereavement support service for the patient and their carers/family. Research has shown that cancer patients comprise the majority of those using palliative care services. This may be due to the difficulties in predicting the disease pathway and estimating prognosis of decline for non-cancer patients compared with cancer patients (AIHW 2011).

This section presents a summary of cancer-related hospitalisations where palliative care was provided within an admitted patient setting in 2012–13 (see Box 4.1).

In 2012–13, nearly 61,600 hospitalisations involved palliative care in Australia (0.7% of all hospitalisations). Of these, 56% (34,379) were cancer related. For most of these hospitalisations (74%), palliative care was the intended mode of clinical care; that is, the care type was recorded as *palliative care*. For the remaining 26%, palliative care was recorded as an additional diagnosis and provided as part of the hospitalisation where the intended care type was *acute care*, *rehabilitation care* or other modes of care.

The most common type of cancer recorded for palliative care hospitalisation was secondary site cancer, which refers to a malignant tumour that originated elsewhere in the body; this principal diagnosis was reported in 23% of all cancer-related hospitalisations where palliative care was provided in 2012–13 (Table 4.7).

Table 4.7: Ten most common cancers as principal diagnosis of the hospitalisation[(a)] where palliative care was provided, persons, Australia, 2012–13

Principal diagnosis (ICD-10-AM codes)	Number	Per cent
Cancer site/type		
Secondary site (C77–C79)	7,859	22.9
Lung (C33–C34)	5,658	16.5
Colorectal (C18–C20)	2,716	7.9
Pancreas (C25)	1,874	5.5
Prostate (C61)	1,618	4.7
Breast (C50)	1,554	4.5
Brain (C71)	1,187	3.5
Stomach (C16)	973	2.8
Liver (C22)	914	2.7
Leukaemia (C91–C95)	803	2.3
All cancer-related hospitalisations where palliative care was provided[(b)]	**34,379**	**100.0**

(a) Hospitalisation for which the care type was reported as *Newborn with no qualified days* and records for 'Hospital boarders' and 'Posthumous organ procurement' have been excluded from the analysis.

(b) Palliative care hospitalisations in which (i) the principal diagnosis is cancer (ICD-10-AM codes C00–C97, D45, D47.1 and D47.3) or (ii) the principal diagnosis is a health service or treatment that may be related to treatment of cancer (see Appendix J).

Source: AIHW NHMD.

Palliative care and deaths in hospital

In 2012–13, among those cancer-related hospitalisations that ended in death, 75% included palliative care. Around 27% of non-cancer-related hospitalisations that ended in death included palliative care. The lower proportion of non-cancer-related hospitalisations that ended in death that included palliative care may be a result of some non-cancer-related conditions not fitting the criteria for palliative care or the progression of these conditions was difficult to predict.

Over the same period, 51% (17,582) of cancer-related hospitalisations involving palliative care ended in death. Of the remaining hospitalisations, 13% (4,380) transferred to another facility and 31% (10,771) were sent to where they usually live, which could be a person's own home or welfare institution.

The proportion of cancer-related hospitalisations involving palliative care that ended in death was similar to that for all hospitalisations involving palliative care.

5 Survival after a diagnosis of cancer

Key findings

In 2007–2011 in Australia:

- 5-year relative survival was 67% for all cancers combined
- females had slightly higher survival than males (5-year relative survival of 68% and 66%, respectively)
- for males diagnosed with cancer, 5-year relative survival was highest for testicular cancer (98%), lip cancer (93%) and prostate cancer (93%)
- for females diagnosed with cancer, 5-year relative survival was highest for thyroid cancer (97%), lip cancer (94%) and melanoma of the skin (94%)
- for all cancers combined, 5-year relative survival decreased with age.

From 1982–1986 to 2007–2011:

- 5-year relative survival increased significantly from 40% to 66% for males and 52% to 68% for females for all cancers combined.

About survival

Information on survival from cancer provides an indication of cancer prognosis and the effectiveness of treatments available. A range of factors influence survival from cancer, including the demographic characteristics of the patient (such as age, sex and genetics), the nature of the tumour (such as site, stage at diagnosis and histology type) and the health-care system (such as availability of health-care services, screening, diagnostic and treatment facilities, and follow-up services) (Black et al. 1998; WCRF & AICR 2007).

Survival in this report refers to 'relative survival'; that is, all survival probabilities presented are relative to those of the general population. It refers to the probability of being alive for a given amount of time after diagnosis compared with the general population, and reflects the impact of a cancer diagnosis. For more information, see Box 5.1 and Appendix H.

This chapter focuses on 5-year survival based on the 2011 ACD (see Appendix F). Data from the National Death Index (NDI) on deaths (from any cause) that occurred up to 31 December 2011 were used to determine which people with cancer had died and when this occurred. Summary pages for selected cancers are at Appendix B.

Box 5.1: Period survival

In this report, relative survival was calculated using the period method for all reported time periods (Brenner & Gefeller 1996). This method calculates survival from a given follow-up or at-risk period. Survival estimates are based on the survival experience of people who were diagnosed before or during this period, and who were at risk of dying during this period. More information about the period method is at Appendix H.

Note that the period method is an alternative to the traditional cohort method, which focuses on a group of people diagnosed with cancer in the past time period, and follows these people over time. By its nature, the period method produces more up-to-date estimates of survival than the cohort method. In this report, all year spans presented were calculated using the period method. As the cohort method was used in previous *Cancer in Australia* reports (for example, AIHW & AACR 2010), survival estimates in this report should not be directly compared with those in earlier reports.

Five-year relative survival

In 2007–2011, 5-year survival was 67% for all cancers combined. This means that people diagnosed with cancer had a 67% chance of surviving for at least 5 years compared with their counterparts in the general population. Females had slightly higher 5-year survival than males, at 68% compared with 66% for males (Table 5.1).

Table 5.1: Five-year relative survival from all cancers combined[(a)], Australia, 2007–2011

Sex	5-year relative survival (%)	95% confidence interval
Males	66.1	65.9–66.3
Females	67.5	67.3–67.7
Persons	**66.7**	**66.5–66.8**

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.

Source: AIHW ACD 2011.

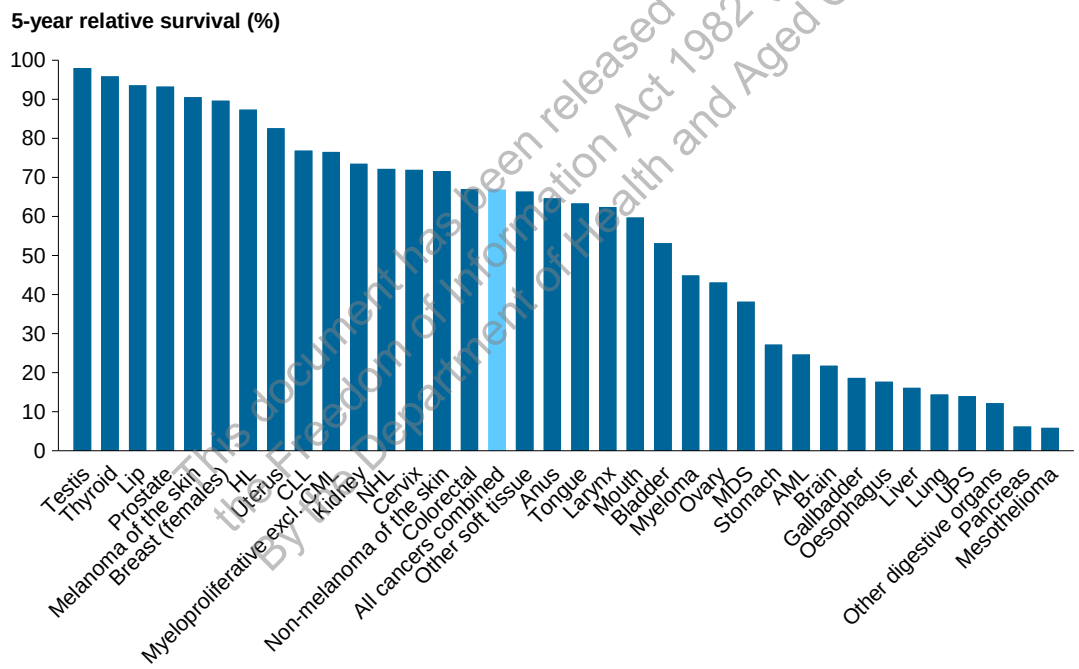
Cancer site

In 2007–2011, 5-year survival was highest for people diagnosed with testicular cancer (98%), thyroid cancer (96%), lip cancer (93%), prostate cancer (93%) and melanoma of the skin (90%) and lowest for those diagnosed with pancreatic cancer (6%) and mesothelioma (6%) (Figure 5.1).

For males, 5-year survival was highest for those diagnosed with testicular cancer (98%), lip cancer (93%) and prostate cancer (93%). For females, it was highest for those diagnosed with thyroid cancer (97%), lip cancer (94%) and melanoma of the skin (94%) (online Table D5.1).

Pancreatic cancer (males 6% and females 6%) and mesothelioma (males 5% and females 8%) accounted for the lowest survival in both males and females.

In 2007–2011, 5-year survival was significantly higher for males than for females for cancer of unknown primary site (1.5 times that for females) and bladder cancer (1.2 times). Five-year survival was significantly higher for females than for males for lung cancer (1.4 times that for males), anal cancer (1.2 times), melanoma of the skin (1.1 times), thyroid cancer (1.1 times), chronic lymphocytic leukaemia (1.1 times), myeloproliferative cancers excluding CML (1.1 times) and mouth cancer (1.1 times).



Notes

1. All cancers combined include cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin. Non-melanoma skin cancer does not include C44 codes that indicate a basal or squamous cell carcinoma of the skin.
2. HL=Hodgkin lymphoma, CLL=Chronic lymphocytic leukaemia, NHL=Non-Hodgkin lymphoma, MDS= Myelodysplastic syndromes, AML=Acute myeloid leukaemia, UPS=Cancer of unknown primary site.
3. Data for this figure are in online Table D5.1.

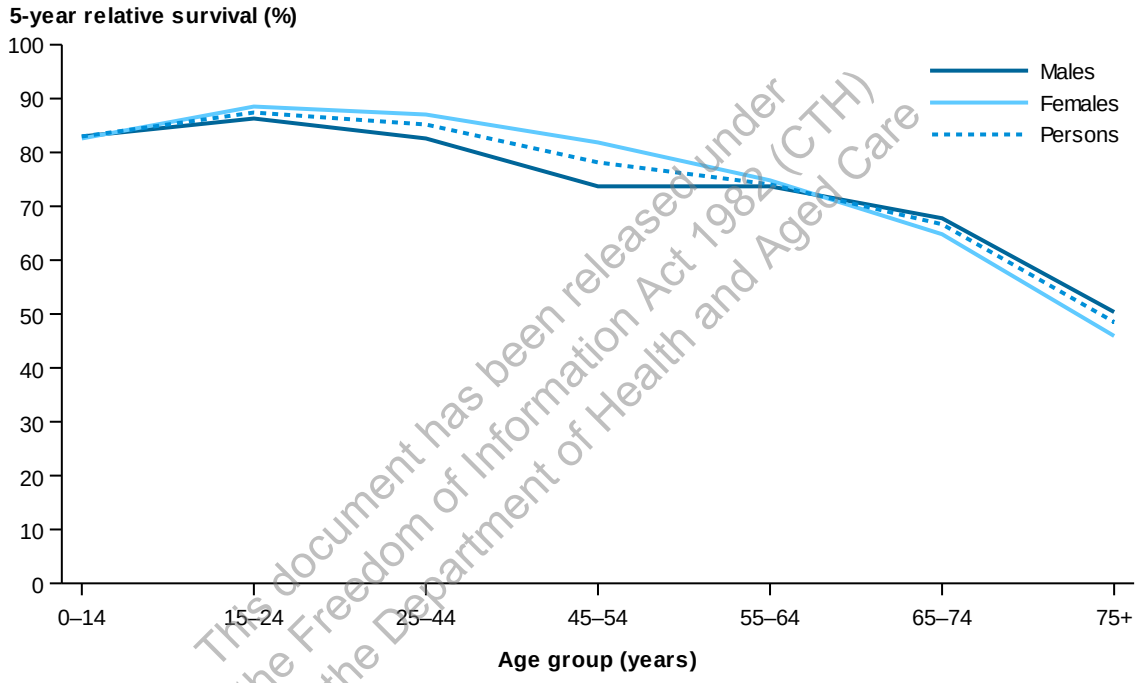
Source: AIHW ACD 2011.

Figure 5.1: Five-year relative survival from selected cancers, Australia, 2007–2011

Difference by age

In 2007–2011 for all cancers combined, 5-year survival was highest for those aged 15–24 (87%); it decreased with age and was lowest (48%) for those aged 75 and over (Figure 5.2). The difference in survival by age may be due to a number of reasons, including the stage at diagnosis of tumours, a greater likelihood of co-morbidity among those diagnosed at an older age, differences in treatments received and inclusion in clinical trials (Brenner & Arndt 2004; Ellison & Gibbons 2006; NCRI & WHC 2006).

Females had a survival advantage up to the 55–64-year age group. The difference was most noticeable for those aged 45–54, where 5-year survival was 82% for females and 74% for males. From the age of 65–74, survival was slightly but significantly higher for males (online table D5.2). The difference in the age-related pattern of survival by sex may be partly due to the age distributions and survival outcomes for prostate cancer and breast cancer.



Note: Data for this figure are in online Table D5.2.

Source: AIHW ACD 2011.

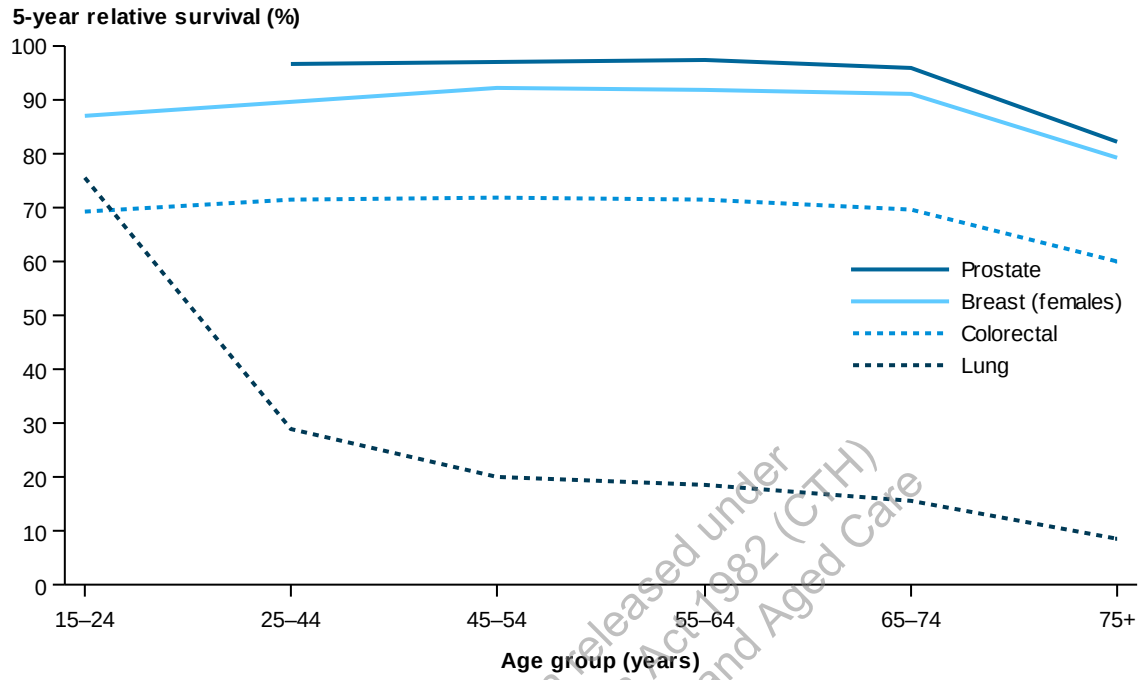
Figure 5.2: Five-year relative survival from all cancers combined by age at diagnosis, Australia, 2007–2011

The age-related pattern of survival for all cancers combined was characteristic of most individual cancer types. The reduction in survival with age was more pronounced in the second half of the lifespan; however, the pattern of decline varied across cancer types.

For example, 5-year survival for colorectal cancer did not vary considerably for those aged under 75 (69% to 72%), but it dropped significantly to 60% for those aged 75 and over. Five-year survival for prostate cancer had a similar pattern. For those aged under 75, 5-year survival was 96% to 97%; it reduced to 82% for those aged 75 and over.

For breast cancer in females, 5-year survival was highest in those aged between 45 and 74 (91% to 92%). This may be related to the population-based BreastScreen program, which targets females in the age group of 50–69.

In contrast, 5-year survival for lung cancer fell sharply, earlier than for other selected cancers. For those aged 15–24, 5-year survival was 76%; it quickly declined to 29% for those aged 25–44. A more gradual decline continued, to 8.7%, for those aged 75 and over (Figure 5.3).



Notes

1. Data on the age group 0–14 for these cancers and the age group 15–24 for prostate cancer cannot be released due to the small number of cases.
2. Data for this figure are presented in online Table D5.2.

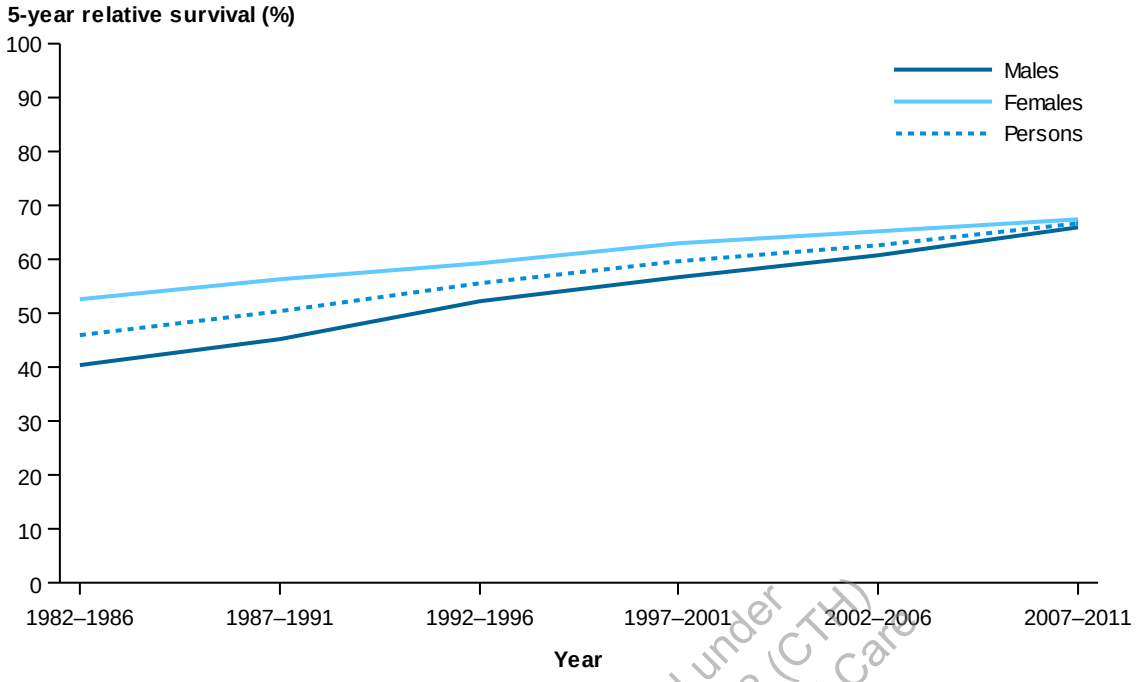
Source: AIHW ACD 2011.

Figure 5.3: Five-year relative survival from selected cancers by age at diagnosis, Australia, 2007–2011

Change over time

Five-year survival for people diagnosed with cancer increased significantly over time, from 46% in 1982–1986 to 67% in 2007–2011 (Figure 5.4).

The increase in 5-year survival over time is evident in both males and females, although the increase was greater for males. For all cancers combined, 5-year survival for males increased from 40% in 1982–1986 to 66% in 2007–2011, compared with 52% to 68% for females. These gains can be partly attributed to better diagnostic methods, earlier detection and improvements in treatment (Dickman & Adami 2006).



Note: Data for this figure are in online Table D5.3.

Source: AIHW ACD 2011.

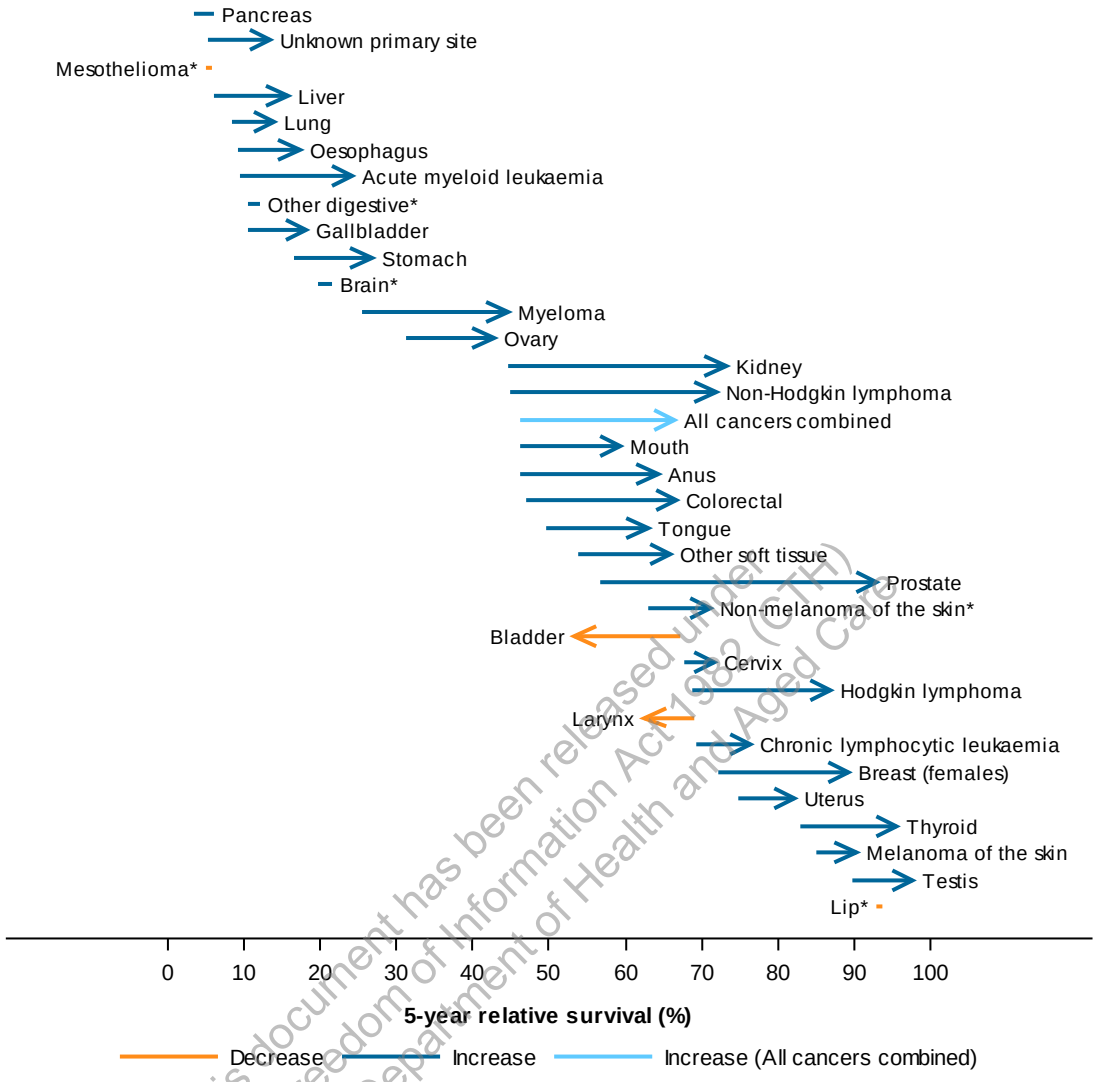
Figure 5.4: Five-year relative survival from all cancers combined, Australia, 1982–1986 to 2007–2011

Between 1982–1986 and 2007–2011, survival from most cancers improved, but the change was not uniform over time or across cancer types (Figure 5.5).

The cancers that had the largest absolute increase in survival were prostate cancer, kidney cancer, non-Hodgkin lymphoma, colorectal cancer, myeloma, Hodgkin lymphoma and anal cancer, where 5-year survival increased by 18 percentage points or more.

Many of the cancers that had low survival in 1982–1986 showed only small improvements, such as cancer of other digestive organs (from 10% to 12%), pancreatic cancer (from 4% to 6%) and lung cancer (from 9% to 14%).

Some cancers had a decrease in survival over time. Cancer of the bladder showed a statistically significant decrease in 5-year survival (67% to 53%). The negative trend in bladder cancer survival may be partly attributed to changes in coding practices and changes in the age at diagnosis over time (Duncombe et al. 2009; English et al. 2007; Luke et al. 2010).



Notes

1. Arrow positions indicate survival estimates and arrow lengths indicate the change in survival between the periods 1982–1986 and 2007–2011. Cancers labelled with an asterisk (*) indicate changes that were not statistically significant.
2. Data for 1987–1991, instead of 1982–1986, are used for liver cancer, mesothelioma and cancer of other digestive organs due to the small number of cases from the earlier time period.
3. All cancers combined include cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin. Non-melanoma skin cancer does not include C44 codes that indicate a basal or squamous cell carcinoma of the skin.
4. Data for this figure are in online Table D5.4.

Source: AIHW ACD 2011.

Figure 5.5: Survival trends for selected cancers, Australia, between 1982–1986 and 2007–2011

Conditional survival

Conditional survival estimates show the probability of surviving a given number of years provided that an individual has *already* survived a specified amount of time after diagnosis. Ordinary relative survival shows the probability of survival at diagnosis.

Note that all conditional survival estimates in this report are conditional relative survival estimates. That is, they have been derived from relative survival but are referred to simply as 'conditional survival'.

For all cancers combined, the prospect of surviving for at least 5 more years after having already survived for 1, 5, 10 or 15 years, increased markedly. At diagnosis, the probability of surviving for at least 5 years was 67%. However, by 1 year after diagnosis, individuals with cancer had an 80% chance of surviving at least 5 more years (Table 5.2). This increased further to 97% by 15 years after diagnosis, at which survival prospects were almost the same as for the general population.

Table 5.2: Summary of conditional survival from all cancers combined[(a)], Australia, 2007–2011

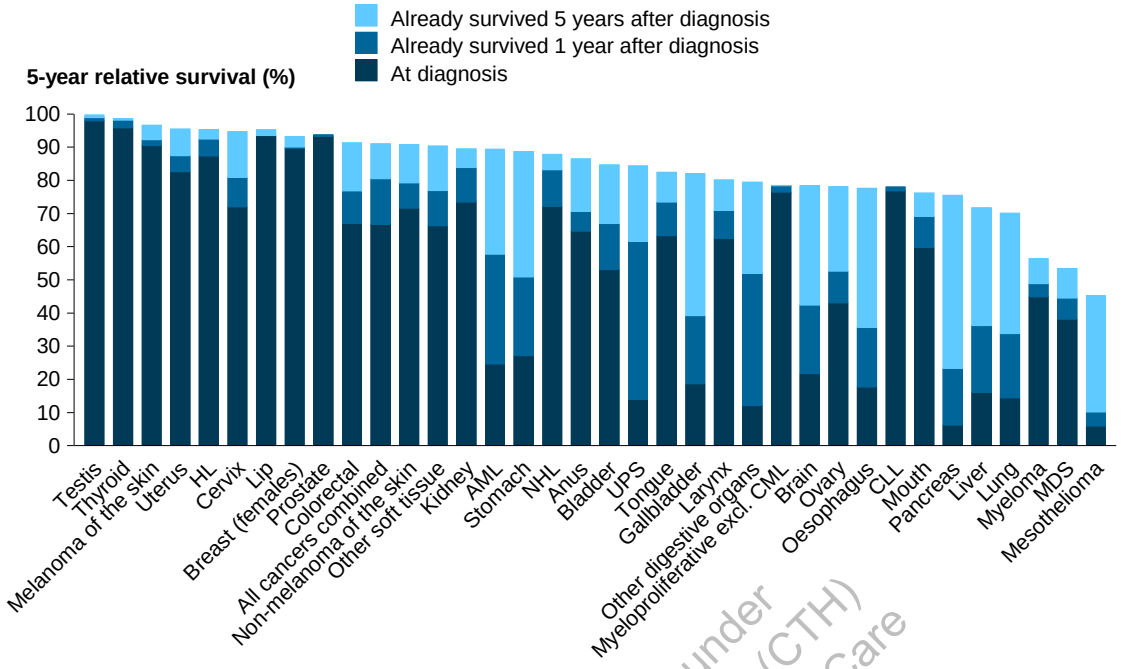
Years already survived	5-year conditional relative survival (%)	95% confidence interval
At diagnosis	66.7	66.5–66.3
Already survived 1 year after diagnosis	80.4	80.3–80.6
Already survived 5 years after diagnosis	91.0	90.8–91.2
Already survived 10 years after diagnosis	93.8	93.6–94.0
Already survived 15 years after diagnosis	96.5	96.2–96.7

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate basal cell and squamous cell carcinoma of the skin.

Source: AIHW ACD 2011.

The relationship between conditional survival and survival at diagnosis varied for different cancer sites. Some cancers that had poor survival prospects at diagnosis were observed to have substantial increases in conditional survival with the number of additional years survived. These included stomach cancer, cancer of the gallbladder and extrahepatic bile ducts, cancer of unknown primary site and acute myeloid leukaemia. All of these had a 5-year relative survival at diagnosis of less than 30%. However, 5 years after diagnosis, survival for an additional 5 years was more than 80%.

Some cancers that had relatively high survival at diagnosis were observed to have little increase in conditional survival by 5 years after diagnosis. For example, survival from testicular cancer, thyroid cancer, melanoma of the skin, lip cancer and prostate cancer was comparatively high at diagnosis (more than 90%), with only marginal gains in conditional survival after having already survived for 1 or 5 years (Figure 5.6).



Notes

1. The three columns for each cancer are overlapping, such that the area for *Already survived 5 years after diagnosis* includes those for *Already survived 1 year after diagnosis* and *At diagnosis*.
2. All cancers combined include cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin. Non-melanoma skin cancer does not include C44 codes that indicate a basal or squamous cell carcinoma of the skin.
3. HL= Hodgkin lymphoma, AML=Acute myeloid leukaemia, NHL=Non-Hodgkin lymphoma, UPS=Cancer of unknown primary site, CLL=Chronic lymphocytic leukaemia, MDS= Myelodysplastic syndromes.
4. Data for this figure are in online Table D5.5.

Source: AIHW ACD 2011.

Figure 5.6: Five-year survival by number of years already survived, Australia, 2007–2011

6 Prevalence of cancer

Key findings

At the end of 2009 in Australia:

- 370,474 people were alive who had been diagnosed with cancer within the previous 5 years; this represented 1.7% of the Australian population
- 5-year prevalence was higher in males than in females (56% and 44% of all prevalent cases, respectively)
- among males, 5-year prevalence was highest for prostate cancer (42% of total male 5-year prevalence), followed by melanoma of the skin (13%) and colorectal cancer (13%)
- among females, 5-year prevalence was highest for breast cancer (36% of total female 5-year prevalence), followed by colorectal cancer (13%) and melanoma of the skin (13%).

About prevalence

Prevalence, or survivorship population, refers to the number of people alive who have ever been diagnosed with cancer. The combined effect of several factors—increasing incidence, decreasing mortality, improving survival, and developments in treatment—is leading to an increase in the population who have ever been diagnosed with cancer (see Box 6.1).

Prevalence is a direct product of incidence and survival. Cancers with high incidence and high survival (such as melanoma of the skin) tend to have high prevalence, whereas cancers with low incidence and low survival (such as pancreatic cancer) tend to have low prevalence. In other cases, prevalence may represent a balance between conflicting incidence and survival patterns. For example, lung cancer has high incidence but low survival and therefore has low prevalence (AIHW & CA 2011).

This chapter presents limited-duration prevalence with an index date of 31 December 2009, based on the 2011 ACD, which contains actual national cancer data from 1982 to 2009 (see Appendix F). Data from the National Death Index (NDI) on deaths (from any cause) that occurred up to 31 December 2011 were used to determine which people with cancer had died and when this occurred. Note that a person who was diagnosed with two separate cancers contributed separately to the prevalence of each cancer. However, this person would contribute only once towards prevalence of all cancers combined.

Box 6.1: Survivorship experience

Survivorship is increasingly recognised as starting at diagnosis and, in some cases, continuing long after treatment ends. It is more than simply not dying from cancer; it focuses on living with (and after) a cancer diagnosis (Jackson et al. 2013). Cancer survivors often face emotional, physical and financial challenges as a result of the detection, diagnosis and treatment of cancer. These factors—and the associated stressors and reduced quality of life for cancer survivors and their family, friends and caregivers—highlight the importance of follow-up health care and of survivorship as part of the cancer control continuum (Hawkins et al. 2010; Jackson et al. 2013).

A summary of prevalence data is provided in this chapter. Summary pages for selected cancers are at Appendix B.

Cancer prevalence

At the end of 2009, 370,474 people were alive who had been diagnosed with cancer in the previous 5 years (Table 6.1). This represented 1.7% of the Australian population. Males made up 56% of the 5-year prevalent cases. At the end of 2009, the 10-year prevalence of cancer was 581,208 and the 28-year prevalence was 861,057 (Table 6.1).

Table 6.1: Limited-duration prevalence of all cancers combined[(a)], by sex, Australia, as at end of 2009

	Number[(b)]	Per cent of prevalent cases	Per cent of population[(c)]
		5-year prevalence	
Males	206,437	55.7	1.9
Females	164,037	44.3	1.5
Persons	**370,474**	**100.0**	**1.7**
		10-year prevalence	
Males	310,625	53.4	2.9
Females	270,583	46.6	2.5
Persons	**581,208**	**100.0**	**2.7**
		28-year prevalence	
Males	429,083	49.8	3.9
Females	431,974	50.2	3.9
Persons	**861,057**	**100.0**	**3.9**

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate basal cell and squamous cell carcinoma of the skin.

(b) Prevalence refers to number of living people previously diagnosed with cancer, not the number of cancer cases.

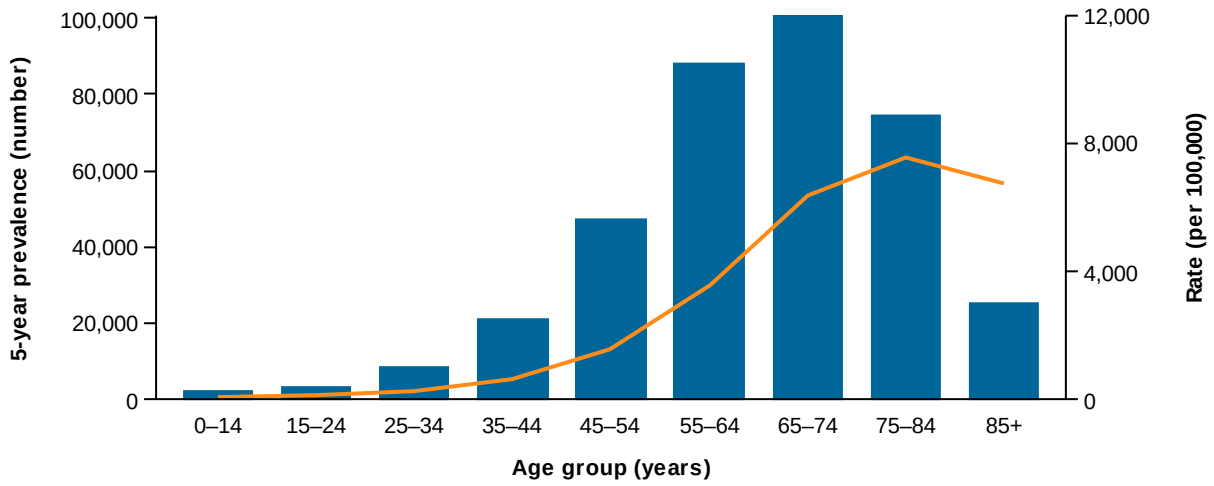
(c) Based on the Australian population at 31 December 2009.

Source: AIHW ACD 2011.

Differences by age

Five-year prevalence for all cancers combined increased with age from those aged 0–14 to those aged 65–74, before decreasing for those aged 75–84 and 85 years and older. Note that in these prevalence statistics, age refers to the age of a person on the index date of 31 December 2009. At the end of 2009, Australians aged 75 years and over accounted for 27% of 5-year prevalence cases.

Five-year prevalence was highest for those aged 65–74 (100,648) and lowest for those aged 0–14 (2,173) (Figure 6.1).



Notes

1. Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.
2. Data for this figure are in online Table D6.1.

Source: AIHW ACD 2011.

Figure 6.1: Five-year prevalence of all cancers combined by age group, Australia, as at end of 2009

Cancer sites

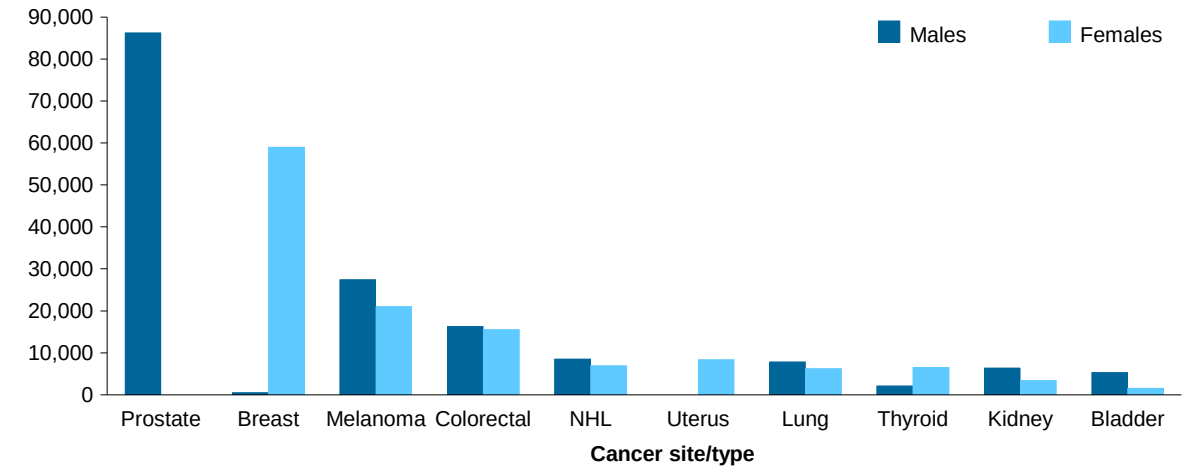
Among males, prostate cancer had the highest 5-year prevalence of 86,207 males at the end of 2009. This was followed by melanoma of the skin (27,402) and colorectal cancer (26,700). Prostate cancer accounted for 42% of the total 5-year prevalence in males, while melanoma of the skin contributed 13% and colorectal cancer contributed 13%.

Among females, breast cancer had the highest 5-year prevalence (58,955 females), followed by colorectal cancer (21,896) and melanoma of the skin (20,962). Breast cancer accounted for 36% of the total 5-year prevalence in females, while colorectal cancer contributed 13% and melanoma of the skin contributed 13%.

For the majority of cancer sites, 5-year prevalence was higher in males than in females. 5-year prevalence for mesothelioma was 4 times higher in males than in females, and liver cancer and lip cancer were 2.8 times as high in males as in females.

Of the selected cancer sites, the lowest 5-year prevalence was observed for bladder cancer (Figure 6.2).

Of the selected cancers, the trend was most pronounced for bladder cancer, where 5-year prevalence was more than 3 times as high in males as in females (5,241 males and 1,498 females. 5-year prevalence for kidney cancer was nearly twice as high in males (6,291) as in females (3,336). In contrast, the 5-year prevalence for thyroid cancer was more than 3 times as high in females (6,482) as in males (2,057).



Notes

1. Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.
2. NHL=Non-Hodgkin lymphoma. Melanoma refers to melanoma of the skin.
3. Data for this figure are in Online Table D6.2.

Source: AIHW ACD 2011.

Figure 6.2: Five-year prevalence of selected cancers, Australia, as at the end of 2009

7 Mortality from cancer

Key findings

In Australia, it is estimated that in 2014:

- 45,780 people will die from cancer, an average of 125 deaths every day
- males will account for more than half of all deaths from cancer (57%)
- lung cancer will be the leading cause of cancer death among males (5,150 deaths), followed by prostate cancer (3,390), colorectal cancer (2,210), pancreatic cancer (1,360) and cancer of unknown primary site (1,160)
- the most common cancers causing death in females will be lung cancer (3,480 deaths), breast cancer (3,000), colorectal cancer (1,910), pancreatic cancer (1,280) and cancer of unknown primary site (1,180)
- the age-standardised mortality rate for all cancers combined will be 168 per 100,000, a fall of 20% from 1982 (209 per 100,000).

About mortality

In this report, mortality refers to the number of deaths for which the underlying cause was a primary cancer. The cancer that led to the death of the person may have been diagnosed many years previously, in the same year in which the person died or, in some cases, after death (for example at autopsy). Information on the underlying cause of death is derived from the medical certificate of cause of death, which is usually completed by a medical practitioner.

The main data source used in this chapter was the AIHW National Mortality Database (NMD), which contains information about all deaths registered in Australia (see Appendix I for more information).

This chapter focuses on the estimated deaths from cancer for 2014 and mortality trends from 1982 to 2014. It should be noted that the estimates are only indicative of the future trends, and the actual numbers may differ from these estimates. They are not forecasts and do not attempt to allow for future changes in cancer treatments. Actual mortality data from 1982 to 2011 are based on the *year of occurrence* of the death, and data for 2012 are based on the *year of registration* of the death (see Appendix I).

Summary pages for selected cancers on latest mortality data (2012) and estimates for 2014–2016 are at Appendix B. An overview of mortality statistics for all cancers is at Appendix C.

Estimated number of deaths from cancer

It is estimated that cancer will account for about 3 of every 10 deaths (30%) registered in Australia in 2014.

In 2014, it is estimated that 45,780 people will die from cancer in Australia, an average of 125 deaths every day. More males (57%) than females (43%) are expected to die from cancer in 2014, with cancer accounting for 33% of all male deaths and 27% of all female deaths.

The age-standardised mortality rate for all cancers combined is estimated to be 168 per 100,000 in 2014. The mortality rate of males (212 per 100,000) is estimated to be considerably higher than that of females (134 per 100,000) (Table 7.1).

Table 7.1: Estimated deaths from all cancers combined[(a)], Australia, 2014[(b)]

	Males	Females	Persons
Number of deaths	26,010	19,770	45,780
ASR[(c)]	211.5	133.7	167.7
Per cent of all cancer deaths (%)	56.8	43.2	100.0
Per cent of all deaths (%)	32.6	26.7	30.2

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.

(b) The 2014 estimates are based on 2002–2012 mortality data (see appendixes G and I). They are rounded to the nearest 10. The estimates for males and females may not add to the estimates for persons due to rounding.

(c) The rates were standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

Source: AIHW NMD.

Most common causes of death from cancer

In 2014, it is estimated that the most common causes of death from cancer in Australia were:

- lung cancer (8,630 deaths)
- colorectal cancer (4,120)
- prostate cancer (3,390)
- breast cancer (3,030)
- pancreatic cancer (2,640).

Together, these five cancers represent just under half (48%) of the total mortality from cancer, with lung cancer alone accounting for 1 in every 5 deaths due to cancer (19%).

Males

For males, lung cancer is estimated to be the leading cause of death from cancer, with 5,150 deaths in 2014 (Table 7.2). It is estimated that prostate cancer (3,390) and colorectal cancer (2,210) will be the second and third leading cause of cancer deaths in males, respectively, followed by pancreatic cancer (1,360) and cancer of unknown primary site (1,160). These five cancers account for around 51% of all cancer deaths in males.

Females

For females, lung cancer is estimated to be the most common cause of death from cancer in 2014 (3,480 deaths) (Table 7.2). This is followed by breast cancer (3,000), colorectal cancer (1,910), pancreatic cancer (1,280) and cancer of unknown primary site (1,180). These five cancers account for around 55% of all cancer deaths in females (Table 7.2).

Table 7.2: Estimated 10 most common causes of death from cancer, Australia, 2014[a]

Males				Females			
Cancer site/type (ICD-10 codes)	**Deaths**	**Crude rate**	**ASR**[b]	**Cancer site/type (ICD-10 codes)**	**Deaths**	**Crude rate**	**ASR**[b]
Lung (C33–C34)	5,150	44.0	41.5	Lung (C33–C34)	3,480	29.5	24.1
Prostate (C61)	3,390	28.9	28.2	Breast (C50)	3,000	25.4	20.9
Colorectal (C18–C20)	2,210	18.9	17.9	Colorectal (C18–C20)	1,910	16.2	12.6
Pancreas (C25)	1,360	11.6	10.9	Pancreas (C25)	1,280	10.8	8.6
Unknown primary site (C80)	1,160	9.9	9.4	Unknown primary site (C80)	1,180	10.0	7.6
Melanoma of the skin (C43)	1,120	9.6	9.1	Ovary (C56)	1,000	8.5	6.9
Liver (C22)	1,080	9.2	8.7	Leukaemia (C91–C95)	695	5.9	4.6
Leukaemia (C91–C95)	1,040	8.9	8.5	Other digestive organs (C26)	680	5.8	4.3
Oesophagus (C15)	975	8.3	7.7	Lymphoma (C81–C85)	640	5.4	4.2
Lymphoma (C81–C85)	855	7.3	7.0	Brain (C71)	540	4.6	4.0
All cancers[c]	**26,010**	**222.1**	**211.5**	**All cancers**[c]	**19,770**	**167.3**	**133.7**

(a) The 2014 estimates are based on 2002–2012 mortality data (see appendixes G and I). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to nearest 5.

(b) The rates were standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

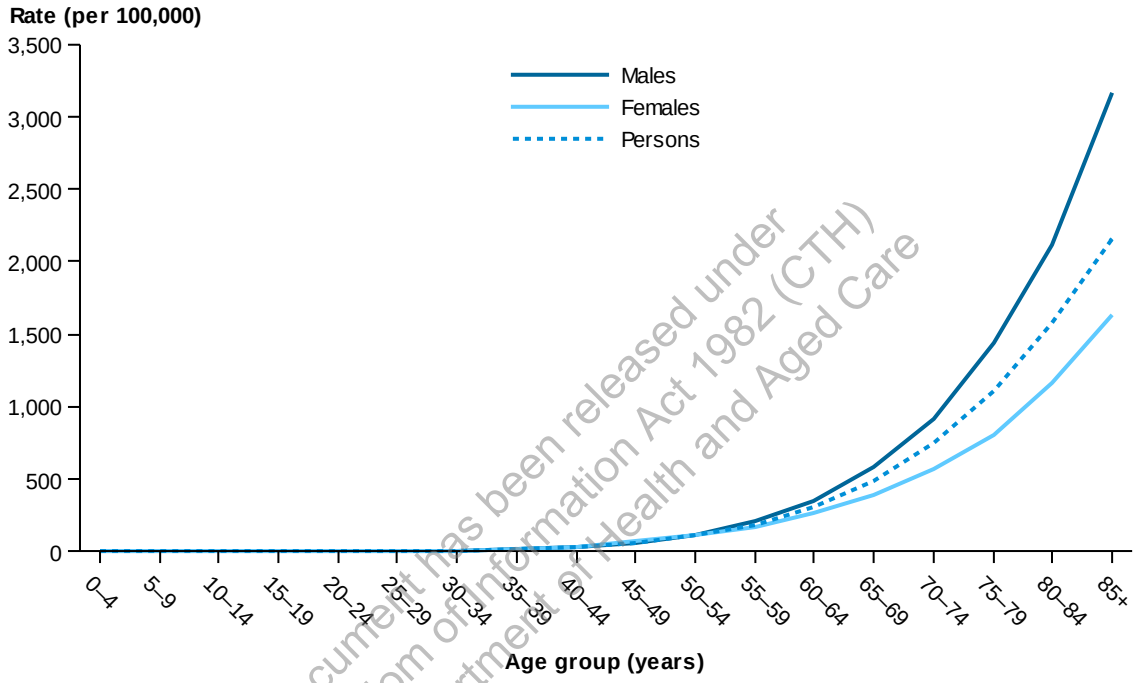
(c) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.

Source: AIHW NMD.

Mortality by age

The age-specific mortality rate of all cancers combined increases with age (Figure 7.1). In 2014, it is estimated that 87% of all cancer deaths in males and 84% of all cancer deaths in females occurred in people aged over 60.

For those aged under 50, the estimated age-specific mortality rate is similar for males and females. After 55, the mortality rate increased more steeply for males. Mortality from lung cancer, prostate cancer and colorectal cancer may be attributed to the high cancer mortality rate in older males.



Notes

1. The 2014 estimates are based on 2002–2012 mortality data (see appendixes G and I). The estimates for males and females may not add to the estimates for persons due to rounding.
2. Data pertain to cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.
3. Data for this figure are in online Table D7.1.

Source: AIHW NMD.

Figure 7.1: Estimated mortality from all cancers combined by age at death, Australia, 2014

Risk of death from cancer

In 2014, it is estimated that the risk of dying from cancer before the age of 75 is 1 in 9 for males and 1 in 13 for females. By the age of 85, the risk is estimated to increase to 1 in 4 for males and 1 in 6 for females (Table 7.3) (see Appendix H for an explanation of how these risks are calculated).

The risk of dying from lung cancer before the age of 75 was estimated to be 1 in 40 for males and 1 in 59 for females. By the age of 85, the risk of dying from lung cancer doubled to 1 in 17 for males and 1 in 29 for females.

Table 7.3: Estimated risk of death from all cancers combined[(a)], by sex, Australia, 2014

Sex	Risk to age 75	Risk to age 85
Males	1 in 9	1 in 4
Females	1 in 13	1 in 6
Persons	**1 in 11**	**1 in 5**

(a) The 2014 estimates are based on 2002–2012 mortality data (see appendixes G and I). Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.

Source: AIHW NMD.

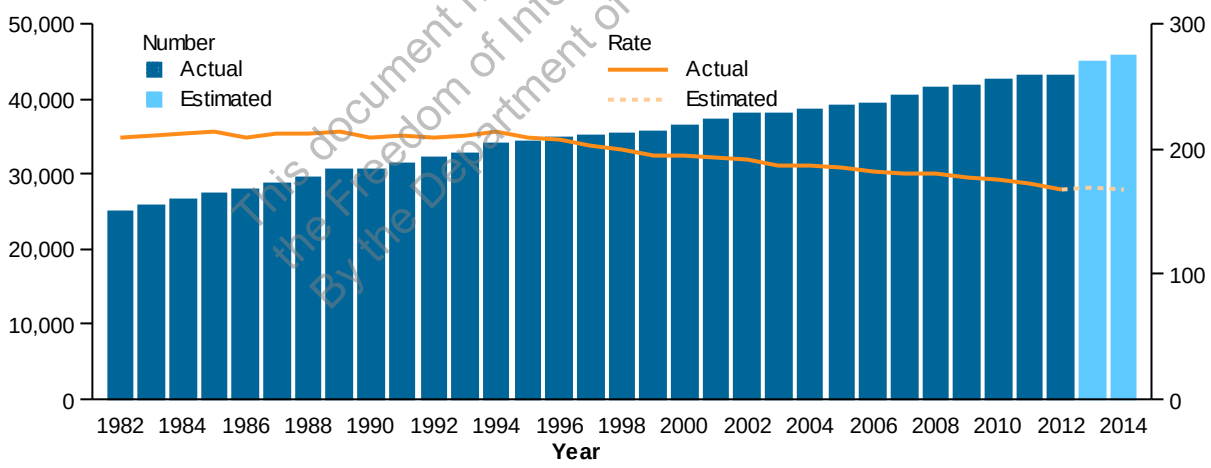
Change over time

In this section, trends in mortality from all cancers combined and selected cancer sites are presented for actual data for 1982–2012 and estimated for 2013 and 2014.

Trends for all cancers combined

The number of deaths from all cancers combined has steadily increased over time. In 2014, it is estimated that 45,780 Australians will die from cancer, compared with 24,922 in 1982, an increase of 84%. The number of deaths estimated for 2014 will be the largest number reported in any year to date.

In contrast, it is estimated that there will be a decrease in the age-standardised mortality rate for cancer between 1982 and 2014. Over this time, it is estimated that the mortality rate from cancer will fall by 20%, from 209 to 168 per 100,000 (Figure 7.2)



Notes

1. Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS.
2. The 2013 and 2014 estimates are based on 2002–2012 mortality data (see appendixes G and I). Estimates are displayed on the graph as a dotted line or as bars in a lighter shade.
3. Actual mortality data from 1982 to 2011 are based on the year of occurrence of the death, and data for 2012 are based on the year of registration of the death (see Appendix I).
4. The rates were age-standardised to the Australian population as at 30 June 2001.
5. Data pertain to cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.
6. Data for this figure are in online Table D7.2.

Source: AIHW NMD.

Figure 7.2: Trends in mortality from all cancers combined, Australia, 1982 to 2014

Males

For males, after the mortality rate reached a peak in 1994, it is estimated that it will fall by 26% over the period from 1994 to 2014 (from 285 to 212 per 100,000; see online Table D7.2). The trend of cancer mortality in males can be largely attributed to declines in mortality rates for lung cancer, prostate cancer and colorectal cancer, which accounted for most of the total decrease between 1994 and 2014.

Females

For females, the cancer mortality rate was consistently lower than that for males. The female mortality rate remained fairly steady before 1993 and decreased thereafter (online Table D7.2). The mortality rate among females is estimated to fall by 18% from 1993 (164 per 100,000) to 2014 (134 per 100,000). The fall could be largely attributed to declines in mortality rates of breast cancer and colorectal cancer.

Trends for specific cancers

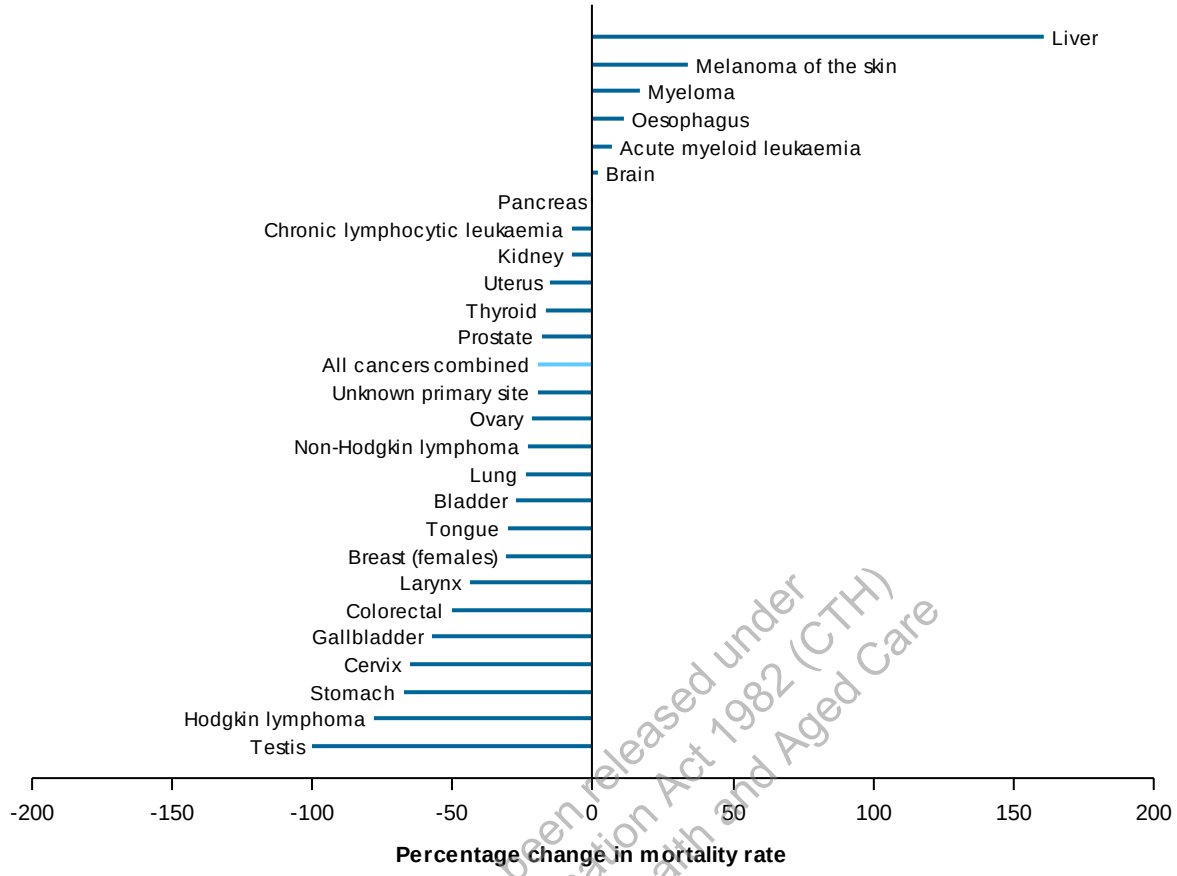
Between 1982 and 2014, the age-standardised mortality rate of many cancers decreased. Figure 7.3 summarises the estimated percentage change in age-standardised mortality rates.

Cancers that showed the greatest decrease in the age-standardised mortality rate include:

- stomach cancer (from 12.3 to 4.0 per 100,000 persons)
- cervical cancer (5.2 to 1.8 per 100,000)
- colorectal cancer (31.5 to 15.6 per 100,000)
- breast cancer in females (30.4 to 20.9 per 100,000)
- lung cancer (42.3 to 32.2 per 100,000)
- ovarian cancer (8.8 to 6.9 per 100,000)
- cancer of unknown primary site (10.1 to 8.1 per 100,000)
- prostate cancer (34.5 to 28.2 per 100,000).

Cancers that showed an increase in the age-standardised mortality rate include:

- liver cancer (from 2.3 to 6.0 per 100,000)
- melanoma of the skin (4.7 to 6.3 per 100,000)
- myeloma (3.0 to 3.5 per 100,000)
- oesophageal cancer (4.4 to 4.9 per 100,000)
- brain cancer (5.0 to 5.1 per 100,000) (Figure 7.3).



Notes

1. The 2014 estimates are based on 2002–2012 mortality data (see appendixes G and I). Estimates for 2015 and 2016 are also available at Appendix B.
2. The bars indicate the percentage change in mortality rates between1982 and 2014.
3. The percentage change between 1982 and 2014 is a summary measure that allows the use of a single number to describe the change over a period of multiple years. However, it is not always reasonable to expect that a single measure can accurately describe the trend over the entire period.
4. The rates were age-standardised to the Australian population as at 30 June 2001.
5. Data for this figure are in online Table D7.3.

Source: AIHW NMD.

Figure 7.3: Estimated percentage change in age-standardised mortality rates between 1982 and 2014, Australia

8 Focus on key population groups

Key findings

Incidence

In the 5 years from 2005 to 2009:

- the age-standardised incidence rate was higher for Indigenous than for non-Indigenous Australians for liver cancer (2.8 times as high), cervical cancer (2.3), cancer of unknown primary site (1.8), lung cancer (1.7), uterine cancer (1.6), and pancreatic cancer (1.3)
- the incidence rate for all cancers combined was highest in Tasmania (530 per 100,000) and lowest in the Northern Territory (456 per 100,000)
- people living in *Inner regional* areas of Australia had the highest incidence rate in six of the selected cancers: prostate cancer (206 per 100,000), breast cancer in females (120 per 100,000), colorectal cancer (70 per 100,000), melanoma of the skin (62 per 100,000), non-Hodgkin lymphoma (19 per 100,000) and kidney cancer (13 per 100,000).

In the 4 years from 2006 to 2009 (2005 data were not included as some data were not available):

- those living in the most disadvantaged areas of Australia accounted for the highest age-standardised incidence rate for six of the selected cancers: colorectal cancer (66 per 100,000), lung cancer (52 per 100,000), cancer of unknown primary site (14 per 100,000), bladder cancer (11 per 100,000), pancreatic cancer (11 per 100,000) and cervical cancer (8 per 100,000).

In 2014, the most common cancers diagnosed by life stage are estimated to be:

- leukaemia for people aged 0–24 (315 new cases), breast cancer for people aged 25–49 (3,300 new cases) prostate cancer for people aged 50–64 (6,090 new cases) and colorectal cancer for people aged 65 and over (11,490 new cases).

Mortality

In the 5 years from 2008 to 2012:

- the age-standardised mortality rate was higher for Indigenous than for non-Indigenous Australians for cervical cancer (3.4 times as high), liver cancer (3.0), lung cancer (1.7), uterine cancer (1.6), cancer of unknown primary site (1.5), pancreatic cancer (1.2) and breast cancer in females (1.1)
- the age-standardised mortality rate for all cancers combined was highest in the Northern Territory (217 per 100,000) followed by Tasmania (192 per 100,000); the lowest mortality rate was in the Australian Capital Territory (152 per 100,000)
- the age-standardised mortality rate for all cancers combined was 15% higher in *Remote* and *Very remote* areas than in *Major cities*.

In the 4 years from 2009 to 2012:

- those living in the most disadvantaged areas of Australia accounted for the highest age-standardised mortality rate for nine of the selected cancers: lung cancer (40 per 100,000), breast cancer in females (22 per 100,000), colorectal cancer (17 per 100,000), pancreatic cancer (11 per 100,000), cancer of unknown primary site (11 per 100,000), non-Hodgkin lymphoma (6 per 100,000), bladder cancer (5 per 100,000) kidney cancer (4 per 100,000) and cervical cancer (3 per 100,000).

Differences across population groups

Cancer incidence and mortality data in this chapter are presented according to five population groups:

- Aboriginal and Torres Strait Islander people
- State and territory
- Remoteness areas
- Socioeconomic disadvantage
- Life stages (represented by four broad age groups).

Actual incidence and mortality data are presented in this chapter, except for the 'Life stages' section of the chapter, where incidence and mortality estimates for 2014 are presented. Data are presented for all cancers combined and for selected cancers for each of the focus population groups.

The cancers discussed in the Aboriginal and Torres Strait Islander section have been selected, due to the higher diagnosis and mortality rates of certain cancers in this population group.

For Aboriginal and Torres Strait Islander people, data are presented for the following cancers: breast cancer in females, cancer of unknown primary site, cervical cancer, colorectal cancer, liver cancer, lung cancer, non-Hodgkin lymphoma uterine cancer, pancreatic cancer and prostate cancer.

For the population groups by state and territory, by remoteness area, and by socioeconomic disadvantage, data are presented for the following cancers: cervical cancer, colorectal cancer, bladder cancer, breast cancer in females, kidney cancer, lung cancer, melanoma of the skin, non-Hodgkin lymphoma, pancreatic cancer, prostate cancer, cancer of unknown primary site.

Data have been presented for multiple years to reduce random variations in rates. This is especially important for small population groups. Apart from breast cancer in females, cervical cancer and prostate cancer, results are presented for males and females combined in a further attempt to reduce the random variation in the data.

Life stages are presented according to four broad age groups: 0–24 years, 24–49 years, 50–64 years, and 65 years and older. Data are presented as estimates for 2014 for all cancers combined and for the top five cancers for incidence and mortality. Incidence data are presented as an average over 5 years (2005 to 2009) for Indigenous, state and territory and remoteness areas sections of this report. Due to the unavailability of some data for socioeconomic disadvantage, 4 years of data (2006 to 2009) are used.Mortality data are presented as an average over 5 years (2008 to 2012) for Indigenous, state and territory, and remoteness areas sections of this report. For consistency, mortality data for socioeconomic disadvantage are also presented as the average of 4 years of data (2009 to 2012). Mortality data are based on the *year of occurrence* of the death, except for the most recent year (namely 2012), where the number of people whose death was *registered* is used (see Appendix I).

ASRs are provided for incidence and mortality to account for differences in the age structure and the size of the population groups.

Observed differences by the characteristics examined in this section may result from a number of factors, including variations in:

- population characteristics (for example, a relatively greater proportion of Indigenous people living in remote areas)
- the prevalence of risk and/or protective factors (for example, tobacco consumption, physical activity)
- the availability and usage of diagnostic services.

The main data source for this chapter was the 2011 Australian Cancer Database (ACD) and the National Mortality Database (NMD). The 5 years of incidence data from 2005 to 2009 were used for this chapter because 2009 is the latest year for which actual data were available for all states and territories (see Appendix F).

Care must be exercised when interpreting differences in rates based on small counts and/or population groups as such rates may be volatile.

Due to the differences in data sources and analysis approaches, mortality data in this chapter are not directly comparable with those published by individual state and territory cancer registries (see Box 8.1).

Box 8.1: Differences in reporting mortality data

Mortality due to cancer shown in this report may not be comparable with data published by individual state and territory cancer registries for a number of reasons, including those below:

- The mortality data in this chapter were derived using the place of a person's residence at the time of *death*. In contrast, some state and territory cancer registries present mortality information based on a person's place of residence at the time of *diagnosis*. In the latter data, the deaths may or may not have occurred in the state or territory indicated.
- Different approaches were used to assign cause of death. In this report, data on mortality for each jurisdiction were derived from the NMD (see Appendix I). Information on cause of death in the NMD is coded by the ABS. This process uses an automated coding system which selects the underlying cause of death from all the information documented on the death certificate. In contrast, the state and territory cancer registries may use information from a number of different sources, including pathology reports and other notifications, to assign a cause of death.

Aboriginal and Torres Strait Islander people

Aboriginal and Torres Strait Islander people are disadvantaged across a range of health-related and socioeconomic indicators compared with other Australians. Many factors contribute to the gap between Indigenous and non-Indigenous health, including social disadvantage such as lower education and employment rates, as well as higher smoking rates, poor nutrition, physical inactivity and poor access to health services (AIHW 2014a).

Aboriginal and Torres Strait Islander people are also more likely to live in remote areas of Australia than the non-Indigenous population.

Note that rates presented in this report for Indigenous and non-Indigenous Australians are not comparable with rates presented in the previous report *Cancer in Australia: an overview 2012*. Rates presented in this report are derived from population estimates from the ABS 2011

Census of Population and Housing, while the report *Cancer in Australia: an overview 2012* derived population estimates from the 2006 Census.

Incidence by Indigenous status

Reliable national data on the diagnosis of cancer for Indigenous Australians are not available. All state and territory cancer registries collect information on Indigenous status; however, in some jurisdictions the quality of Indigenous status data is insufficient for analyses. Information in the ACD on Indigenous status is considered to be of sufficient completeness for reporting for New South Wales, Queensland, Western Australia and the Northern Territory. Data for these four jurisdictions are used to examine the incidence of cancer by Indigenous status. While the majority (83%) of Australian Indigenous people live in these four jurisdictions, the degree to which data for these jurisdictions are representative of data for all Indigenous people is unknown (ABS 2012b).

For the four jurisdictions analysed, the overall level of missing data on Indigenous status for all cancers combined that were diagnosed between 2005 and 2009 was 12%. It should be noted, however, that the level of missing data was particularly high for prostate cancer (15%).

Between 2005 and 2009, an average of 840 Indigenous Australians were diagnosed with cancer each year—this comprised 1% of all cancer cases diagnosed in that period.

Of the selected cancers, lung cancer (average of 130 cases per year) was the most commonly diagnosed cancer among Indigenous Australians, followed by breast cancer in females (95 cases per year), colorectal cancer (79 cases per year) and prostate cancer (66 cases per year).

Between 2005 and 2009, the age-standardised incidence rate of all cancers combined was slightly lower for Indigenous Australians than for their non-Indigenous counterparts (421 and 443 per 100,000, respectively). This contrasts with findings in the 2012 edition of this report, where Indigenous Australians had a higher incidence rate for all cancers combined than non-Indigenous Australians (AIHW & AACR 2012). The reason for this reversal is that the ABS has revised upwards the estimated population of Indigenous Australians. This increase in population leads to an apparent decrease in incidence rate.

The age-standardised incidence rate was significantly higher for Indigenous than for non-Indigenous Australians for:

- liver cancer (2.8 times as high)
- cervical cancer (2.3)
- cancer of unknown primary site (1.8)
- lung cancer (1.7)
- uterine cancer (1.6).

While the incidence rate of pancreatic cancer was also higher for Indigenous Australians than for non-Indigenous Australians (1.3 times as high), the difference was not significant.

The higher incidence rates of lung cancer and liver cancer are consistent with Indigenous Australians' higher rates of smoking and heavy alcohol consumption. The higher rate of cervical cancer diagnosed for Indigenous Australians may be partly attributed to lower levels of participation in cervical screening programs (Condon 2004; Condon et al. 2005) and to greater exposure to risk factors associated with cervical cancer (such as higher rates of

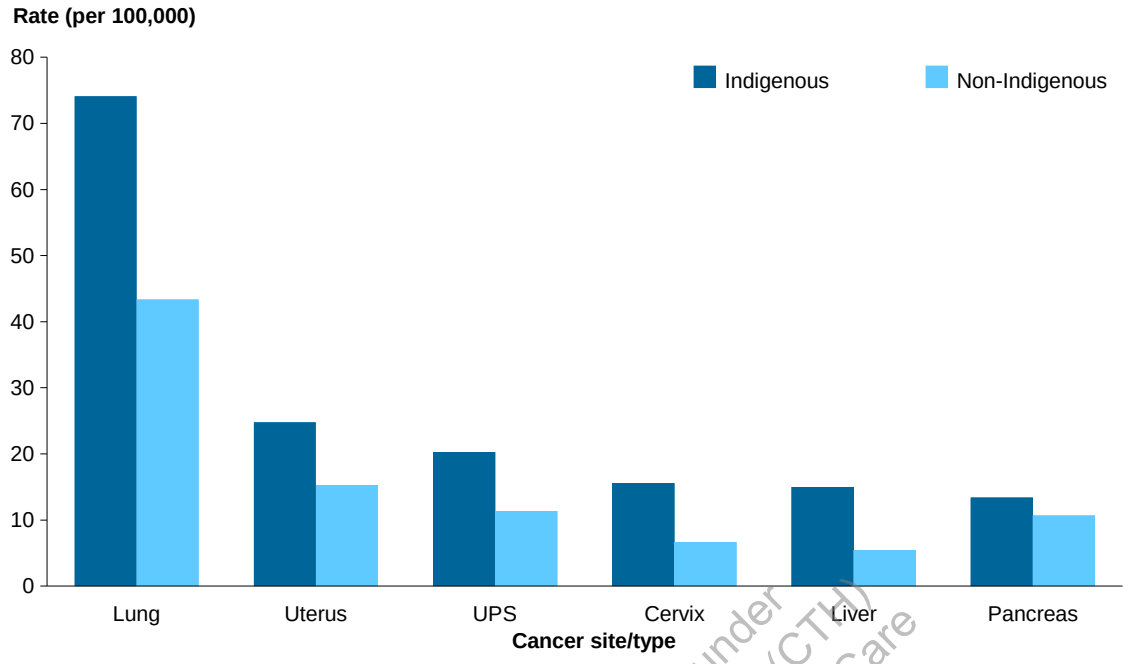
smoking and having more children) (Garland et al. 2011; Roder 2005). Indigenous Australians have poorer access to health-care services and are more likely to have cancers that are diagnosed at a later stage than non-Indigenous Australians, when the primary site is no longer apparent (Cunningham et al. 2008; Roder 2005). This contributes to an incidence rate of cancer of unknown primary site that is higher for Indigenous Australians than for non-Indigenous Australians.

There are also some cancers for which the age-standardised incidence rate was lower for Indigenous than non-Indigenous Australians, namely:

- colorectal cancer (rate ratio of 0.8)
- breast cancer in females (0.7)
- non-Hodgkin lymphoma (0.7)
- prostate cancer (0.6) (Figure 8.1).

In fact, these selected cancers with lower incidence rates for Indigenous Australians are the most commonly diagnosed cancers in non-Indigenous Australians.

The reasons for the lower incidence rate of some cancers among Indigenous Australians are not clear. Indigenous Australians are more likely to have cancers that are diagnosed at a later stage than non-Indigenous Australians, when the primary site is no longer apparent (Cunningham et al. 2008; Roder 2005). This may contribute to lower incidence rates for specific primary sites. The uptake of screening and diagnostics testing (such as breast and bowel screening and PSA testing) is lower among Indigenous people (ABS 2014c; Condon et al. 2001; Roder 2005; Stumpers & Thomson 2009; Threlfall & Thompson 2009), which may also contribute to a lower rate of diagnosis.



Notes

1. The rates were age-standardised to the Australian population as at 30 June 2001 and based on the total number of cases over the 5 years from 2005 to 2009.
2. Some states and territories use an imputation method to determine Indigenous cancers, which may lead to differences between these data and those shown in jurisdictional cancer incidence reports.
3. UPS stands for cancer of unknown primary site.
4. Data for this figure are in online tables D8.4, D8.7, D8.8, D8.11, D8.13 and D8.14.

Source: AIHW ACD 2011.

Figure 8.1: Incidence of lung cancer, uterine cancer, cancer of unknown primary site, cervical cancer, liver cancer and pancreatic cancer by Indigenous status, New South Wales, Queensland, Western Australia and the Northern Territory, 2005–2009

Mortality by Indigenous status

Information in the NMD on Indigenous status from 2008 to 2012 is considered to be of sufficient quality for use for five jurisdictions: New South Wales, Queensland, Western Australia, South Australia and the Northern Territory. Almost 9 in 10 (89%) Indigenous people live in these jurisdictions (ABS 2012b). In the NMD, the level of missing data on Indigenous status for all cancers combined was about 2% for these five jurisdictions (online Table D8.1).

Between 2008 and 2012, Indigenous Australians accounted for an annual average of 459 cancer deaths (1.5% of all deaths due to cancer).

The age-standardised mortality rate of all cancers combined was significantly higher for Indigenous Australians than for their non-Indigenous counterparts (221 and 172 per 100,000, respectively). The higher mortality rate for Indigenous Australians may be partly explained by their greater likelihood of being diagnosed with cancers where the prospect of successful treatment and survival is poorer (for example, lung cancer and cancer of unknown primary site) (Condon et al. 2003; Threlfall & Thompson 2009) or by being diagnosed at an advanced stage, as well as their lesser likelihood of receiving adequate treatment (AIHW 2012a; Cunningham et al. 2008).

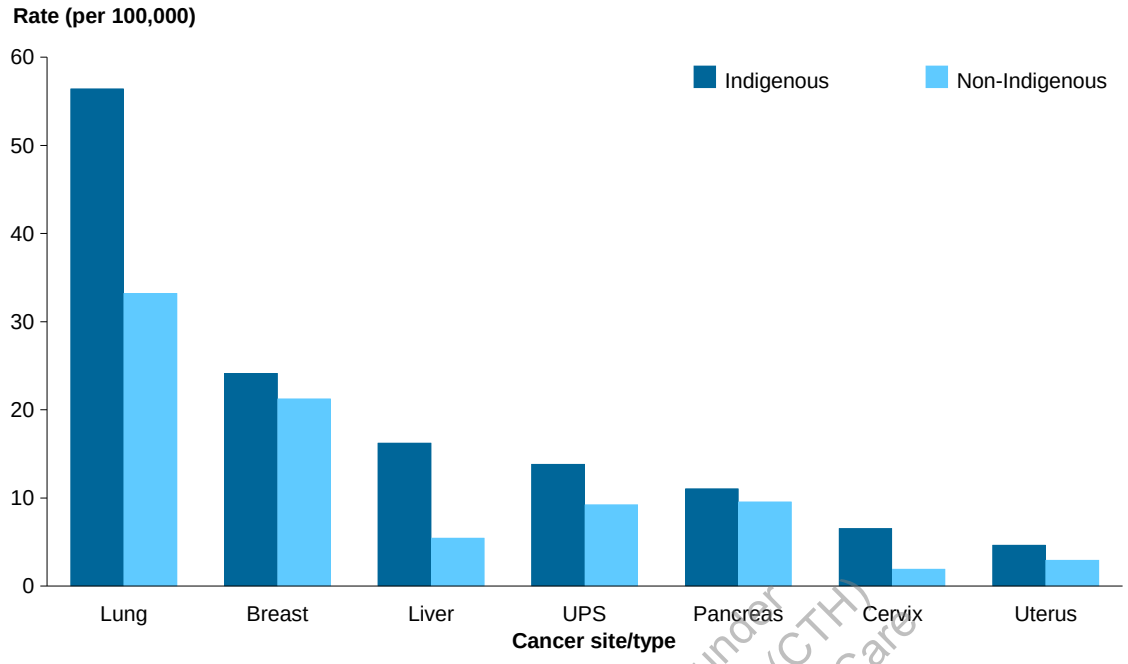
Between 2008 and 2012, lung cancer accounted for the highest average number of cancer-related deaths for Indigenous Australians, totalling 115 deaths per year (25% of all Indigenous deaths from cancer), followed by liver cancer with 34 deaths (7%), breast cancer in females with 30 deaths (6%) and cancer of unknown primary site with 27 deaths (6%).

The age-standardised mortality rate was significantly higher for Indigenous than for non-Indigenous Australians for:

- cervical cancer (3.4 times as high)
- liver cancer (3.0)
- lung cancer (1.7)
- cancer of unknown primary site (1.5).

Mortality rates for uterine cancer, pancreatic cancer and breast cancer in females were also higher for Indigenous Australians than for non-Indigenous Australians (1.6, 1.2 and 1.1 times as high, respectively), but the differences were not statistically significant (Figure 8.2).

Conversely, mortality rates were lower for Indigenous Australians than non-Indigenous Australians for non-Hodgkin lymphoma (rate ratio of 0.9), colorectal cancer (0.8) and prostate cancer (0.8), but the differences were not statistically significant.



Notes

1. The rates were age-standardised to the Australian population as at 30 June 2001 and based on the total number of deaths over the 5-year period from 2008 to 2012.
2. Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. These data have not been adjusted for the additional deaths arising from outstanding registrations of deaths in Queensland in 2010. For more detail, refer to Technical note 3 in *Causes of death, Australia, 2010* (ABS cat. no. 3303.0).
3. Data for this figure are in online tables D8.3, D8.4, D8.7, D8.8, D8.11, D8.13 and D8.14.
4. Breast cancer is for females only. UPS stands for cancer of unknown primary site.

Source: AIHW NMD.

Figure 8.2: Mortality from lung cancer, breast cancer in females, liver cancer, cancer of unknown primary site, pancreatic cancer, cervical cancer and uterine cancer, by Indigenous status, New South Wales, Queensland, Western Australia, South Australia and the Northern Territory, 2008–2012

State and territory

Incidence by state and territory

Between 2005 and 2009, the annual average number of cancer cases diagnosed ranged from 594 cases in the Northern Territory to 36,492 cases in New South Wales.

When the size and age structure of the population in each state and territory is taken into account, the highest incidence rates of all cancers combined were in Tasmania (530 per 100,000 persons) and Queensland (528 per 100,000). In contrast, the incidence rates were lowest in the Australian Capital Territory (458 per 100,000) and the Northern Territory (456 per 100,000) (Table 8.1).

Table 8.1: Incidence of all cancers combined[a] by state and territory, Australia, 2005–2009

State or territory	Average annual number of cases[b]	Total number of cases	Age-standardised rate[c]
New South Wales	36,492	182,462	490.6
Victoria	26,992	134,962	486.4
Queensland	22,077	110,383	528.2
Western Australia	10,182	50,912	483.6
South Australia	8,964	44,820	482.9
Tasmania	3,069	15,344	530.3
Australian Capital Territory	1,405	7,025	457.6
Northern Territory	594	2,969	456.0
Total	**109,775**	**548,877**	**495.7**

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.

(b) Numbers may not sum to the total due to rounding.

(c) The rates were age-standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population. The rates were based on the total number of cases over the 5 years from 2005 to 2009.

Source: AIHW ACD 2011.

Between 2005 and 2009, the highest age-standardised incidence rates for selected cancers were in:

- South Australia for non-Hodgkin lymphoma (21 per 100,000)
- Queensland for melanoma of the skin (67 per 100,000)
- Tasmania for prostate cancer (212 per 100,000), colorectal cancer (75 per 100,000), bladder cancer (17 per 100,000) and kidney cancer (14 per 100,000)
- Northern Territory for lung cancer (65 per 100,000), cancer of unknown primary site (20 per 100,000) and cervical cancer (14 per 100,000)
- the Australian Capital Territory for breast cancer in females (127 per 100,000).

New South Wales, Victoria and Western Australia all accounted for the highest age-standardised incidence rate for pancreatic cancer (11 per 100,000).

Mortality by state and territory

Between 2008 and 2012, the average annual number of deaths from cancer ranged from 253 in the Northern Territory to 14,196 in New South Wales.

After taking the size and age structure of the population in each state and territory into account, the mortality rate for all cancers combined was highest in the Northern Territory (217 per 100,000) followed by Tasmania (192 per 100,000) (Table 8.2).

In contrast, the mortality rates of all cancers combined were lowest in the Australian Capital Territory (152 per 100,000), Western Australia (170 per 100,000) and Victoria (172 per 100,000) (Table 8.2).

Note that mortality data by state and territory presented in this section are not directly comparable with those data published by individual state and territory cancer registries (see Box 8.1).

Table 8.2: Mortality from all cancers combined[a] by state and territory, Australia, 2008–2012[b]

State or territory[c]	Average annual number of deaths[d]	Total number of deaths	Age-standardised rate[e]
New South Wales	14,196	70,981	172.4
Victoria	10,591	52,953	172.0
Queensland	8,163	40,816	179.8
Western Australia	3,871	19,354	169.6
South Australia	3,605	18,025	173.5
Tasmania	1,218	6,091	191.8
Australian Capital Territory	481	2,405	151.7
Northern Territory	253	1,265	217.1
Total	**42,379**	**211,896**	**173.9**

(a) Cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.

(b) Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. These data have not been adjusted for the additional deaths arising from outstanding registrations of deaths in Queensland in 2010. For more detail, refer to Technical note 3 in *Causes of death, Australia, 2010* (ABS cat. no. 3303.0).

(c) Mortality data may not be comparable with mortality data published in state and territory cancer reports since the data shown in this report relate to the place of residence at the time of *death*, not the place of residence at the time of *diagnosis*, as shown in some state and territory reports. Further, the state and territory cancer registries may use a different methodology from that used by the AIHW to determine the cause of death (see Box 8.1).

(d) Numbers may not sum to the total due to rounding.

(e) The rates were age-standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population. The rates were based on the total number of deaths over the 5 years from 2008 to 2012.

Source: AIHW NMD.

Between 2008 and 2012, the highest age-standardised mortality rates for selected cancers were in:

- Northern Territory for lung cancer (51 per 100,000), cancer of unknown primary site (15 per 100,000), bladder cancer (5 per 100,000) and cervical cancer (4 per 100,000)
- Tasmania for breast cancer in females (23 per 100,000), colorectal cancer (20 per 100,000), pancreatic cancer (10 per 100,000) and kidney cancer (4 per 100,000, equal with South Australia)
- Queensland for prostate cancer (34 per 100,000) and melanoma of the skin (8 per 100,000)
- South Australia for non-Hodgkin lymphoma (6 per 100,000).

Remoteness area

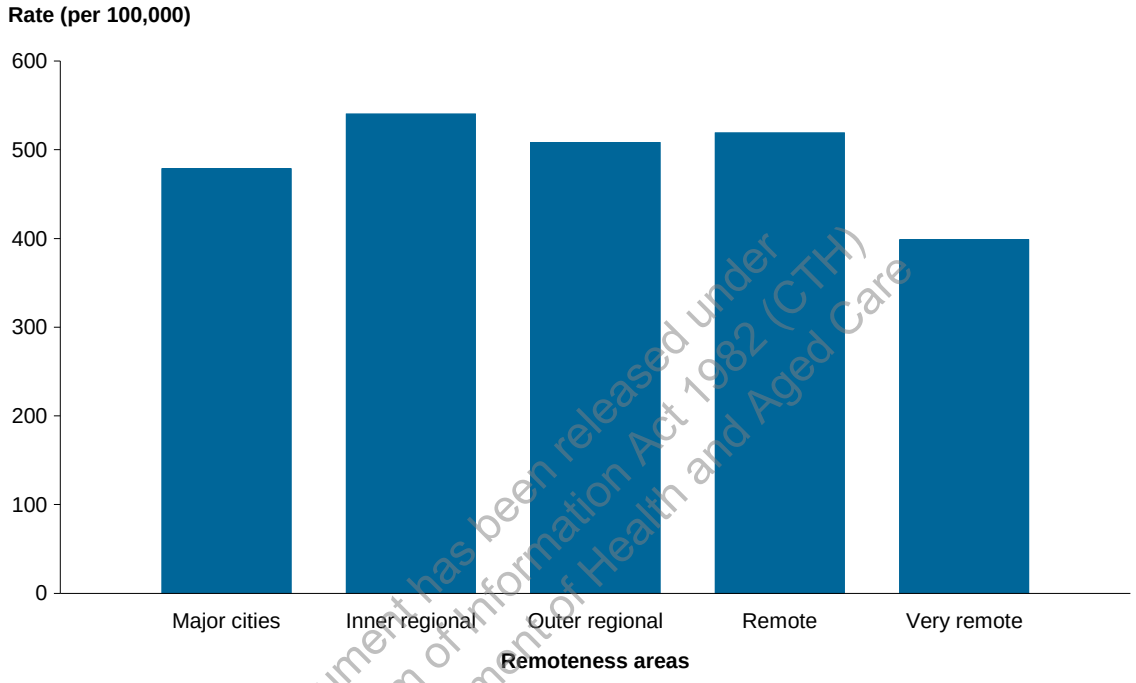
People living in remote areas of Australia are often disadvantaged in relation to access to primary health-care services, educational and employment opportunities, and income. Further, they are more likely to have higher rates of risky health behaviours, such as smoking, heavy alcohol use and poor nutrition (AIHW 2014a).

Incidence and mortality rates were calculated according to the level of remoteness area of residence at diagnosis or death. The Remoteness Areas (RAs) divide Australia into broad geographic regions that share common characteristics of remoteness for statistical purposes. The Remoteness Structure divides each state and territory into several regions on the basis of

their relative access to services. More information about the RAs classification is at Appendix E. Incidence and mortality rates are presented by five categories: *Major cities*, *Inner regional*, *Outer regional*, *Remote* and *Very remote.*

Incidence by remoteness area

Between 2005 and 2009, the age-standardised incidence rate of all cancers combined was highest in *Inner regional* areas (540 per 100,000) and lowest in *Very remote* areas (398 per 100,000) (Figure 8.3).



Notes

1. Remoteness was classified according to the Australian Standard Geographical Classification (ASGC) Remoteness Areas (see Appendix E).
2. The rates were age-standardised to the Australian population as at 30 June 2001 and based on the total number of cases over the 5 years from 2005 to 2009.
3. Data for this figure are in online Table D8.1.

Source: AIHW ACD 2011.

Figure 8.3: Incidence of all cancers combined by remoteness area, Australia, 2005–2009

Between 2005 and 2009, *Inner regional* areas of Australia had the highest observed age-standardised incidence rate for:

- prostate cancer (206 per 100,000)
- breast cancer in females (120 per 100,000)
- colorectal cancer (70 per 100,000)
- melanoma of the skin (62 per 100,000)
- non-Hodgkin lymphoma (19 per 100,000)
- kidney cancer (13 per 100,000).

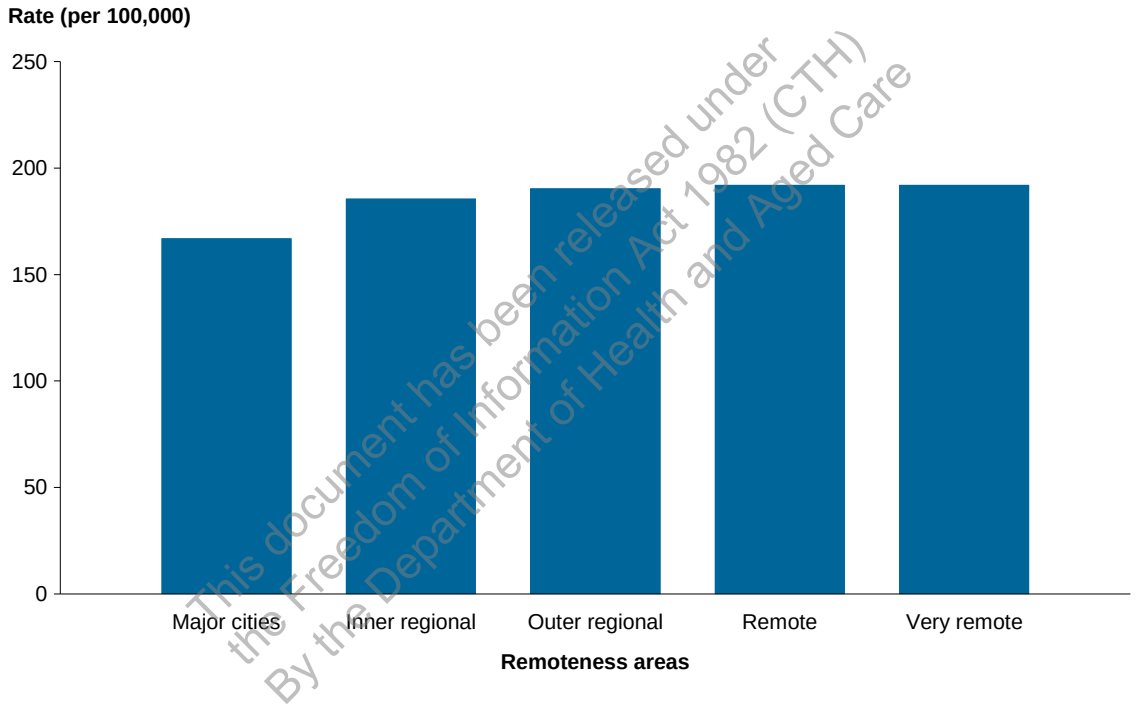
Remote areas of Australia had the highest observed age-standardised incidence rate for:

- cancer of unknown primary site (16 per 100,000)
- bladder cancer (13 per 100,000)
- pancreatic cancer (12 per 100,000)
- cervical cancer (10 per 100,000).

Very remote areas accounted for the highest age-standardised incidence rate for lung cancer (57 per 100,000).

Mortality by remoteness area

Between 2008 and 2012, the age-standardised mortality rates of all cancers combined were higher in *Very remote* and *Remote* areas (both 192 per 100,000) and lower in *Major cities* (167 per 100,000) (Figure 8.4).



Notes

1. Remoteness was classified according to the Australian Statistical Geography Standard (ASGS) Remoteness Areas (see Appendix E).
2. Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS.
3. The rates were age-standardised to the Australian population as at 30 June 2001 and based on the total number of deaths over the 5 years from 2008 to 2012.
4. The data for this figure are in online Table D8.1.

Source: AIHW NMD.

Figure 8.4: Mortality from all cancers combined by remoteness area, Australia, 2008–2012

Between 2008 and 2012, *Very remote* and *Inner regional* areas had the highest age-standardised mortality rate for:

Very remote

- lung cancer (43 per 100,000 persons)
- prostate cancer (35 per 100,000, equal with *Outer regional* areas)
- cancer of unknown primary site (14 per 100,000)
- bladder cancer (5 per 100,000)
- cervical cancer (5 per 100,000).

Inner regional

- colorectal cancer (17 per 100,000)
- breast cancer in females (23 per 100,000)
- melanoma of the skin (7 per 100,000)
- non-Hodgkin lymphoma (6 per 100,000).

Remote areas of Australia had the highest age-standardised mortality rate for kidney cancer (5 per 100,000), and *Major cities* and *Outer regional* areas of Australia had the highest mortality rates for pancreatic cancer (both 10 per 100,000).

Socioeconomic disadvantage

The Index of Relative Socio-economic Disadvantage (IRSD) is used to indicate socioeconomic disadvantage. The IRSD scores each area by summarising attributes of the population, such as low income, low educational attainment, high unemployment and jobs in relatively unskilled occupations.

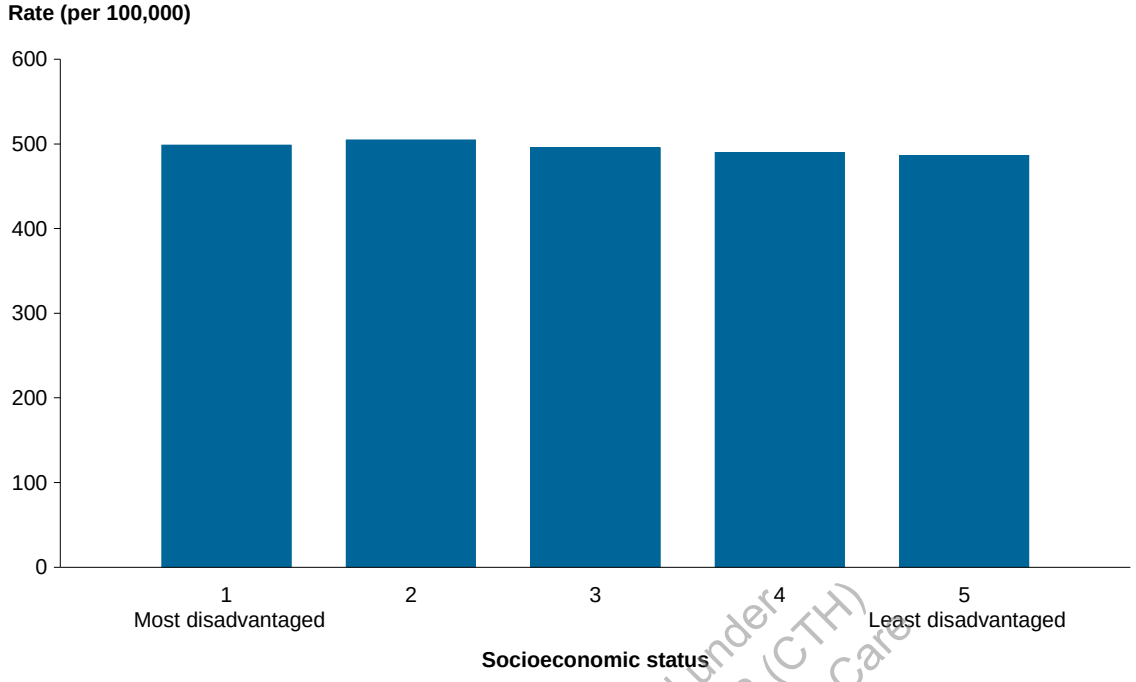
The distribution of cancer incidence (between 2006 and 2009) and mortality (between 2009 and 2012) by quintile of relative socioeconomic disadvantage reflects the population distribution, with approximately 20% of records in each quintile.

Note that the IRSD is an area-based measure of socioeconomic status rather than a person-based measure. It is used as a proxy for the socioeconomic status of people living in those areas and would not be correct for each person living in that area.

Incidence by socioeconomic disadvantage

In this report, the first socioeconomic status group (quintile 1) corresponds to geographical areas containing the 20% of the population living in the area with the most disadvantaged socioeconomic status according to the IRSD, and the fifth group (quintile 5) to the 20% of the population living in areas with the least disadvantaged socioeconomic status. More information is at Appendix E: Index of Relative Socio-economic Disadvantage.

Between 2006 and 2009, the age-standardised incidence rate for all cancers combined was slightly higher for those living in the three most disadvantaged (quintile 1, 2 and 3) areas and slightly lower for those living in the least disadvantaged (quintile 4 and 5) areas (Figure 8.5).



Notes

1. Socioeconomic status was classified using the ABS IRSD (see Appendix E).
2. The rates were age-standardised to the Australian population as at 30 June 2001 and based on the total number of cases over the 4-year period from 2006 to 2009.
3. Data for this figure are in online Table D8.1.

Source: AIHW ACD 2011.

Figure 8.5: Incidence of all cancers combined by quintile of relative socioeconomic disadvantage, Australia, 2006–2009

Of the selected cancers, those living in the most disadvantaged (quintile 1) areas accounted for the highest age-standardised incidence rate for:

- colorectal cancer (66 per 100,000 persons)
- lung cancer (52 per 100,000)
- cancer of unknown primary site (14 per 100,000)
- bladder cancer (11 per 100,000)
- pancreatic cancer (11 per 100,000, equal with quintile 2)
- cervical cancer (8 per 100,000).

Those living in the second most disadvantaged (quintile 2) areas accounted for the highest incidence rate for:

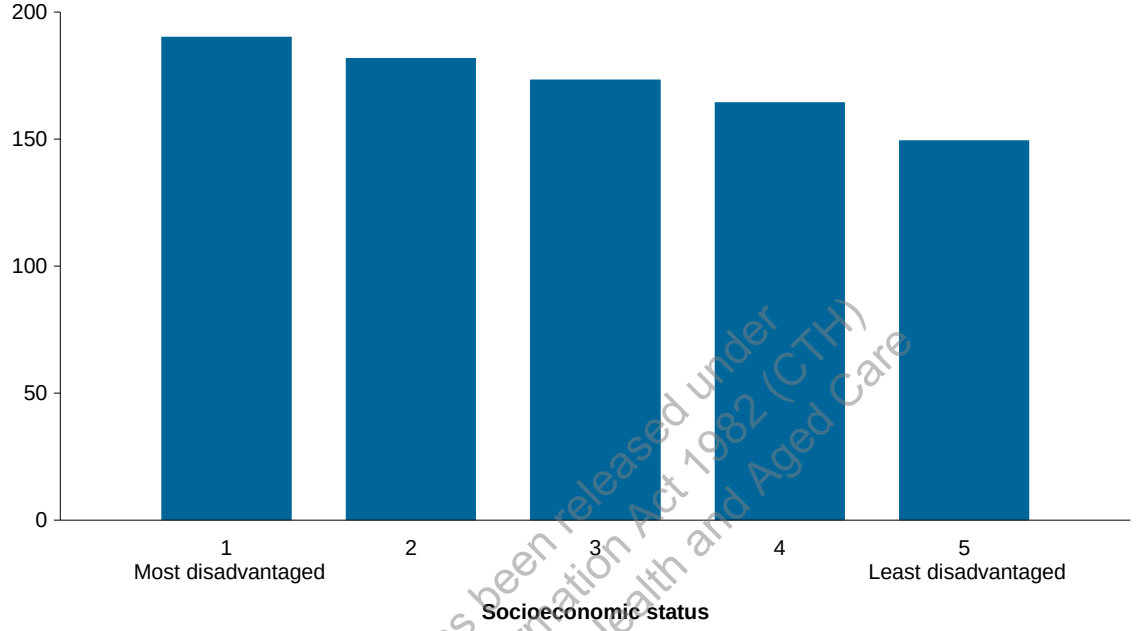
- melanoma of the skin (52 per 100,000, equal with quintile 5)
- kidney cancer (13 per 100,000)
- pancreatic cancer (11 per 100,000, equal with quintile 1).

Those living in the least disadvantaged (quintile 5) areas accounted for the highest incidence rate for:

- prostate cancer (205 per 100,000)
- breast cancer in females (124 per 100,000)
- melanoma of the skin (52 per 100,000, equal with quintile 2)
- non-Hodgkin lymphoma (20 per 100,000).

Mortality by socioeconomic disadvantage

Between 2009 and 2012, the age-standardised mortality rate for all cancers combined was highest among those living in the most disadvantaged (quintile 1) areas (190 per 100,000 persons) and lowest among those living in the least disadvantaged (quintile 5) areas (149 per 100,000) (Figure 8.6).



Notes

1. Socioeconomic status was classified using the ABS IRSD (see Appendix E).
2. Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS.
3. The rates were age-standardised to the Australian population as at 30 June 2001 and based on the total number of deaths over the 5 years from 2009 to 2012.
4. Data for this figure are in online Table D8.1.

Source: AIHW NMD.

Figure 8.6: Mortality from all cancers combined, by quintile of relative socioeconomic disadvantage, Australia, 2009–2012

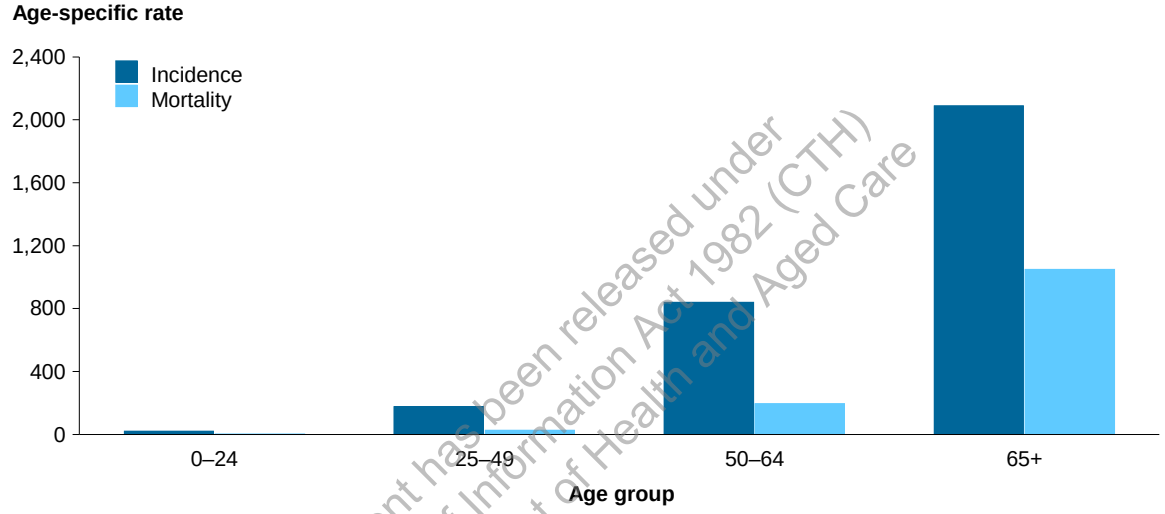
Those living in the most disadvantaged (quintile 1) areas had the highest age-standardised mortality rate for:

- lung cancer (40 per 100,000 persons)
- breast cancer in females (22 per 100,000)
- colorectal cancer (17 per 100,000)
- pancreatic cancer (11 per 100,000)
- cancer of unknown primary site (11 per 100,000)
- non-Hodgkin lymphoma (6 per 100,000, equal with quintiles 2 and 3)
- bladder cancer (5 per 100,000)
- kidney cancer (4 per 100,000, equal with quintile 2)
- cervical cancer (3 per 100,000).

Those living in the second most disadvantaged (quintile 2) areas had the highest age-standardised mortality rate for prostate cancer (32 per 100,000) and for melanoma of the skin (6 per 100,000, equal with quintile 3).

Life stages

This section focuses on the differences in cancer diagnoses and mortality according to the following four broad age groups (which are used to represent different life stages): 0–24 years, 25–49 years, 50–64 years and 65 years and over. The incidence of cancer and deaths from cancer increases with age (Figure 8.7). While cancer cases and deaths are rare among younger people, the types of cancer and treatment options differ depending on age at diagnosis.



Notes

1. The 2014 incidence estimates are based on 2002–2011 incidence data (see Appendix G). The 2014 mortality estimates are based on 2002–2012 mortality data (see Appendix G). The mortality estimates for males and females may not add to the estimates for persons due to rounding.
2. Incidence data pertain to cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3, except those C44 codes that indicate a basal or squamous cell carcinoma of the skin.
3. Mortality data pertain to cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3.
4. Data for this figure are in online Table D8.15.

Source: AIHW ACD 2011.

Figure 8.7: Estimated incidence rates of all cancers combined by age at diagnosis and estimated mortality from all cancers combined by age at death, Australia, 2014

Incidence by life stage (broad age groups)

This section focuses on estimated cancer incidence for 2014. Estimates are based on 2002–2011 incidence data (see Appendix G). The estimated numbers of cancer cases diagnosed are rounded to the nearest 10 and the estimates for males and females may not add up to the estimates for persons due to rounding.

Aged 0–24

For people aged 0–24, it is estimated that 1,540 new cases of cancer will be diagnosed in 2014. People aged 0–24 tend to be diagnosed with different cancer types than older people. For this age group, leukaemia is estimated to be the most commonly diagnosed cancer, with 315 new

cases (21% of all cancers diagnosed in this age group). This is followed by lymphoma, with 255 cases (17%) and brain cancer with 135 cases (9%).

Males

For males, it is estimated that 840 new cases of cancer will be diagnosed in 2014 (55% of all cancers diagnosed in this age group). Leukaemia is estimated to be the most commonly diagnosed cancer, with 180 new cases (22% of all cancers diagnosed for males in this age group). This is followed by lymphoma, with 150 cases (18%), and testicular cancer, with 120 cases (14%).

Females

For females, it is estimated that 695 new cases of cancer will be diagnosed in 2014 (45% of all cancers diagnosed in this age group). Leukaemia is estimated to be the most commonly diagnosed cancer, with 135 new cases (19% of all cancers diagnosed for females in this age group). This is followed by lymphoma, with 106 cases (15%), and melanoma of the skin, with 70 cases (10%).

Aged 25–49

For people aged 25–49, it is estimated that 14,590 new cases of cancer will be diagnosed in 2014. Breast cancer is estimated to be the most commonly diagnosed cancer, with 3,300 new cases (23% of all cancers diagnosed in this age group). This is followed by melanoma of the skin, with 2,560 cases (18%), and colorectal cancer, with 1,100 cases (8%).

Males

For males, it is estimated that 5,810 new cases of cancer will be diagnosed in 2014 (40% of all cancers diagnosed in this age group). Melanoma of the skin is estimated to be the most commonly diagnosed cancer, with 1,170 new cases (20% of all cancers diagnosed for males in this age group). This is followed by colorectal cancer, with 590 cases (10%), and testicular cancer with 560 cases (10%).

Females

For females, it is estimated that 8,790 new cases of cancer will be diagnosed in 2014 (60% of all cancers diagnosed in this age group). For this age group, females represent a greater proportion of cancer diagnosis than males. This may be due to the high proportion of breast cancer diagnosis. Breast cancer is estimated to be the most commonly diagnosed cancer, with 3,300 new cases (38% of all cancers diagnosed for females in this age group). This is followed by melanoma of the skin, with 1,380 cases (16%), and thyroid cancer, with 810 cases (9%).

Aged 50–64

For people aged 50–64, it is estimated that 35,720 new cases of cancer will be diagnosed in 2014. Prostate cancer is the most commonly diagnosed cancer, with 6,090 new cases (17% of all cancers diagnosed in this age group). This is followed by breast cancer, with 5,880 cases (16%) and colorectal cancer with 4,020 cases (11%). National breast and bowel screening programs are targeted at people aged 50 and over, which could impact on the number of cancers diagnosed in this age group.

Males

For males, it is estimated that 19,480 new cases of cancer will be diagnosed in 2014 (55% of all cancers diagnosed in this age group). Prostate cancer is estimated to be the most commonly

diagnosed cancer, with 6,090 new cases (31% of all cancers diagnosed for males in this age group). This is followed by colorectal cancer, with 2,380 cases (12%), and melanoma of the skin, with 2,240 cases (11%).

Females

For females, it is estimated that 16,240 new cases of cancer will be diagnosed in 2014 (45% of all cancers diagnosed in this age group). Breast cancer is estimated to be the most commonly diagnosed cancer, with 5,840 new cases (36% of all cancers diagnosed for females in this age group). This is followed by colorectal cancer, with 1,640 cases (10%), and melanoma of the skin, with 1,570 cases (10%).

Aged 65 and over

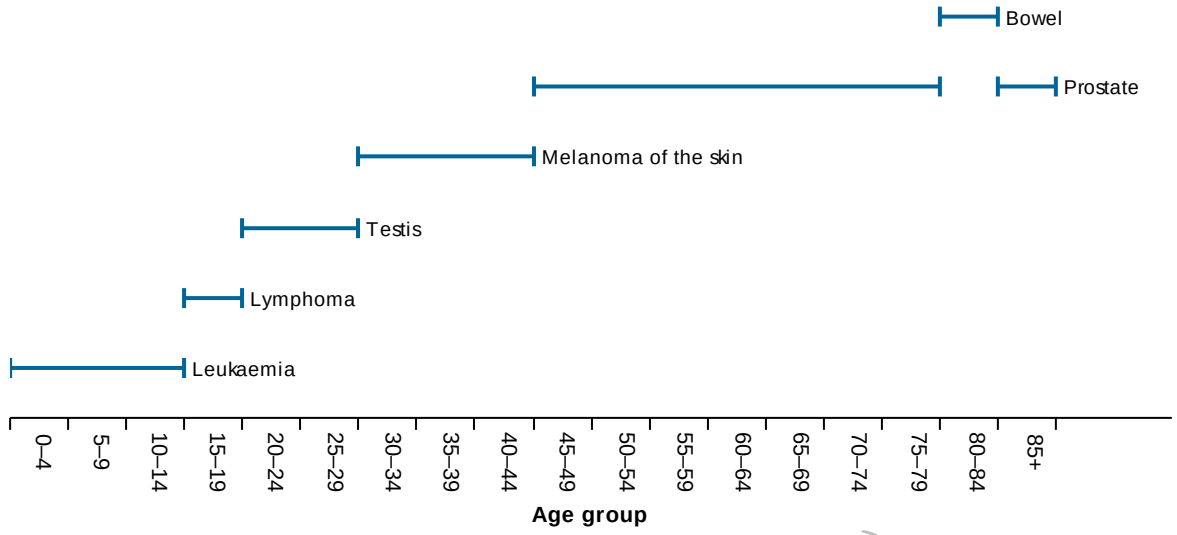
For people aged 65 years and older, it is estimated that 72,070 new cases of cancer will be diagnosed in 2014. Colorectal cancer is estimated to be the most commonly diagnosed cancer, with 11,490 new cases (16% of all cancers diagnosed in this age group). This is followed by prostate cancer, with 10,520 cases (15%), and lung cancer, with 8,440 cases (12%). Population-based screening programs are targeted at people in this age group, which could have an impact on the number of cancers diagnosed.

Males

For males, it is estimated that 42,130 new cases of cancer will be diagnosed in 2014 (58% of all cancers diagnosed in this age group). Prostate cancer is estimated to be the most commonly diagnosed cancer, with 10,520 new cases (25% of all cancers diagnosed for males in this age group). This is followed by colorectal cancer, with 6,310 cases (15%), and melanoma of the skin, with 5,120 cases (12%).

Females

For females, it is estimated that 29,940 new cases of cancer will be diagnosed in 2014 (42% of all cancers diagnosed in this age group). Breast cancer is estimated to be the most commonly diagnosed cancer, with 6,120 new cases (20% of all cancers diagnosed for females in this age group). This is followed by colorectal cancer, with 5,180 cases (17%), and lung cancer, with 3,320 cases (11%).

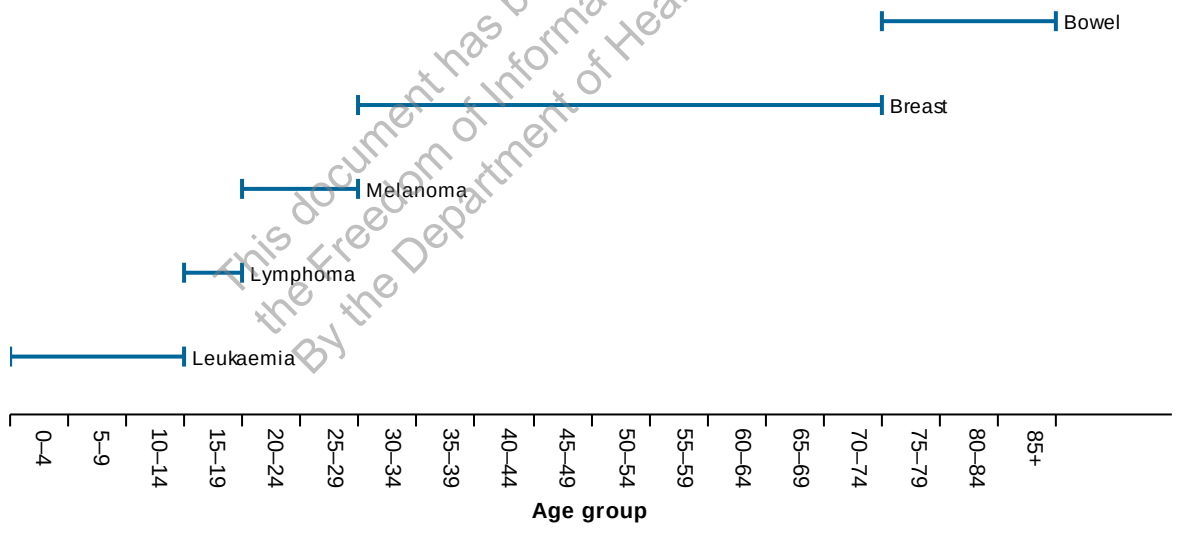


Notes

1. The 2014 incidence estimates are based on 2002–2011 incidence data (see Appendix G).
2. Data for this figure are in online Table D8.16.

Source: AIHW ACD 2011.

Figure 8.8: Estimated most commonly diagnosed cancer at each age group, male, 2014



Notes

1. The 2014 incidence estimates are based on 2002–2011 incidence data (see Appendix G).
2. Data for this figure are in online Table D8.16.

Source: AIHW ACD 2011.

Figure 8.9: The estimated most commonly diagnosed cancer at each age group, female, 2014

Mortality by life stage (broad age groups)

This section focuses on the estimated deaths from cancer for 2014. Estimates are based on 2002–2012 mortality data (see Appendix G). Estimates are rounded to the nearest 10 and the estimates for males and females may not add to the estimates for persons due to rounding.

Aged 0–24

For people aged 0–24, it is estimated that there will be 180 cancer-related deaths in 2014. While the number of cancer-related deaths is low compared with that for other age groups, cancer is the leading cause of death for people in this age group according to the most recent actual data (2012) (AIHW 2014). People aged 0–24 tend to die from different cancers types than those for older people. For this age group, brain cancer and leukaemia are estimated to be leading cause of death from cancer in 2014, both with 40 deaths (22% of all cancer deaths in this age group). This is followed by bone cancer, with 25 deaths (14%).

Males

For males, it is estimated that, in 2014, there will be 100 cancer-related deaths (56% of all cancers diagnosed in this age group) in 2014. Brain cancer and leukaemia are estimated to be the leading causes of death from cancer in 2014, both with 25 deaths (25% of all cancer deaths for males in this age group). This is followed by bone cancer, with 10 deaths (10%).

Females

For females, it is estimated that, in 2014, there will be 85 cancer-related deaths (47% of all cancers diagnosed in this age group). Brain cancer is estimated to be the leading cause of death from cancer in 2014, with 20 deaths (24% of all cancer deaths for females in this age group). This is followed by leukaemia, with 15 deaths (18%).

Aged 25–49

For people aged 25–49, it is estimated that there will be 2,140 cancer-related deaths in 2014. Breast cancer is estimated to be the leading cause of death from cancer in 2014, with 405 deaths (19% of all cancer deaths in this age group). This is followed by lung cancer, with 255 deaths (12%), and colorectal cancer, with 210 deaths (10%).

Males

For males, it is estimated that, in 2014, there will be 1,000 cancer-related deaths (47% of all cancers diagnosed in this age group). Lung cancer is estimated to be the leading cause of death from cancer in 2014, with 140 deaths (14% of all cancer deaths for males in this age group). This is followed by brain cancer, with 115 deaths (12%), and colorectal cancer, with 100 deaths (10%).

Females

For females, it is estimated that, in 2014, there will be 1,130 cancer-related deaths (53% of all cancers diagnosed in this age group). For this age group, females represent a greater proportion of cancer-related deaths than males. This may be due to the high proportion of deaths related to breast cancer. Breast cancer is estimated to be the leading cause of death from cancer in 2014, with 325 deaths (29% of all cancer deaths for females in this age group). This is followed by lung cancer, with 130 deaths (12%), and colorectal cancer, with 100 deaths (9%).

Aged 50–64

For people aged 50–64 years, it is estimated that there will be 8,290 cancer-related deaths in 2014. Lung cancer is estimated to be the leading cause of death from cancer in 2014, with 1,660 deaths (20%). This is followed by breast cancer, with 975 deaths (12%), and colorectal cancer, with 935 deaths (9%).

Males

For males, it is estimated that, in 2014, there will be 4,570 cancer-related deaths (55% of all cancers diagnosed in this age group). Lung cancer is estimated to be the leading cause of death from cancer in 2014, with 970 deaths (21%). This is followed by colorectal cancer, with 420 deaths (9%), and liver cancer, with 345 deaths (8%).

Females

For females, it is estimated that, in 2014, there will be 3,730 cancer-related deaths (45% of all cancers diagnosed in this age group). Breast cancer is estimated to be the leading cause of death from cancer in 2014, with 825 deaths (22% of all cancer deaths for females in this age group). This is followed by lung cancer, with 770 deaths (21%), and colorectal cancer, with 340 deaths (9%).

Aged 65 and over

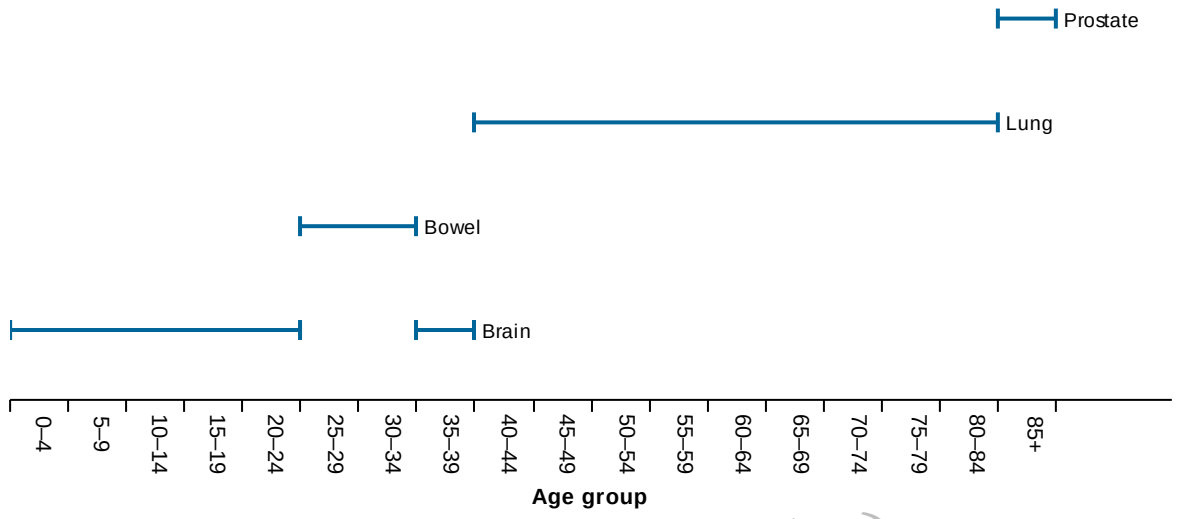
For people aged 65 and older, it is estimated that there will be 36,220 cancer-related deaths in 2014. Lung cancer is estimated to be the leading cause of death from cancer in 2014, with 6,860 deaths (19%). This is followed by prostate cancer, with 3,310 deaths (9%), and colorectal cancer, with 3,220 deaths (9%).

Males

For males, it is estimated that, in 2014, there will be 20,890 cancer-related deaths (58% of all cancers diagnosed in this age group). Lung cancer is estimated to be the leading cause of death from cancer in 2014, with 4,080 deaths (20%). This is followed by prostate cancer, with 3,310 deaths (16%), and colorectal cancer, with 1,720 deaths (8%).

Females

For females, it is estimated that, in 2014, there will be 15,310 cancer-related deaths (42% of all cancers diagnosed in this age group). Lung cancer is estimated to be the leading cause of death from cancer in 2014, with 2,680 deaths (18% of all cancer deaths for females in this age group), followed by breast cancer with 1,900 deaths (12%) and colorectal cancer with 1,430 deaths (9%).

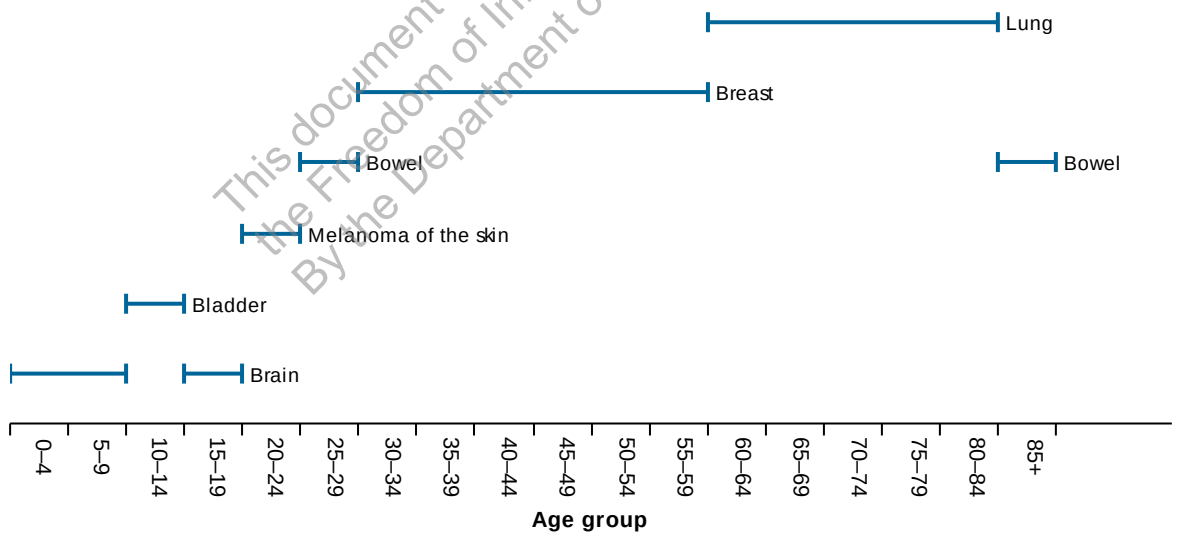


Notes

1. The 2014 mortality estimates are based on 2002–2012 mortality data (see Appendix G). The mortality estimates for males and females may not add to the estimates for persons due to rounding.
2. Data for this figure are in online Table D8.17.

Source: AIHW NMD.

Figure 8.10: Estimated leading cause of death from cancer at each age group, male, 2014



Notes

1. The 2014 mortality estimates are based on 2002–2012 mortality data (see Appendix G). The mortality estimates for males and females may not add to the estimates for persons due to rounding.
2. Data for this figure are in online Table D8.17.

Source: AIHW NMD.

Figure 8.11: Estimated leading cause of death from cancer at each age group, female, 2014

9 International comparisons

Key findings

In 2012, based on ASRs:

- the incidence rate for all cancer combined in Australia (323 per 100,000) was higher than that for all other country groups (regions)
- Australia had the world's second highest incidence rate for melanoma of the skin (35 per 100,000), which was more than 11 times the average world rate (3.0 per 100,000). New Zealand had a slightly higher incidence rate for melanoma of the skin, at 36 per 100,000
- the incidence rate of prostate cancer in Australia (115 per 100,000) was higher than that for all other regions
- Australia had a slightly lower cancer mortality rate (96 per 100,000) than the average world rate (102 per 100,000)
- cancer survival (as shown by the MIR) was higher in Australia than in all other regions.

About international comparisons

Comparing international cancer data—including for incidence, mortality and survival—is a valuable way to compare the Australian experience of cancer with that in other countries and regions.

International cancer data are available from the GLOBOCAN database, which is prepared by the International Agency for Research on Cancer (IARC) (Ferlay et al. 2013). The most recent GLOBOCAN estimates are for 2012, and are based on cancer incidence and mortality rates from about 3 to 5 years earlier. The GLOBOCAN data for all cancers combined pertain to cancers coded in the ICD-10 as C00–C97, excluding those for C44 (that is, non-melanoma skin cancer). They thus encompass a narrower range of cancers than is generally considered in this report (see Appendix I). Australian estimates used in the international context are age-standardised to the World Standard Population and are therefore not comparable with national data presented elsewhere.

For more information on international data and interpreting differences by countries and regions, see Box 9.1 and *A working guide to international comparisons of health* (AIHW 2012b).

Box 9.1: Interpreting international comparisons

Incidence and mortality

Incidence and mortality estimates for international comparisons are derived from national data and standardised to the World Standard Population. Take care when comparing cancer data from different countries as observed differences may be influenced not only by the underlying number of cancer cases (or number of cancer deaths when considering mortality data), but also by differences in:

- age distribution and composition of the populations
- underlying differences in cancer risk and population exposure to modifiable risk factors
- cancer detection and screening
- cancer coding and registration practices (Ferlay et al. 2013)
- features at diagnosis (for example, stage at diagnosis and cancer histology type)
- availability and quality of treatment (CCS & NCIC 2007)
- individual's level of co-morbidity.

In Australia, cancer is a notifiable disease and the completeness of cancer data is relatively high compared with that in a number of countries or regions (Curado et al. 2007).

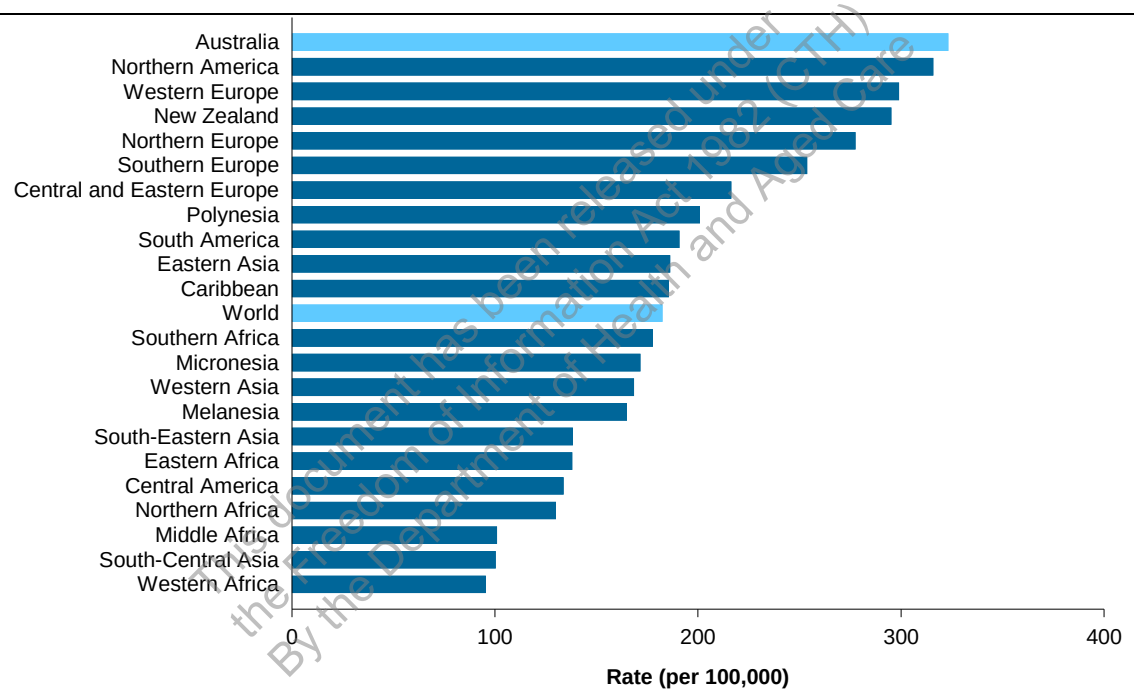
Mortality-to-incidence ratio

The mortality-to-incidence ratio (MIR) is used as a proxy measure of survival in the international context. This ratio describes the number of cancer deaths in a given year, relative to the number of new cases of cancer diagnosed in the same year, using age-standardised data. It is a number between 0 and 1, although it can exceed 1 in certain circumstances. The MIR is a measure of the fatality of the cancer in question: if no-one ever died of the cancer, the MIR would be 0; if everyone died of the cancer on the same day they were diagnosed, the MIR would be 1. Therefore, low values of the MIR indicate longer survival while high ones indicate shorter survival. Appendix H provides further information about interpreting MIRs.

Incidence

In 2012, the estimated number of new cases of cancer diagnosed around the world was 14.1 million. In the same year, it is estimated that 122,031 new cases of cancer were diagnosed in Australia, accounting for 0.9% of all cancers diagnosed worldwide.

The incidence rate for all cancers combined in Australia (323 per 100,000) was higher than that for other country groups (regions) (Figure 9.1). This could be at least partly attributable to the introduction of national population screening programs in Australia (BreastScreen Australia, the National Bowel Cancer Screening Program and the National Cervical Screening Program) and increased PSA testing, contributing to increased diagnosis of these cancers. In Australia, cancer is a notifiable disease and the completeness of cancer data is relatively high compared with that of a number of countries or regions (Curado et al. 2007). Australia also has the world's second highest rate of melanoma of the skin at 35 per 100,000, (slightly behind New Zealand at 36 per 100,000). Australia's rate of melanoma of the skin was more than 11 times the average world rate (3.0 per 100,000).



Notes

1. Cancer coded in the ICD-10 as C00–C97, excluding C44 non-melanoma skin cancer.
2. Data were estimated for 2012 by the IARC and are based on data from about 3 to 5 years earlier.
3. The ASRs were standardised by the IARC using Doll et al. 1966 World Standard Population and are expressed per 100,000 persons. Countries or regions are ordered in descending order according to the ASRs.
4. Data for this figure are in online Table D9.1.

Source: Ferlay et al. 2013.

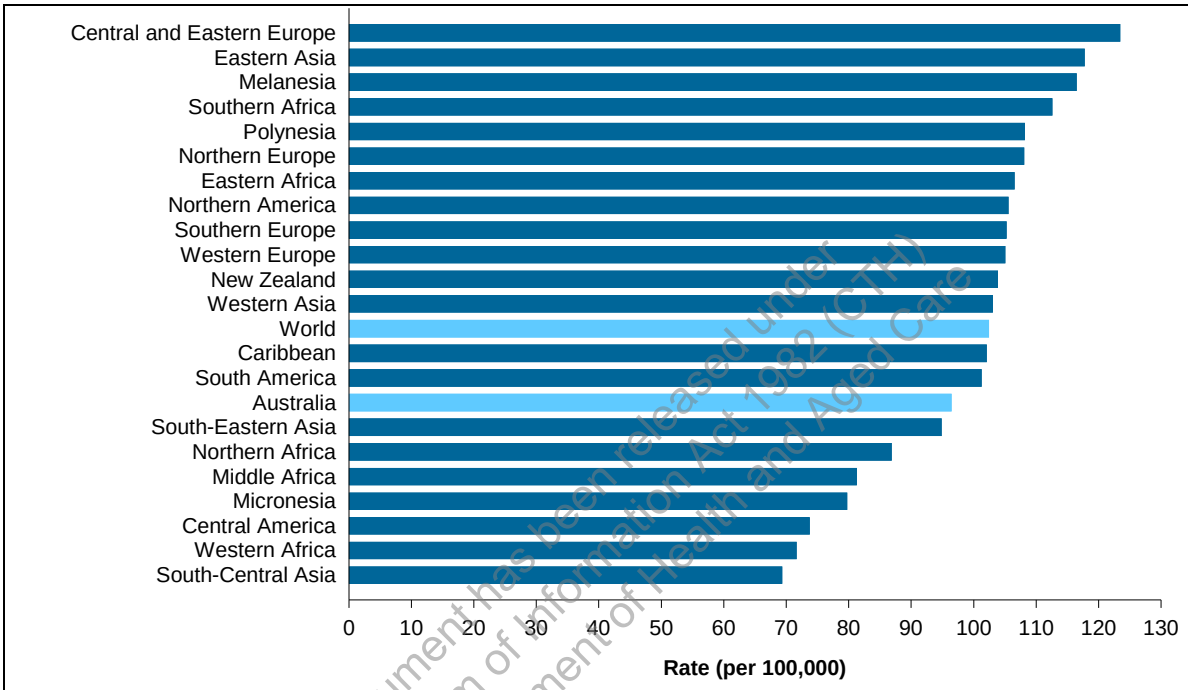
Figure 9.1: International comparison of estimated incidence for all cancers combined, persons, 2012

Mortality

In 2012, the estimated number of deaths from cancer around the world was 8.2 million.

The age-standardised mortality rate for Australia was 96 per 100,000, which was slightly lower than the average world rate (102 per 100,000) (Figure 9.2).

The age-standardised mortality rate for cancer varied considerably between countries and regions. Compared with all other regions, the rate was highest in Central and Eastern Europe (123 per 100,000), and lowest in South-Central Asia (69 per 100,000).



Notes

1. Cancer coded in the ICD-10 as C00–C97, excluding C44 non-melanoma skin cancer.
2. Data were estimated for 2012 by the IARC and are based on data from about 3 to 5 years earlier.
3. The ASRs were standardised by the IARC using the Doll et al. (1966) World Standard Population and are expressed per 100,000 persons. Countries or regions are ordered in descending order according to the ASRs.
4. Data for this figure are in online Table D9.2.

Source: Ferlay et al. 2013.

Figure 9.2: International comparison of estimated mortality for all cancers combined, persons, 2012

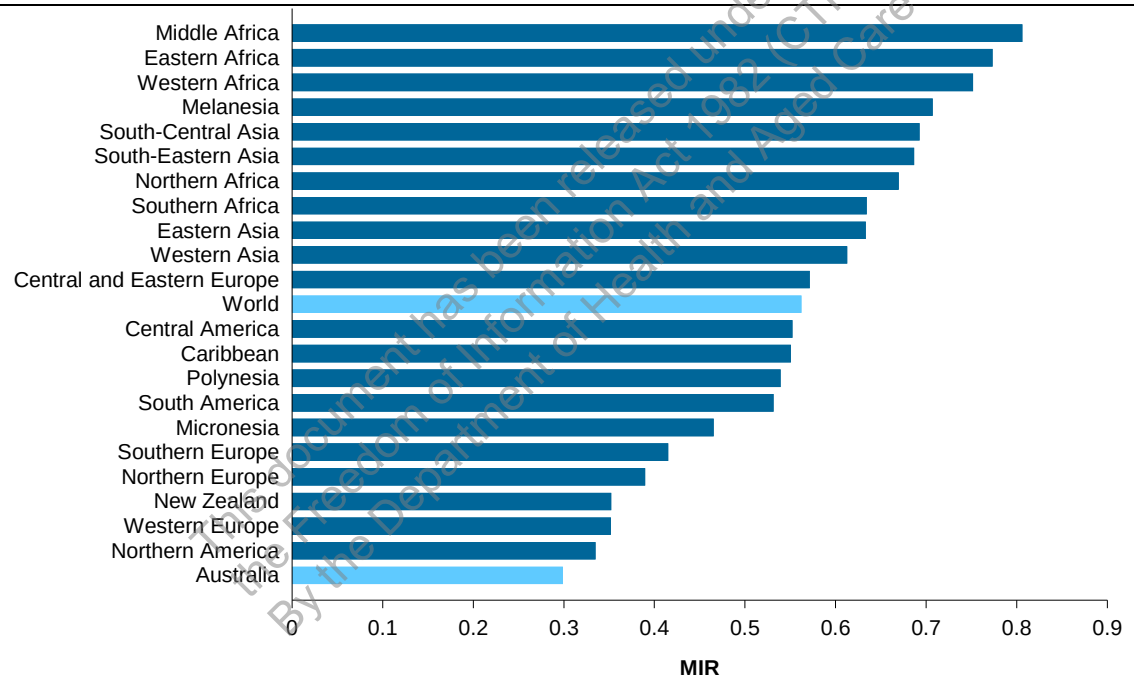
Mortality-to-incidence ratio

The MIR describes the number of cancer deaths in 2012, relative to the number of new cases of cancer diagnosed that year.

Low values of the MIR indicate longer survival while high ones indicate shorter survival. A ratio approaching 1.0 suggests that survival is low, with similar numbers of deaths and incident cases. A ratio approaching zero suggests that survival is higher (see Box 9.1 and Appendix H for more information).

The 2012 GLOBOCAN data suggest that the MIRs for all cancers varied markedly between countries and regions (Ferlay et al. 2013). The MIR for Australia was 0.3, suggesting that the survival of people in Australia who were diagnosed with cancer was higher than that of people in all other regions. By comparison, the MIR for the world was 0.6, indicating that Australia has higher survival from cancer than the world combined. The MIR for African regions and Melanesia was 0.7 or higher, suggesting relatively poorer survival (Figure 9.3).

For more information on MIRs, see Box 9.1.



Notes

1. Cancer coded in the ICD-10 as C00–C97, excluding C44 non-melanoma skin cancer.
2. The ratios are based on incidence and mortality data which were estimated for 2012 by the IARC and are based on data from about 3 to 5 years earlier.
3. The MIR equals the age-standardised mortality rate divided by the age-standardised incidence rate. The ASRs were standardised by the IARC using the Doll et al. (1966) World Standard Population. Countries or regions are ordered in descending order according to the MIR.
4. Data for this figure are in online Table D9.3.

Source: Ferlay et al. 2013.

Figure 9.3: International comparison of MIRs for all cancers combined, persons, 2012

Appendix A: Cancer codes

Table A1: Cancer codes

Cancer site/type	ICD-10 codes
Lip, oral cavity and pharynx	
Lip	C00
Tongue	C01–C02
Mouth	C03–C06
Salivary glands	C07–C08
Oropharynx	C09–C10
Nasopharynx	C11
Hypopharynx	C12–C13
Other sites in pharynx, etc.	C14
Digestive organs	
Oesophagus	C15
Stomach	C16
Small intestine	C17
Colorectal	C18–C20
Anus	C21
Liver	C22
Gallbladder and extrahepatic bile ducts	C23–C24
Pancreas	C25
Other digestive organs	C26
Respiratory system and intrathoracic organs	
Nose, sinuses, etc.	C30–C31
Larynx	C32
Lung	C33–C34
Other thoracic and respiratory organs	C37–C39
Bone	C40–C41
Skin	
Melanoma of the skin	C43
Non-melanoma of the skin	C44[(a)]
Mesothelial and soft tissue	
Mesothelioma	C45
Kaposi sarcoma	C46
Peritoneum	C48
Other soft tissue	C47, C49
Breast	C50

(continued)

Table A1 (continued): Cancer codes

Cancer site/type	ICD-10 codes
Female genital organs	
Vulva	C51
Vagina	C52
Cervix	C53
Uterus	C54–C55
Ovary	C56
Other female genital organs and placenta	C57–C58
Male genital organs	
Penis	C60
Prostate	C61
Testis	C62
Other male genital organs	C63
Urinary tract	
Kidney	C64
Bladder	C67
Other urinary organs	C65–C66, C68
Eye, brain and other parts of the central nervous system	
Eye	C69
Brain	C71
Other central nervous system	C70, C72
Thyroid and other endocrine glands	
Thyroid	C73
Other endocrine glands	C74–C75
Blood and lymphatic system	
Hodgkin lymphoma	C81
Non-Hodgkin lymphoma	C82–C85
Immunoproliferative cancers	C88
Myeloma	C90
Acute lymphoblastic leukaemia (ALL)	C91.0
Chronic lymphocytic leukaemia (CLL)	C91.1
Other and unspecified lymphoid leukaemia	C91.2–C91.9
Acute myeloid leukaemia (AML)	C92.0, C92.3–C92.5, C93.0, C94.0, C94.2, C94.4, C94.5
Chronic myelogenous leukaemia (CML)	C92.1
Other and unspecified myeloid leukaemia	C92.2, C92.7, C92.9, C93.1–C93.9, C94.7
Myeloproliferative cancers excluding CML	C94.1, C94.3, C96.2, D45, D47.1, D47.3
Myelodysplastic syndromes	D46

(continued)

Table A1 (continued): Cancer codes

Cancer site/type	ICD-10 codes
Other cancers of the blood and lymphatic system	C95, C96.0, C96.1, C96.3–C96.9
Other	
Other and ill-defined sites	C76
Unknown primary site	C80[(b)]
Multiple primary	C97[(c)]
All cancers combined	**C00–C97[(a,c)], D45, D46, D47.1, D47.3**

(a) For incidence data, those C44 codes that indicate basal or squamous cell carcinoma of the skin are not included.

(b) For mortality data before 2008, the applicable codes are C77–C80.

(c) C97 is of relevance for mortality data only.

Appendix B: Summary pages for selected cancers

This appendix provides summary pages on the incidence, mortality, survival and prevalence statistics for selected cancers that were commonly diagnosed or were common causes of cancer deaths.

Actual cancer incidence data for 1982–2011 and estimates for 2012–2016 (based on 2002–2011 incidence data) are presented. Actual cancer mortality data for 1982–2012 and estimates for 2013–2016 (based on 2002–2012 mortality data) are presented (see Appendix G).

Data for the figures presented in this appendix are in online supplementary tables.

All cancers combined (C00–C97, D45, D46, D47.1, D47.3)

Risk factors[a]:

Table B1(a): Incidence and mortality of all cancers combined

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	67,117	51,594	118,711	24,341	18,698	43,039
Crude rate	603.7	459.8	531.4	215.2	163.8	189.4
ASR	579.7	403.6	484.1	210.6	133.0	166.8
Risk to age 75	1 in 3	1 in 4	1 in 3	1 in 9	1 in 13	1 in 11
Risk to age 85	1 in 2	1 in 3	1 in 2	1 in 4	1 in 6	1 in 5
Mean age	67.0	65.0	66.1	73.1	73.1	73.1
Estimated number for 2014, 2015 and 2016[c]						
2014	68,260	55,660	123,920	26,010	19,770	45,780
2015	69,790	57,010	126,800	26,470	20,100	46,570
2016	72,050	58,420	130,470	26,950	20,430	47,380

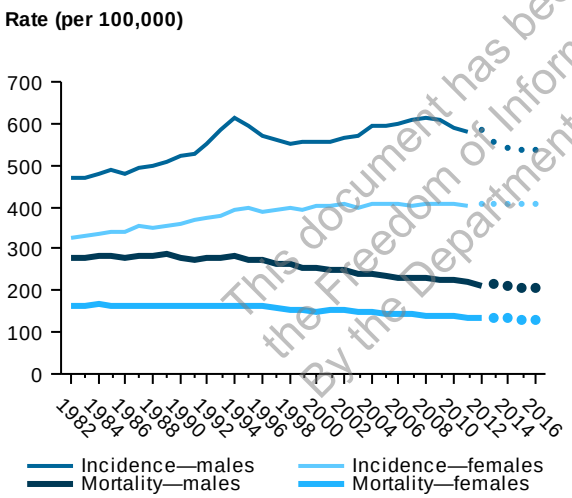


Figure B1(a): Incidence and mortality ASRs[b,c] **of all cancers combined, 1982–2016**

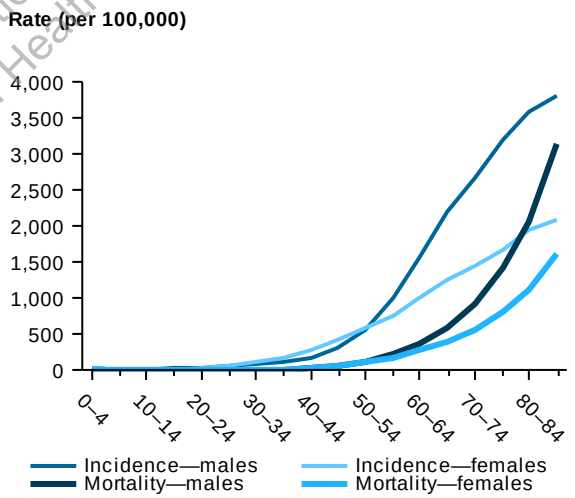


Figure B1(b): Incidence (2011) and mortality (2012) rates of all cancers combined, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) For incidence data, ICD-10 C44 codes that indicate a basal or squamous cell carcinoma of the skin are not included. The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B1(b): Survival and prevalence of all cancers combined[a]

	Males	Females	Persons
Prevalence as at the end of 2009[b]			
1-year prevalence	57,171	42,121	98,292
5-year prevalence	206,437	164,037	370,474
Relative survival in 2007–2011[c]			
1-year relative survival at diagnosis (%)	80.6	81.6	81.0
95% confidence interval	80.4–80.7	81.5–81.8	80.9–81.2
5-year relative survival at diagnosis (%)	66.1	67.5	66.7
95% confidence interval	65.9–66.3	67.3–67.7	66.5–66.8
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	80.0	80.9	80.4
95% confidence interval	79.8–80.3	80.7–81.2	80.3–80.6
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	89.9	92.1	91.0
95% confidence interval	89.7–90.2	91.8–92.3	90.8–91.2

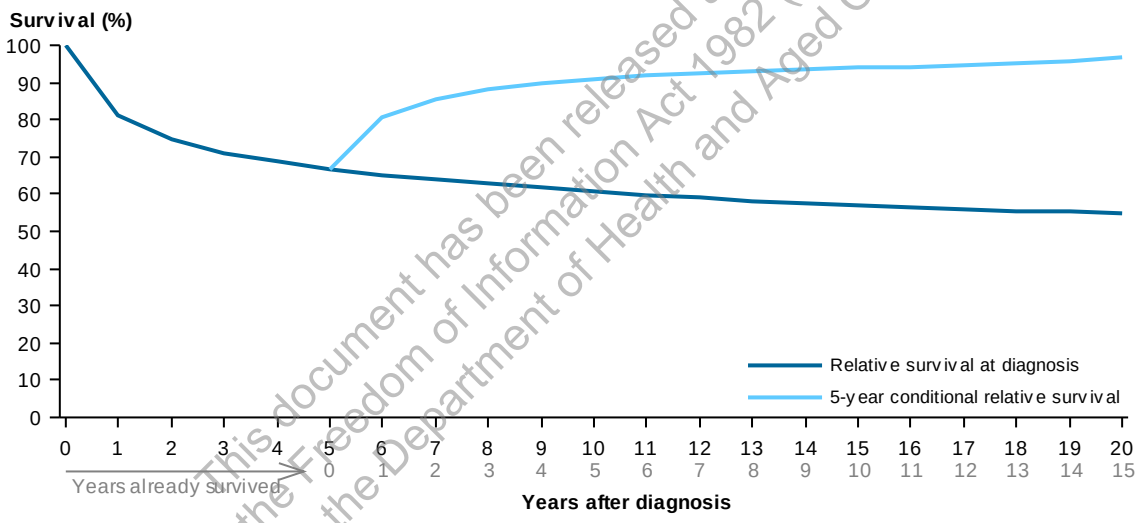


Figure B1(c): Relative survival at diagnosis and 5-year conditional survival from all cancers combined, Australia, 2007–2011

(a) For survival and prevalence data, those ICD-10 C44 codes that indicate a basal or squamous cell carcinoma of the skin are not included.

(b) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(c) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Acute myeloid leukaemia (C92.0, C92.3–C92.5, C93.0, C94.0, C94.2, C94.4, C94.5)

Risk factor[a]**:** 

Table B2(a): Incidence and mortality of acute myeloid leukaemia

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	527	386	913	465	348	813
Crude rate	4.7	3.4	4.1	4.1	3.0	3.6
ASR	4.7	3.0	3.8	4.0	2.6	3.2
Risk to age 75	1 in 328	1 in 478	1 in 390	1 in 444	1 in 608	1 in 514
Risk to age 85	1 in 174	1 in 264	1 in 212	1 in 174	1 in 272	1 in 216
Mean age	63.3	65.4	64.2	72.1	71.5	71.9
Estimated number for 2014, 2015 and 2016[c]						
2014	580	440	1,020	545	375	920
2015	595	450	1,050	565	385	950
2016	610	460	1,070	585	395	980

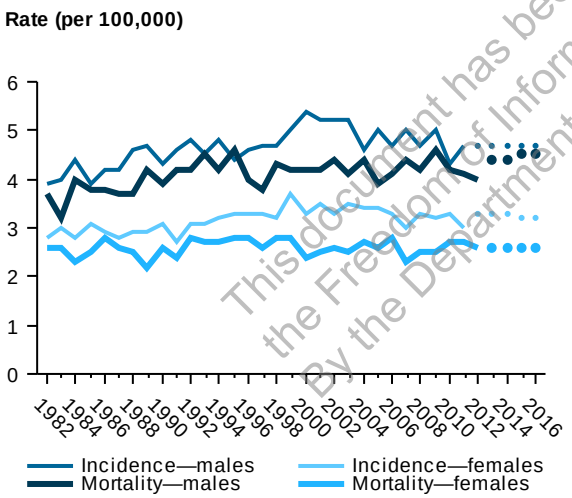


Figure B2(a): Incidence and mortality ASRs[b,c] of acute myeloid leukaemia, 1982–2016

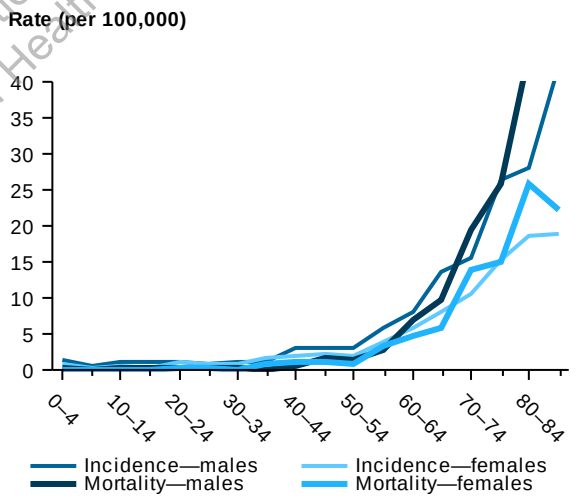


Figure B2(b): Incidence (2011) and mortality (2012) rates of acute myeloid leukaemia, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B2(b): Survival and prevalence of acute myeloid leukaemia

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	310	245	555
5-year prevalence	860	700	1,560
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	40.1	42.0	40.9
95% confidence interval	37.9–42.2	39.5–44.4	39.3–42.5
5-year relative survival at diagnosis (%)	23.4	26.1	24.5
95% confidence interval	21.6–25.2	24.0–28.2	23.2–25.9
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	55.7	60.1	57.7
95% confidence interval	50.8–60.6	55.2–65.0	54.2–61.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	87.6	91.1	89.3
95% confidence interval	84.2–91.0	88.3–93.9	87.1–91.5

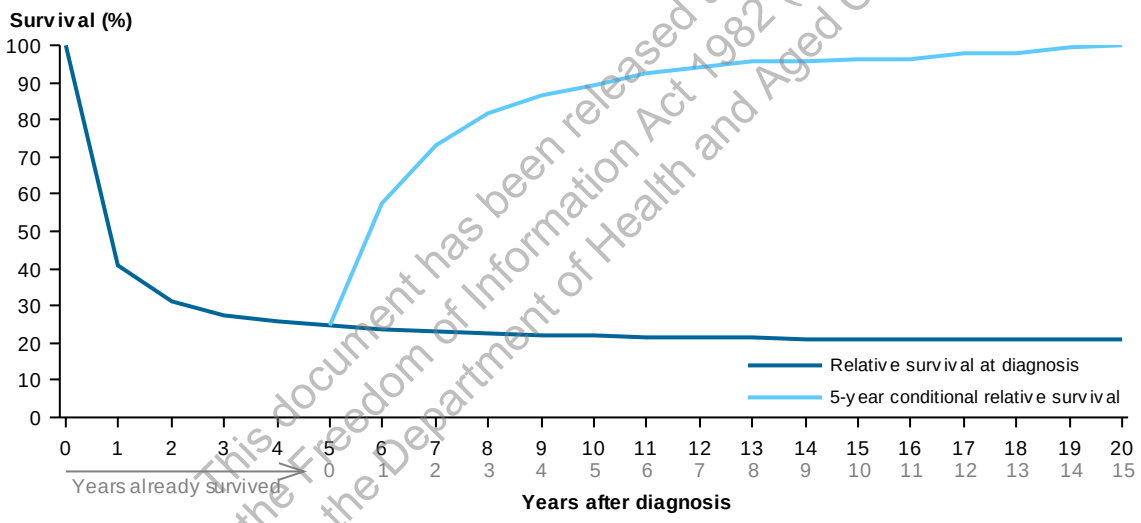


Figure B2(c): Relative survival at diagnosis and 5-year conditional survival from acute myeloid leukaemia, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Anal cancer (C21)

Table B3(a): Incidence and mortality of anal cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	151	218	369	32	39	71
Crude rate	1.4	1.9	1.7	0.3	0.3	0.3
ASR	1.3	1.7	1.5	0.3	0.3	0.3
Risk to age 75	1 in 961	1 in 693	1 in 804	1 in 4,842	1 in 4,000	1 in 4,375
Risk to age 85	1 in 618	1 in 479	1 in 538	1 in 3,465	1 in 3,071	1 in 3,243
Mean age	64.7	64.7	64.7	66.1	63.8	64.8
Estimated number for 2014, 2015 and 2016[b]						
2014	155	230	385	40	40	80
2015	160	235	395	40	40	80
2016	165	245	405	45	40	85

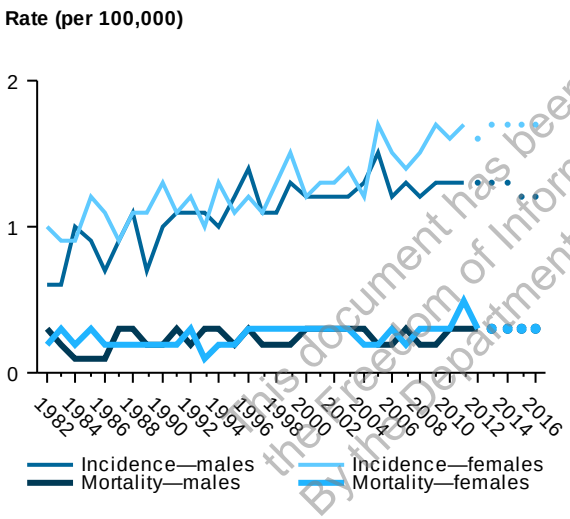


Figure B3(a): Incidence and mortality ASRs[a,b] of anal cancer, 1982–2016

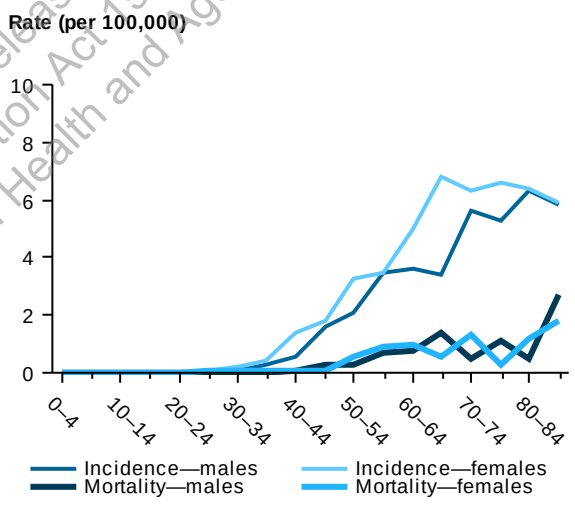


Figure B3(b): Incidence (2011) and mortality (2012) rates of anal cancer, by age group

(a) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B3(b): Survival and prevalence of anal cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	133	195	328
5-year prevalence	474	694	1,168
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	86.4	89.6	88.3
95% confidence interval	83.2–89.1	87.2–91.6	86.4–89.9
5-year relative survival at diagnosis (%)	58.9	68.6	64.5
95% confidence interval	54.4–63.2	65.0–72.1	61.7–67.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	65.1	74.4	70.6
95% confidence interval	59.0–71.2	70.2–78.5	67.1–74.0
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	82.9	88.8	86.5
95% confidence interval	77.0–88.8	84.7–93.0	83.0–89.9

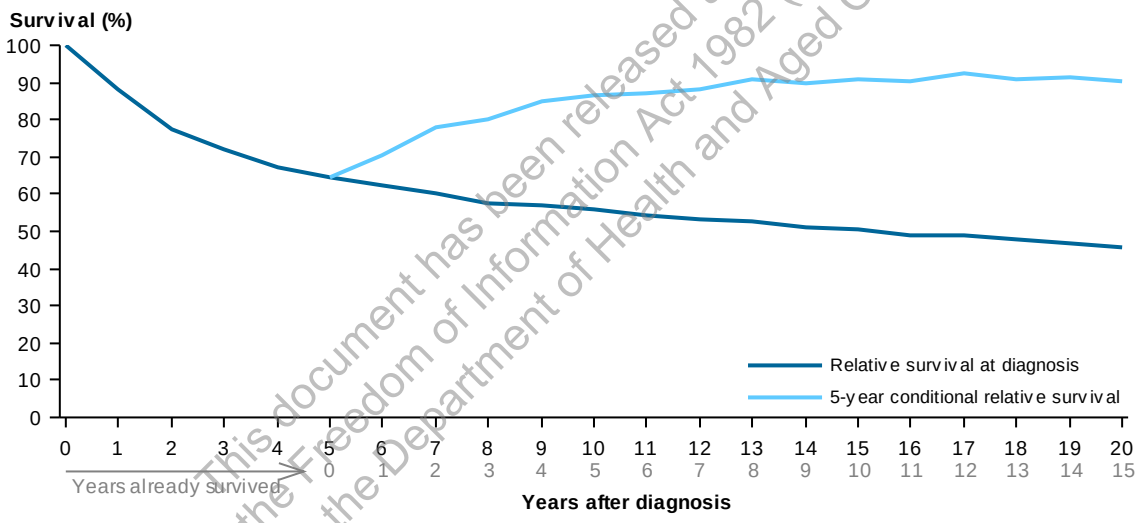


Figure B3(c): Relative survival at diagnosis and 5-year conditional survival from anal cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Bladder cancer (C67)

Risk factors[a]:

Table B4(a): Incidence and mortality of bladder cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	1,806	598	2,404	707	331	1,038
Crude rate	16.2	5.3	10.8	6.3	2.9	4.6
ASR	16.2	4.3	9.6	6.3	2.1	3.9
Risk to age 75	1 in 115	1 in 410	1 in 180	1 in 386	1 in 1,120	1 in 578
Risk to age 85	1 in 43	1 in 166	1 in 71	1 in 125	1 in 347	1 in 191
Mean age	74.4	76.1	74.8	77.9	80.3	78.6
Estimated number for 2014, 2015 and 2016[c]						
2014	2,060	675	2,730	780	335	1,115
2015	2,110	690	2,800	800	340	1,140
2016	2,170	705	2,880	815	350	1,165

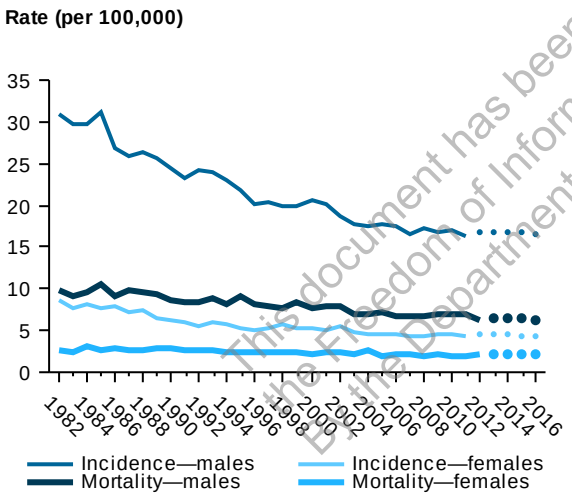


Figure B4(a): Incidence and mortality ASRs[b,c] of bladder cancer, 1982–2016

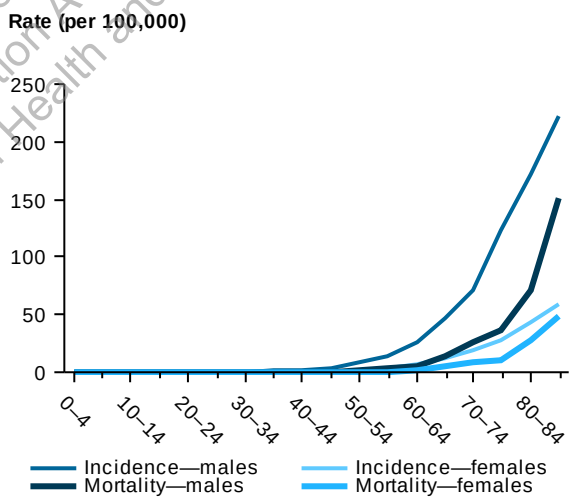


Figure B4(b): Incidence (2011) and mortality (2012) rates of bladder cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B4(b): Survival and prevalence of bladder cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	1,498	468	1,966
5-year prevalence	5,241	1,498	6,739
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	78.8	68.9	76.4
95% confidence interval	77.8–79.8	66.9–70.8	75.5–77.3
5-year relative survival at diagnosis (%)	55.2	46.8	53.1
95% confidence interval	53.8–56.5	44.5–49.0	51.9–54.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	66.9	66.6	66.8
95% confidence interval	64.9–68.8	63.1–70.1	65.1–68.5
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	84.0	86.7	84.7
95% confidence interval	82.1–86.0	83.6–89.9	83.0–86.3

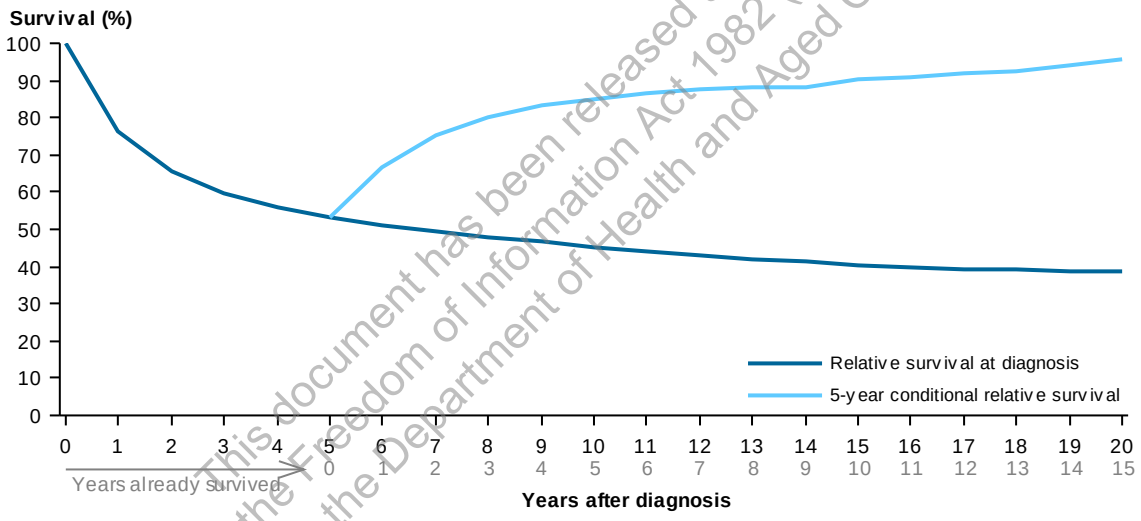


Figure B4(c): Relative survival at diagnosis and 5-year conditional survival from bladder cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Brain cancer (C71)

Table B5(a): Incidence and mortality of brain cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	1,010	714	1,724	737	504	1,241
Crude rate	9.1	6.4	7.7	6.5	4.4	5.5
ASR	8.8	5.8	7.3	6.2	3.9	5.0
Risk to age 75	1 in 145	1 in 220	1 in 175	1 in 201	1 in 327	1 in 249
Risk to age 85	1 in 96	1 in 149	1 in 118	1 in 127	1 in 206	1 in 159
Mean age	58.7	58.7	58.7	62.3	64.3	63.1
Estimated number for 2014, 2015 and 2016[b]						
2014	1,060	740	1,800	790	540	1,330
2015	1,090	755	1,850	805	550	1,355
2016	1,120	775	1,900	825	560	1,385

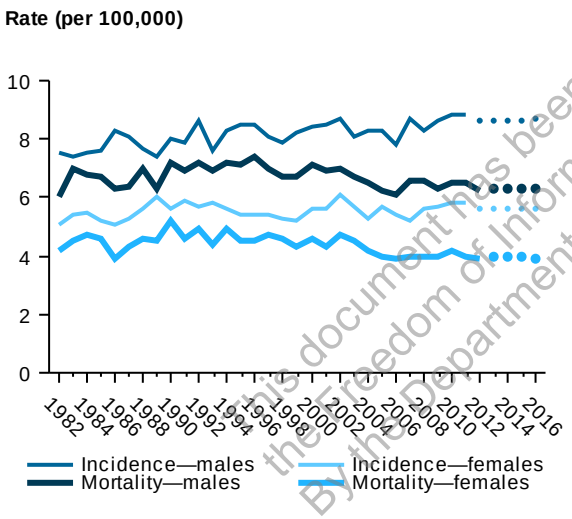


Figure B5(a): Incidence and mortality ASRs[b,c] of brain cancer, 1982–2016

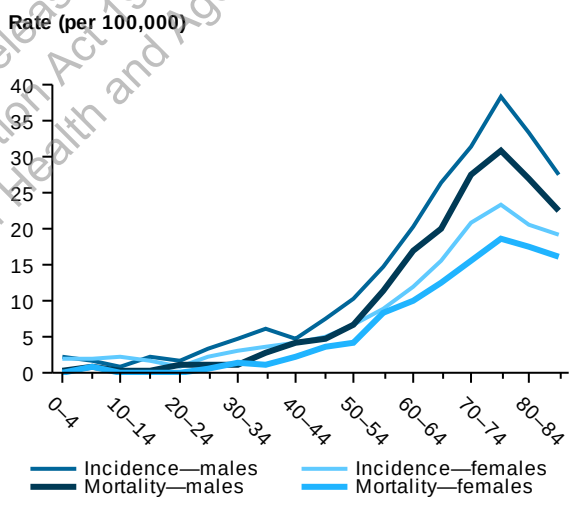


Figure B5(b): Incidence (2011) and mortality (2012) rates of brain cancer, by age group

(a) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B5(b): Survival and prevalence of brain cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	677	459	1,136
5-year prevalence	1,591	1,165	2,756
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	49.4	47.8	48.7
95% confidence interval	47.8–50.9	45.9–49.7	47.5–49.9
5-year relative survival at diagnosis (%)	20.5	23.2	21.6
95% confidence interval	19.2–21.7	21.7–24.8	20.7–22.6
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	38.7	47.4	42.3
95% confidence interval	34.0–43.4	42.7–52.1	38.9–45.6
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	74.6	83.1	78.4
95% confidence interval	70.9–78.3	79.8–86.4	75.9–80.9

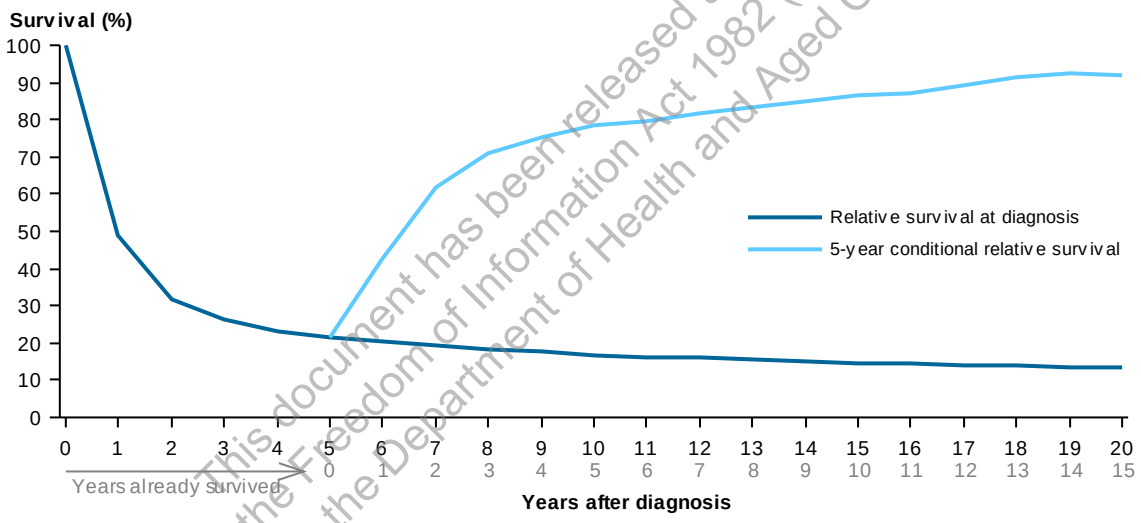


Figure B5(c): Relative survival at diagnosis and 5-year conditional survival from brain cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Breast cancer (C50)

Risk factors[a]:

Table B6(a): Incidence and mortality of breast cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	103	14,465	14,568	24	2,795	2,819
Crude rate	0.9	128.9	65.2	0.2	24.5	12.4
ASR	0.9	116.0	60.2	0.2	20.6	11.0
Risk to age 75	1 in 1,477	1 in 11	1 in 21	1 in 9,098	1 in 67	1 in 131
Risk to age 85	1 in 917	1 in 8	1 in 15	1 in 3,255	1 in 40	1 in 75
Mean age	66.4	61.3	61.3	71.8	68.8	68.8
Estimated number for 2014, 2015 and 2016[c]						
2014	140	15,270	15,410	25	3,000	3,025
2015	145	15,600	15,740	25	3,040	3,065
2016	150	15,930	16,080	25	3,080	3,105

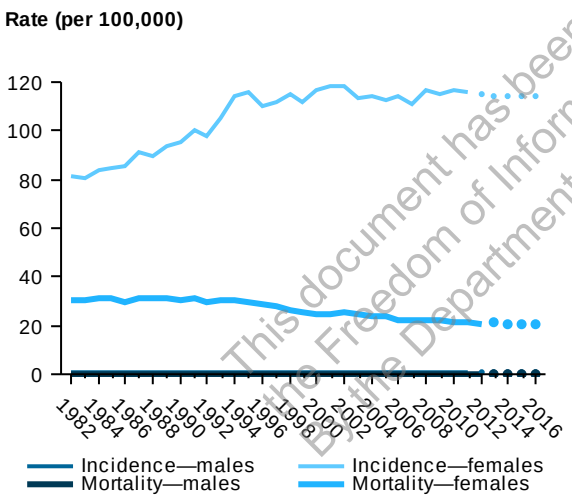


Figure B6(a): Incidence and mortality ASRs[b,c] of breast cancer, 1982–2016

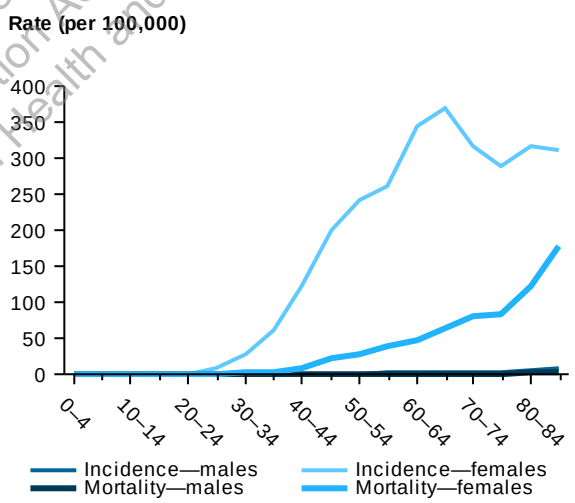


Figure B6(b): Incidence (2011) and mortality (2012) rates of breast cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B6(b): Survival and prevalence of breast cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	107	13,428	13,535
5-year prevalence	445	58,955	59,400
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	99.4	97.9	97.9
95% confidence interval	97.1–100.8	97.7–98.0	97.7–98.0
5-year relative survival at diagnosis (%)	86.4	89.6	89.6
95% confidence interval	81.5–90.8	89.3–89.9	89.2–89.9
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	85.5	90.0	89.9
95% confidence interval	80.7–90.3	89.7–90.3	89.6–90.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	90.0	93.2	93.2
95% confidence interval	84.3–95.6	92.9–93.5	92.9–93.5

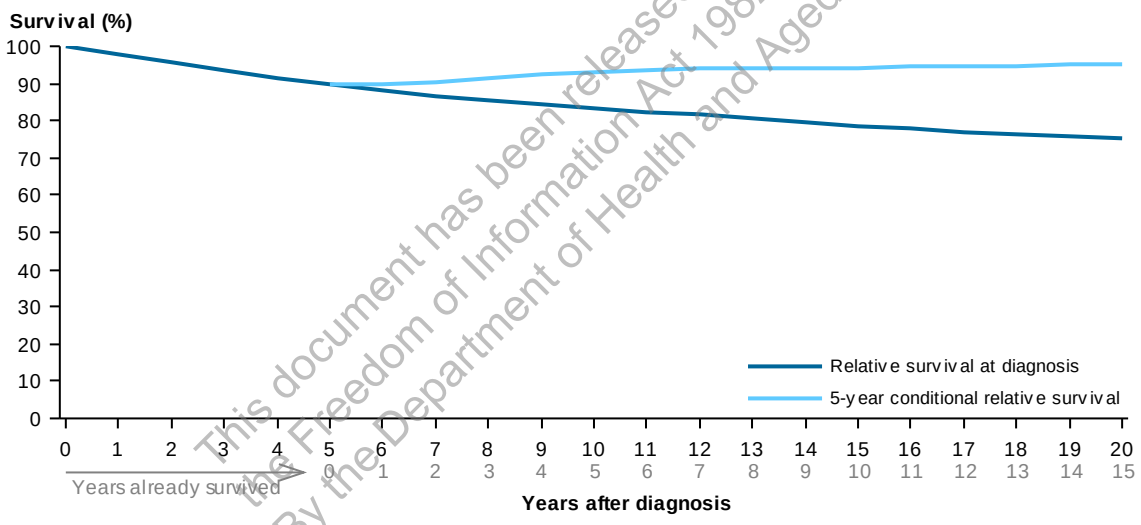


Figure B6(c): Relative survival at diagnosis and 5-year conditional survival from breast cancer in females, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Cervical cancer (C53)

Risk factors[a]**:** 

Table B7(a): Incidence and mortality of cervical cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	. .	801	801	. .	226	226
Crude rate	. .	7.1	. .	. .	2.0	. .
ASR	. .	6.9	. .	. .	1.8	. .
Risk to age 75	. .	1 in 193	. .	. .	1 in 828	. .
Risk to age 85	. .	1 in 162	. .	. .	1 in 496	. .
Mean age	. .	48.7	. .	. .	63.0	. .
Estimated number for 2014, 2015 and 2016[c]						
2014	. .	865	865	. .	245	245
2015	. .	885	885	. .	250	250
2016	. .	905	905	. .	255	255

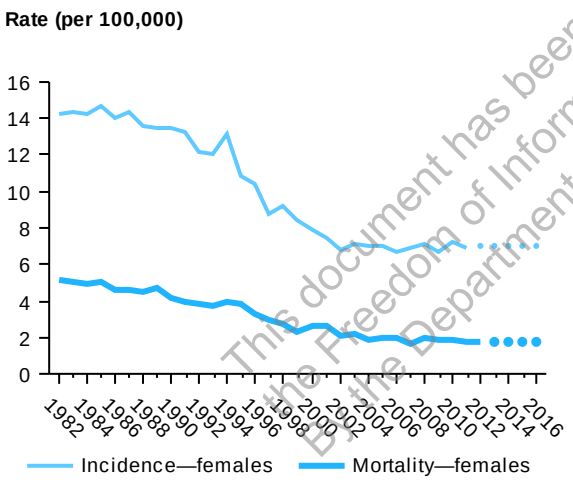


Figure B7(a): Incidence and mortality ASRs[b,c] of cervical cancer, 1982–2016

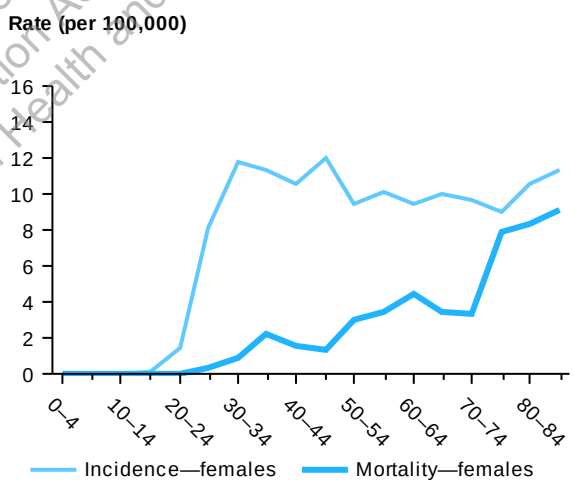


Figure B7(b): Incidence (2011) and mortality (2012) rates of cervical cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B7(b): Survival and prevalence of cervical cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	. .	684	684
5-year prevalence	. .	2,903	2,903
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	. .	87.4	87.4
95% confidence interval	. .	86.2–88.5	86.2–88.5
5-year relative survival at diagnosis (%)	. .	71.9	71.9
95% confidence interval	. .	70.2–73.4	70.2–73.4
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	. .	80.8	80.8
95% confidence interval	. .	79.2–82.3	79.2–82.3
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	. .	94.6	94.6
95% confidence interval	. .	93.6–95.7	93.6–95.7

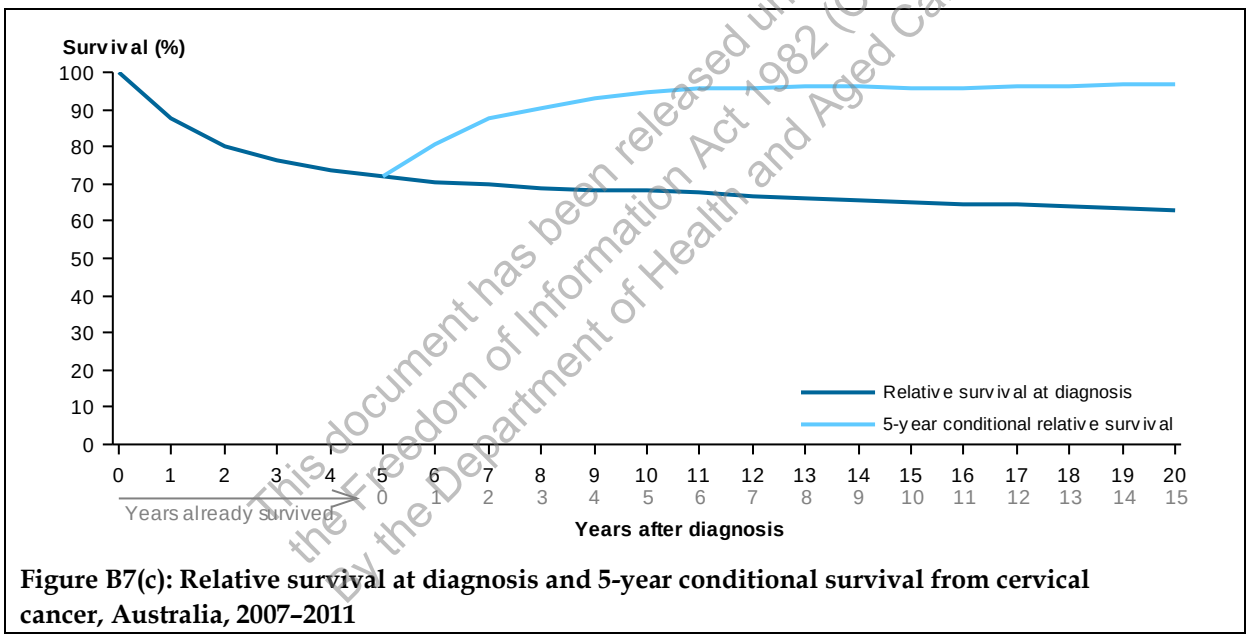


Figure B7(c): Relative survival at diagnosis and 5-year conditional survival from cervical cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Chronic lymphocytic leukaemia (C91.1)

Risk factors[a]**:**

Table B8(a): Incidence and mortality (2012) of chronic lymphocytic leukaemia

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	722	452	1,174	203	139	342
Crude rate	6.5	4.0	5.3	1.8	1.2	1.5
ASR	6.2	3.4	4.7	1.8	0.9	1.3
Risk to age 75	1 in 211	1 in 386	1 in 273	1 in 1,461	1 in 3,843	1 in 2,128
Risk to age 85	1 in 117	1 in 212	1 in 153	1 in 413	1 in 895	1 in 581
Mean age	68.6	72.1	70.0	78.5	82.0	79.9
Estimated number for 2014, 2015 and 2016[c]						
2014	790	510	1,300	230	145	375
2015	805	520	1,330	240	145	385
2016	825	535	1,360	245	150	395

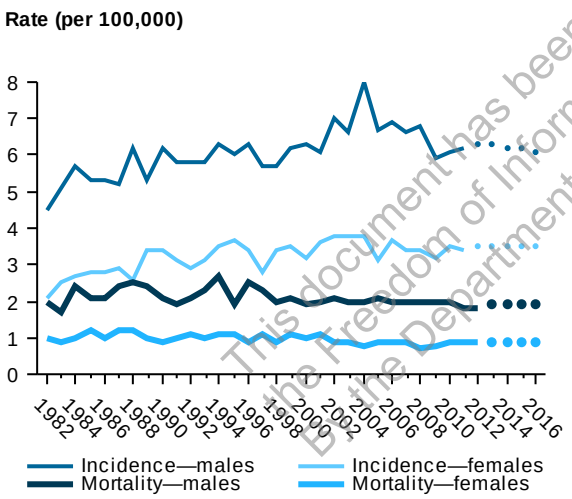


Figure B8(a): Incidence and mortality ASRs[b,c] of chronic lymphocytic leukaemia, 1982–2016

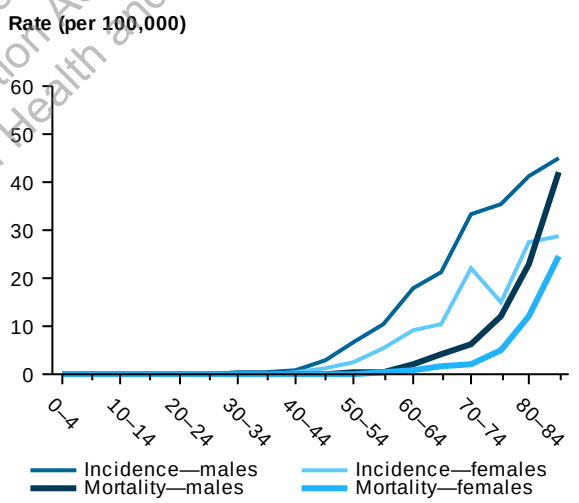


Figure B8(b): Incidence (2011) and mortality (2012) rates of chronic lymphocytic leukaemia, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B8(b): Survival and prevalence of chronic lymphocytic leukaemia

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	579	371	950
5-year prevalence	2,559	1,587	4,146
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	93.1	93.7	93.3
95% confidence interval	92.0–94.2	92.2–94.9	92.4–94.2
5-year relative survival at diagnosis (%)	74.8	79.8	76.7
95% confidence interval	72.8–76.8	77.3–82.2	75.1–78.2
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	75.8	81.6	78.0
95% confidence interval	73.5–78.1	79.0–84.2	76.3–79.7
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	73.0	81.8	76.6
95% confidence interval	69.8–76.2	78.5–85.1	74.3–78.9

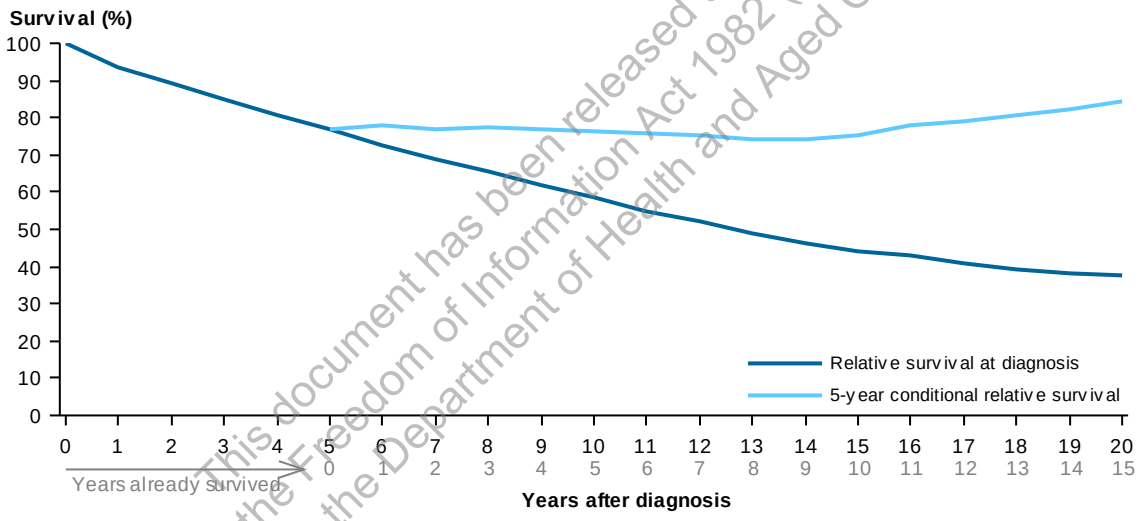


Figure B8(c): Relative survival at diagnosis and 5-year conditional survival from chronic lymphocytic leukaemia, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Colorectal cancer (C18–C20)

Risk factors[a]**:**

Table B9(a): Incidence and mortality of colorectal cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	8,351	6,800	15,151	2,208	1,772	3,980
Crude rate	75.1	60.6	67.8	19.5	15.5	17.5
ASR	72.8	51.5	61.5	19.1	12.4	15.4
Risk to age 75	1 in 19	1 in 28	1 in 23	1 in 91	1 in 145	1 in 112
Risk to age 85	1 in 10	1 in 15	1 in 12	1 in 38	1 in 61	1 in 48
Mean age	69.1	70.6	69.8	72.3	74.6	73.3
Estimated number for 2014, 2015 and 2016[c]						
2014	9,290	7,340	16,640	2,210	1,910	4,120
2015	9,550	7,520	17,070	2,190	1,930	4,120
2016	9,810	7,710	17,520	2,170	1,950	4,120

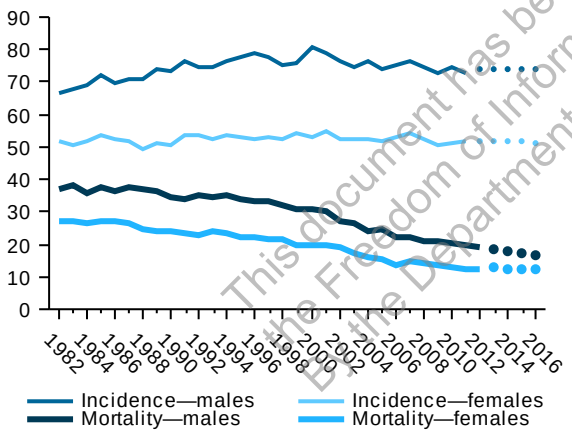


Figure B9(a): Incidence and mortality ASRs[b,c] of colorectal cancer, 1982–2016

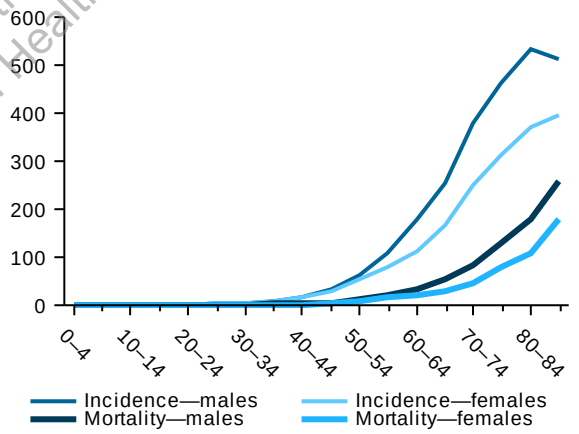


Figure B9(b): Incidence (2011) and mortality (2012) rates of colorectal cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD2011; AIHW NMD.

Table B9(b): Survival and prevalence of colorectal cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	6,835	5,495	12,330
5-year prevalence	26,700	21,896	48,596
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	85.7	84.1	85.0
95% confidence interval	85.3–86.1	83.6–84.6	84.7–85.3
5-year relative survival at diagnosis (%)	66.4	67.4	66.9
95% confidence interval	65.8–67.0	66.7–68.1	66.4–67.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	75.3	78.5	76.7
95% confidence interval	74.6–76.0	77.8–79.3	76.2–77.3
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	90.1	92.7	91.3
95% confidence interval	89.4–90.9	91.9–93.4	90.8–91.8

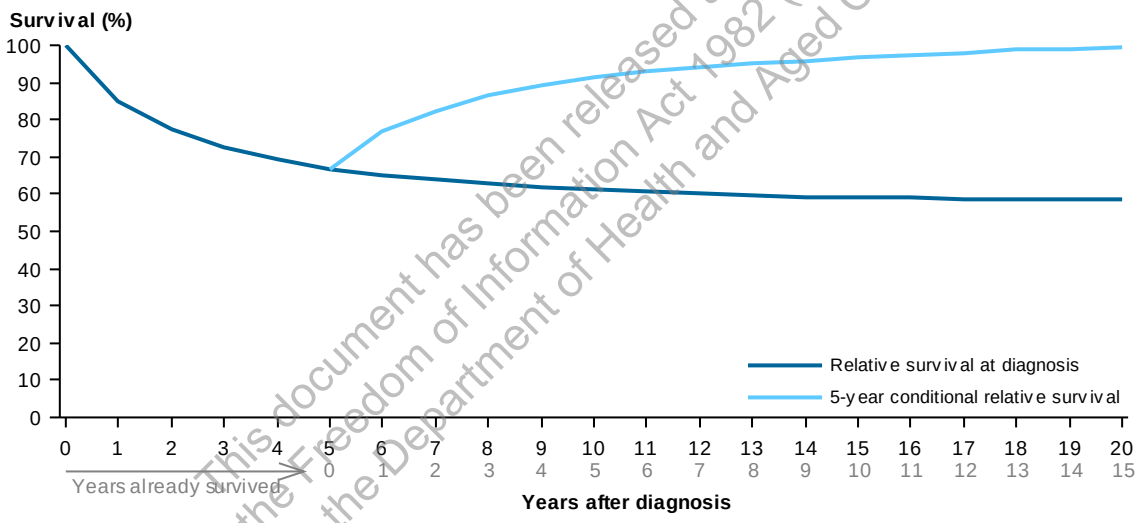


Figure B9(c): Relative survival at diagnosis and 5-year conditional survival from colorectal cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Cancer of the gallbladder and extrahepatic bile ducts (C23–C24)

Risk factors[a]**:** 

Table B10(a): Incidence and mortality of cancer of the gallbladder and extrahepatic bile ducts

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	335	436	771	99	155	254
Crude rate	3.0	3.9	3.5	0.9	1.4	1.1
ASR	3.0	3.2	3.1	0.9	1.1	1.0
Risk to age 75	1 in 523	1 in 499	1 in 511	1 in 2,654	1 in 1,755	1 in 2,107
Risk to age 85	1 in 243	1 in 215	1 in 227	1 in 823	1 in 649	719
Mean age	72.5	73.0	72.8	75.5	1 in 76.7	1 in 76.3
Estimated number for 2014, 2015 and 2016[c]						
2014	355	440	795	110	150	260
2015	365	450	815	115	145	260
2016	380	460	840	120	145	265

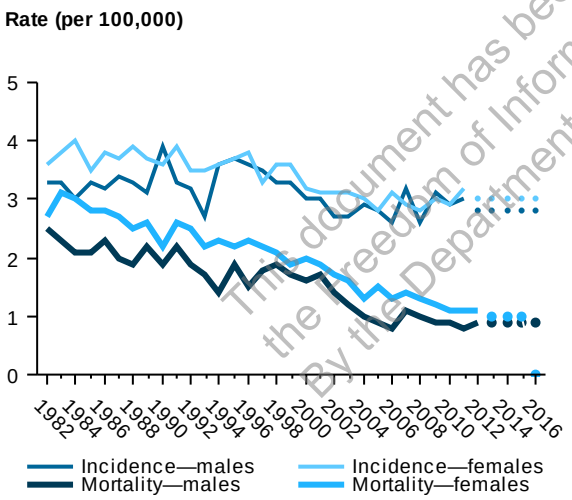


Figure B10(a): Incidence and mortality ASRs[b,c] **of cancer of gallbladder and extrahepatic bile ducts, 1982–2016**

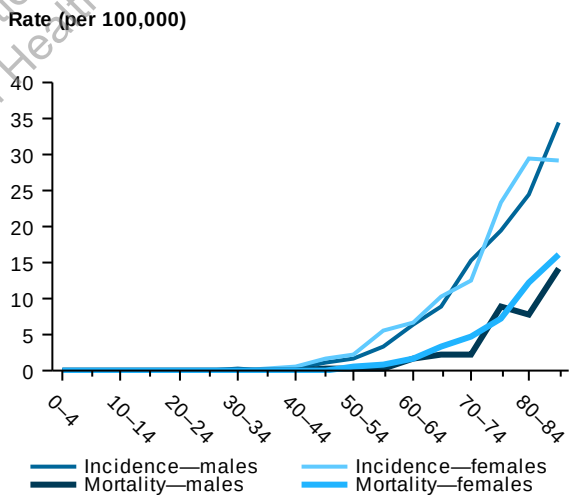


Figure B10(b): Incidence (2011) and mortality (2012) rates of cancer of gallbladder and extrahepatic bile ducts, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011 and AIHW NMD.

Table B10(b): Survival and prevalence of cancer of the gallbladder and extrahepatic bile ducts

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	220	224	444
5-year prevalence	533	535	1,068
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	49.5	39.3	43.9
95% confidence interval	46.8–52.2	36.9–41.7	42.1–45.8
5-year relative survival at diagnosis (%)	20.3	17.0	18.5
95% confidence interval	18.1–22.7	15.2–19.0	17.1–20.1
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	37.7	40.4	39.1
95% confidence interval	28.6–46.9	31.9–48.9	32.9–45.3
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	81.0	82.9	82.0
95% confidence interval	73.4–88.6	76.3–89.5	77.1–87.0

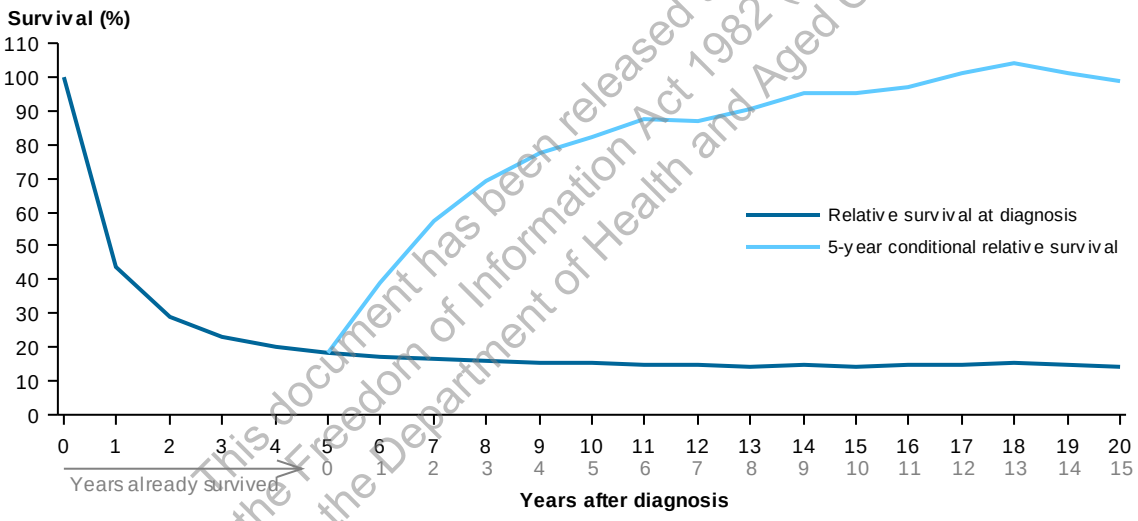


Figure B10(c): Relative survival at diagnosis and 5-year conditional survival from cancer of the gallbladder and extrahepatic bile ducts, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Hodgkin lymphoma (C81)

Risk factors[a]**:**

Table B11(a): Incidence and mortality of Hodgkin lymphoma

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	338	268	606	55	23	78
Crude rate	3.0	2.4	2.7	0.5	0.2	0.3
ASR	3.0	2.3	2.7	0.5	0.2	0.3
Risk to age 75	1 in 437	1 in 596	1 in 505	1 in 3,791	1 in 11,785	1 in 5,784
Risk to age 85	1 in 361	1 in 479	1 in 412	1 in 1,546	1 in 5,655	1 in 2,533
Mean age	43.4	42.4	43.0	71.3	64.8	69.4
Estimated number for 2014, 2015 and 2016[c]						
2014	335	265	605	15	15	30
2015	345	270	615	15	15	30
2016	350	275	630	15	15	30

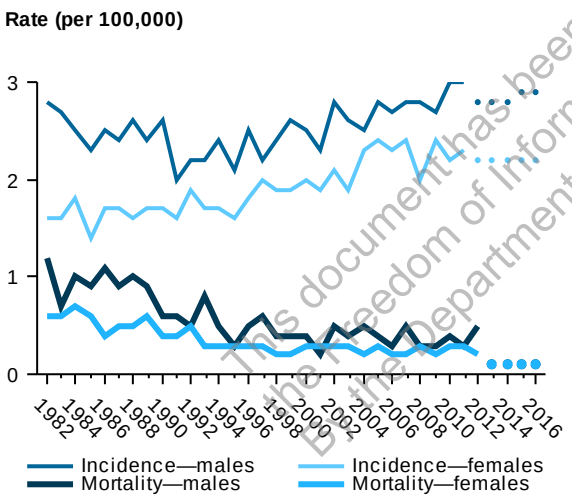


Figure B11(a): Incidence and mortality ASRs[b,c] **of Hodgkin lymphoma, 1982–2016**

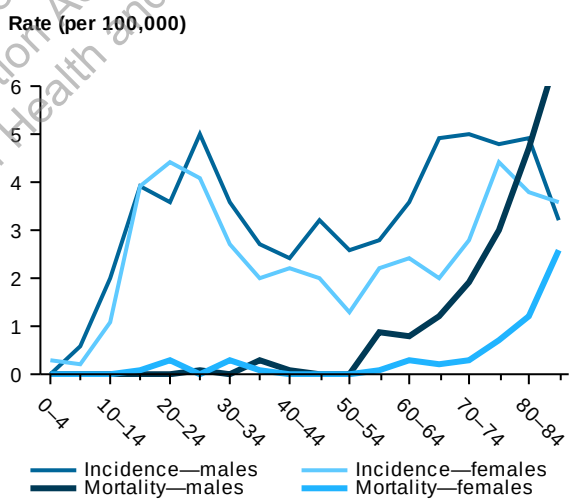


Figure B11(b): Incidence (2011) and mortality (2012) rates of Hodgkin lymphoma, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B11(b): Survival and prevalence of Hodgkin lymphoma

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	281	251	532
5-year prevalence	1,281	1,087	2,368
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	93.8	92.9	93.4
95% confidence interval	92.3–95.1	91.2–94.4	92.3–94.4
5-year relative survival at diagnosis (%)	87.3	87.1	87.2
95% confidence interval	85.1–89.2	84.8–89.1	85.7–88.6
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	91.9	92.9	92.4
95% confidence interval	90.3–93.6	91.3–94.5	91.2–93.5
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	94.9	95.7	95.3
95% confidence interval	93.4–96.4	94.2–97.1	94.2–96.3

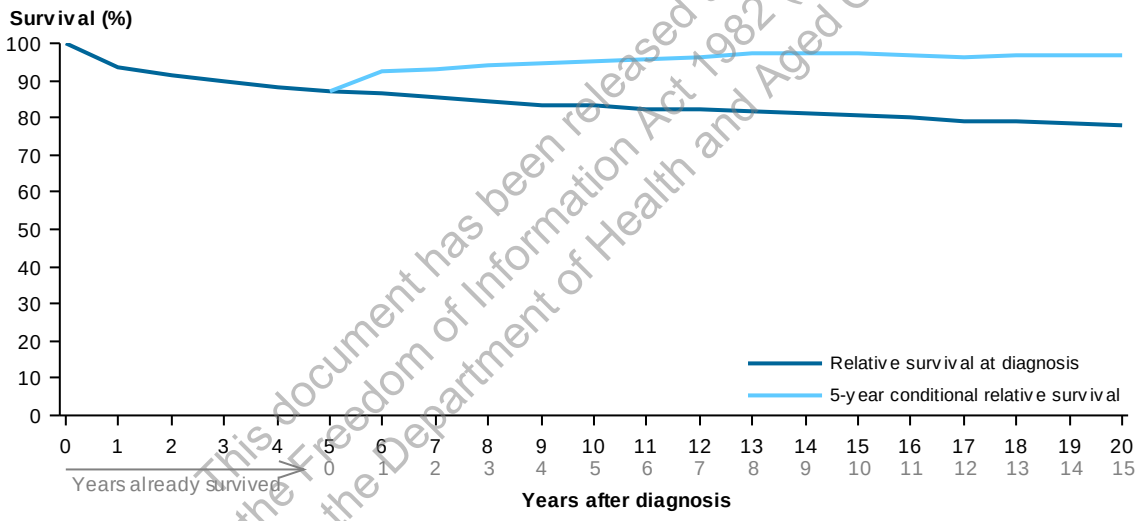


Figure B11(c): Relative survival at diagnosis and 5-year conditional survival from Hodgkin lymphoma, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Kidney cancer (C64)

Risk factors[a]**:**

Table B12(a): Incidence and mortality of kidney cancer

	Incidence			Mortality		
	Males	**Females**	**Persons**	**Males**	**Females**	**Persons**
2011 incidence/2012 mortality[b]						
Number	1,861	985	2,847	574	333	907
Crude rate	16.7	8.8	12.7	5.1	2.9	4.0
ASR	16.0	7.7	11.7	4.9	2.3	3.5
Risk to age 75	1 in 78	1 in 159	1 in 105	1 in 318	1 in 855	1 in 466
Risk to age 85	1 in 51	1 in 104	1 in 69	1 in 156	1 in 314	1 in 212
Mean age	63.5	64.7	63.9	70.5	76.2	72.6
Estimated number for 2014, 2015 and 2016[c]						
2014	2,000	1,060	3,060	625	355	980
2015	2,060	1,080	3,150	635	360	995
2016	2,120	1,110	3,230	650	365	1,015

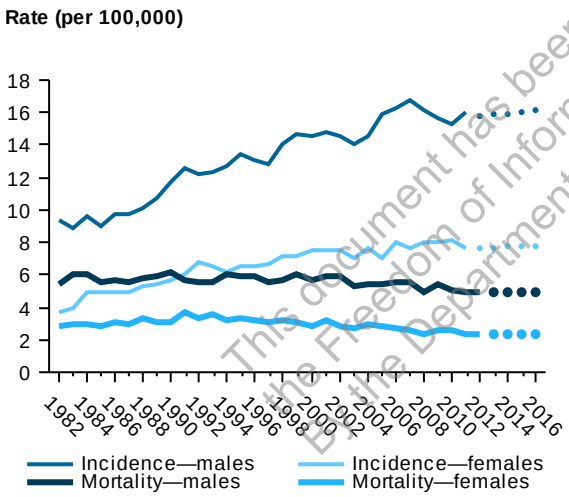


Figure B12(a): Incidence and mortality ASRs[b,c] **of kidney cancer, 1982–2016**

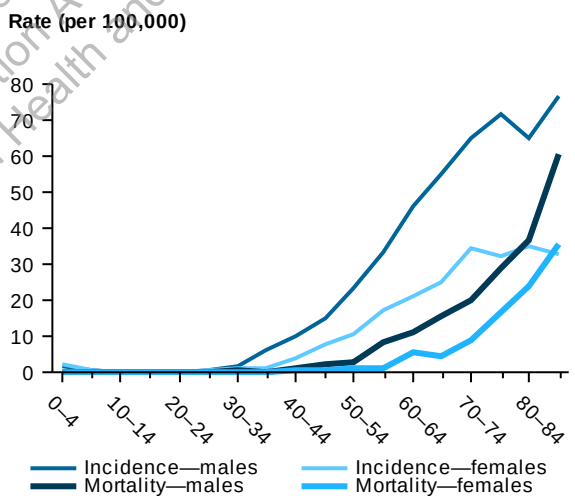


Figure B12(b): Incidence (2011) and mortality (2012) rates of kidney cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B12(b): Survival and prevalence of kidney cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	1,528	844	2,372
5-year prevalence	6,291	3,336	9,627
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	86.0	85.1	85.7
95% confidence interval	85.1–86.8	83.9–86.2	85.0–86.3
5-year relative survival at diagnosis (%)	72.9	74.2	73.4
95% confidence interval	71.7–74.1	72.6–75.7	72.4–74.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	82.8	85.6	83.8
95% confidence interval	81.6–84.1	84.1–87.1	82.8–84.8
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	88.3	91.3	89.4
95% confidence interval	86.8–89.7	89.7–92.9	88.3–90.5

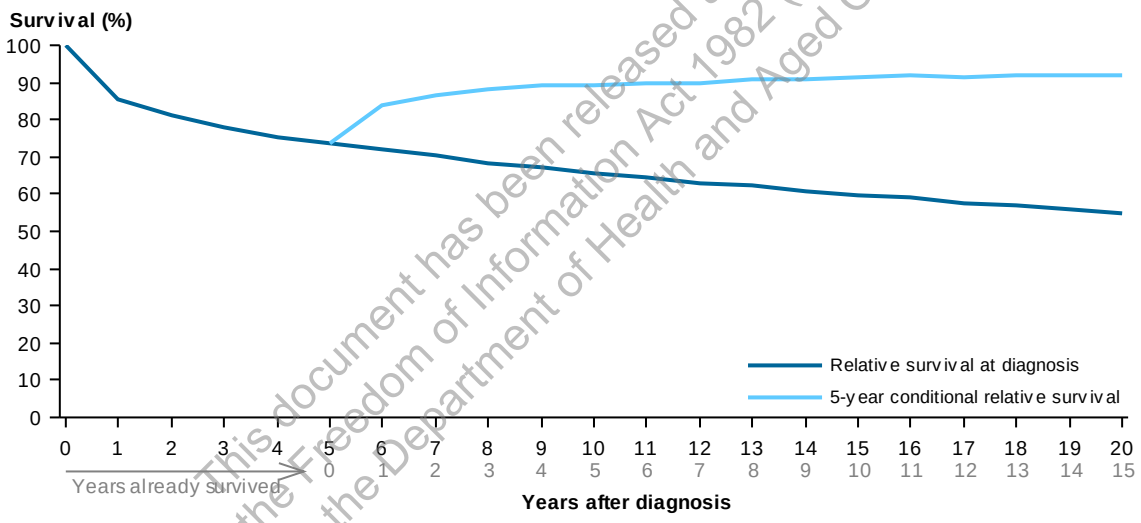


Figure B12(c): Relative survival at diagnosis and 5-year conditional survival from kidney cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Laryngeal cancer (C32)

Risk factors[a]**:** 

Table B13(a): Incidence and mortality of laryngeal cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	526	64	590	184	24	208
Crude rate	4.7	0.6	2.6	1.6	0.2	0.9
ASR	4.5	0.5	2.4	1.6	0.2	0.8
Risk to age 75	1 in 276	1 in 2,420	1 in 499	1 in 988	1 in 7,008	1 in 1,747
Risk to age 85	1 in 166	1 in 1,482	1 in 310	1 in 419	1 in 3,984	1 in 802
Mean age	67.2	67.6	67.2	71.5	72.9	71.6
Estimated number for 2014, 2015 and 2016[c]						
2014	585	80	665	200	40	240
2015	595	80	675	205	40	245
2016	605	85	690	205	40	245

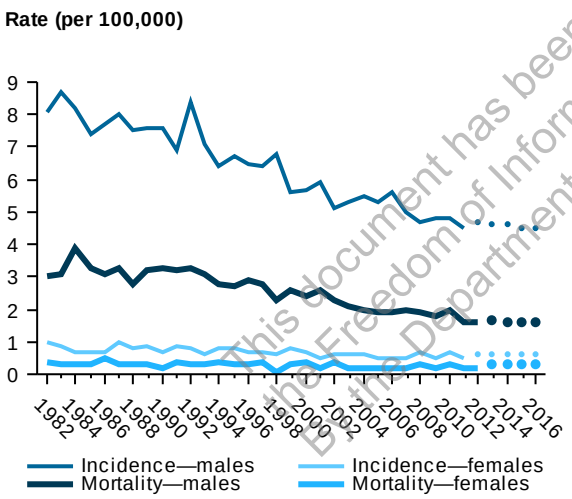


Figure B13(a): Incidence and mortality ASRs[b,c] **of laryngeal cancer, 1982–2016**

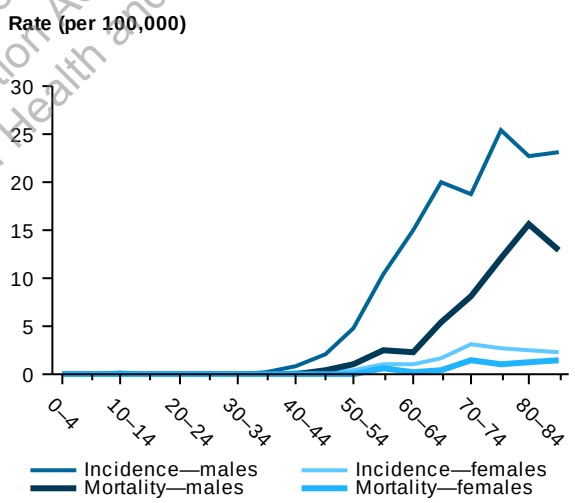


Figure B13(b): Incidence (2011) and mortality (2012) rates of laryngeal cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B13(b): Survival and prevalence of laryngeal cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	482	56	538
5-year prevalence	1,891	220	2,111
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	84.7	81.9	84.4
95% confidence interval	83.1–86.3	76.8–86.1	82.9–85.9
5-year relative survival at diagnosis (%)	62.7	59.4	62.3
95% confidence interval	60.4–64.9	53.1–65.4	60.2–64.4
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	71.0	69.7	70.8
95% confidence interval	68.2–73.7	61.8–77.6	68.2–73.4
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	80.4	77.8	80.1
95% confidence interval	77.4–83.3	69.3–86.3	77.3–82.9

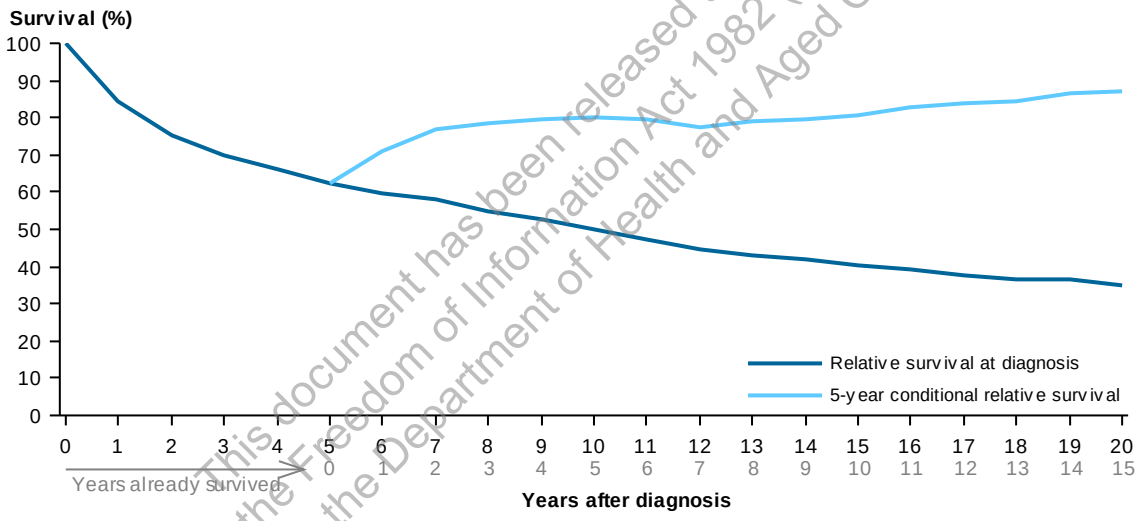


Figure B13(c): Relative survival at diagnosis and 5-year conditional survival from laryngeal cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Lip cancer (C00)

Risk factors[a]**:**

Table B14(a): Incidence and mortality of lip cancer

	Incidence			Mortality		
	Males	**Females**	**Persons**	**Males**	**Females**	**Persons**
2011 Incidence/2012 mortality[b]						
Number	677	235	912	11	1	12
Crude rate	6.1	2.1	4.1	0.1	0.0	0.1
ASR	5.9	1.8	3.8	0.1	0.0	0.1
Risk to age 75	1 in 220	1 in 839	1 in 350	1 in 20,589	. .	1 in 41,555
Risk to age 85	1 in 149	1 in 450	1 in 227	1 in 7,252	1 in 61,118	1 in 13,758
Mean age	60.8	69.0	62.8	61.3	77.0	62.6
Estimated number for 2014, 2015 and 2016[c]						
2014	740	265	1,010	10	5	15
2015	750	270	1,020	10	5	15
2016	760	270	1,030	10	5	15

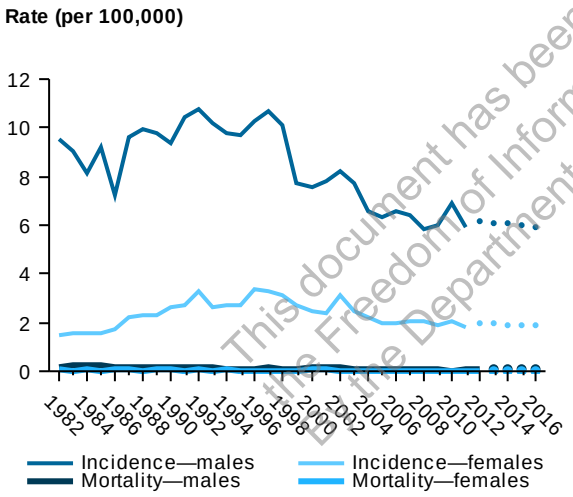


Figure B14(a): Incidence and mortality ASRs[b,c] **of lip cancer, 1982–2016**

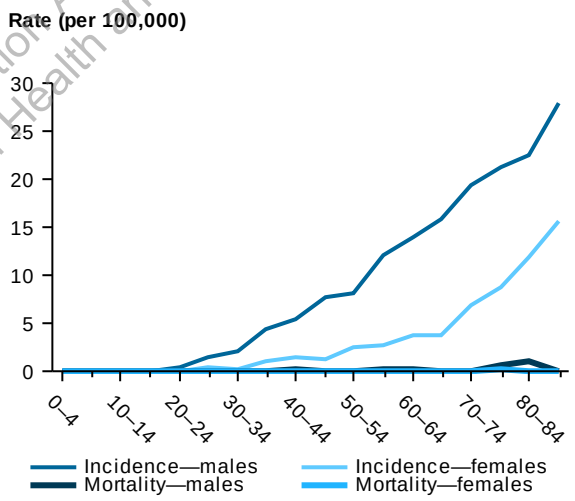


Figure B14(b): Incidence (2011) and mortality (2012) rates of lip cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: ABS 2014b; AIHW ACD 2011; AIHW NMD.

Table B14(b): Survival and prevalence of lip cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	642	233	875
5-year prevalence	2,924	1,057	3,981
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	99.3	98.5	99.1
95% confidence interval	98.6–99.8	97.0–99.6	98.5–99.6
5-year relative survival at diagnosis (%)	93.3	93.8	93.4
95% confidence interval	91.8–94.7	91.0–96.4	92.1–94.7
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	92.6	93.4	92.8
95% confidence interval	91.2–93.9	90.9–95.8	91.6–94.0
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	94.8	93.9	94.6
95% confidence interval	93.5–96.2	91.4–96.4	93.4–95.8

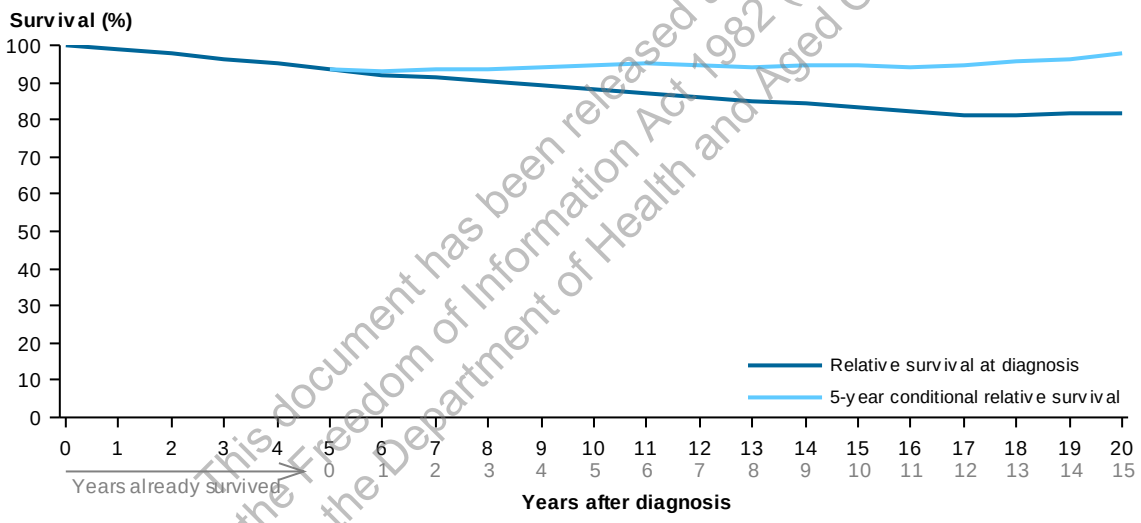


Figure B14(c): Relative survival at diagnosis and 5-year conditional survival from lip cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Liver cancer (C22)

Risk factors[a]**:**

Table B15(a): Incidence and mortality of liver cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	1,041	406	1,446	976	514	1,490
Crude rate	9.4	3.6	6.5	8.6	4.5	6.6
ASR	9.0	3.1	5.9	8.3	3.7	5.9
Risk to age 75	1 in 150	1 in 451	1 in 226	1 in 171	1 in 417	1 in 244
Risk to age 85	1 in 84	1 in 242	1 in 127	1 in 87	1 in 196	1 in 123
Mean age	66.7	69.0	67.4	69.1	72.1	70.1
Estimated number for 2014, 2015 and 2016[c]						
2014	1,260	430	1,690	1,080	535	1,615
2015	1,320	445	1,760	1,150	565	1,715
2016	1,380	460	1,840	1,210	595	1,805

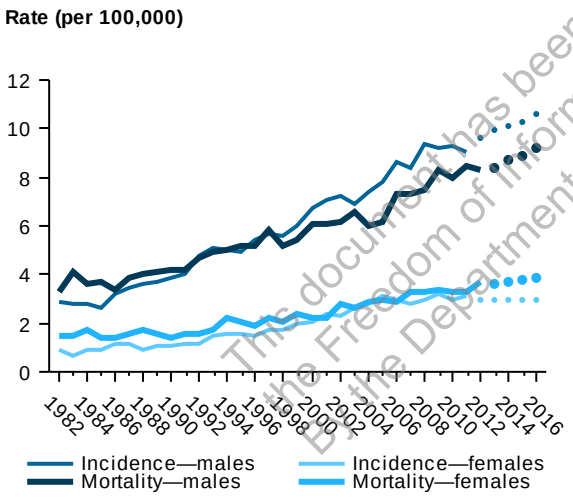


Figure B15(a): Incidence and mortality ASRs[b,c] **of liver cancer, 1982–2016**

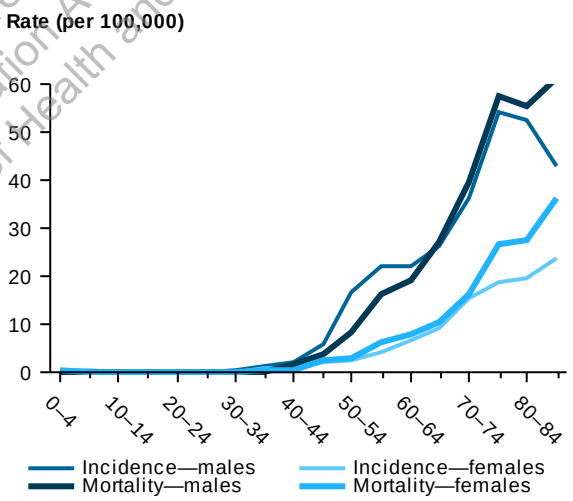


Figure B15(b): Incidence (2011) and mortality (2012) rates of liver cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B15(b): Survival and prevalence of liver cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	579	214	793
5-year prevalence	1,408	512	1,920
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	41.0	37.4	40.0
95% confidence interval	39.5–42.6	35.0–39.9	38.8–41.3
5-year relative survival at diagnosis (%)	16.3	15.1	16.0
95% confidence interval	15.2–17.6	13.4–17.0	15.0–17.0
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	35.6	37.5	36.1
95% confidence interval	29.7–41.6	28.0–46.9	31.1–41.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	70.6	74.6	71.7
95% confidence interval	64.6–76.6	65.5–83.6	66.7–76.7

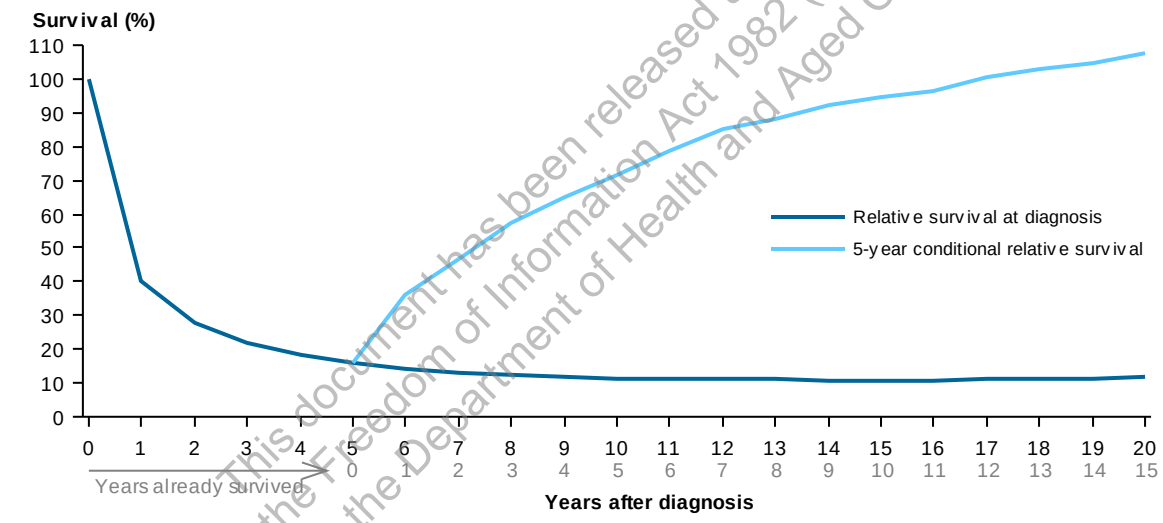


Figure B15(c): Relative survival at diagnosis and 5-year conditional survival from liver cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Lung cancer (C33–C34)

Risk factors[a]:

Table B16(a): Incidence and mortality of lung cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	6,409	4,102	10,511	4,882	3,255	8,137
Crude rate	57.6	36.6	47.1	43.2	28.5	35.8
ASR	56.2	31.4	42.5	41.8	23.7	31.8
Risk to age 75	1 in 26	1 in 41	1 in 32	1 in 38	1 in 58	1 in 46
Risk to age 85	1 in 13	1 in 23	1 in 17	1 in 17	1 in 29	1 in 22
Mean age	71.5	70.2	71.0	72.4	72.2	72.3
Estimated number for 2014, 2015 and 2016[c]						
2014	6,860	4,720	11,580	5,150	3,480	8,630
2015	6,990	4,890	11,880	5,190	3,600	8,790
2016	7,130	5,070	12,200	5,240	3,720	8,960

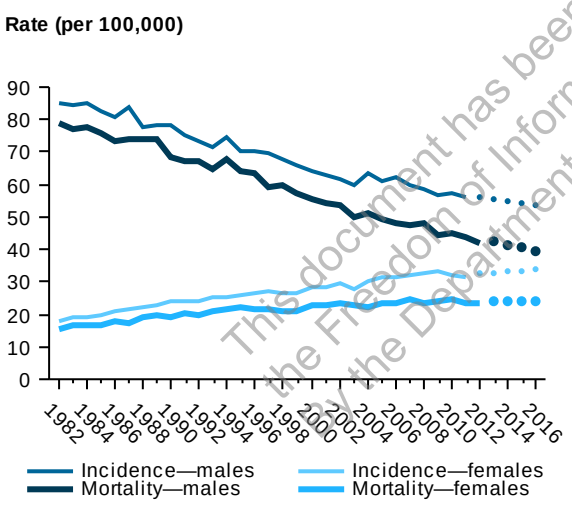


Figure B16(a): Incidence and mortality ASRs[b,c] **of lung cancer, 1982–2016**

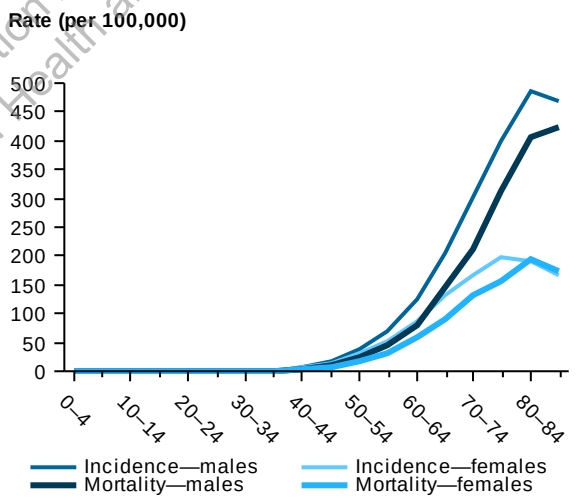


Figure B16(b): Incidence (2011) and mortality (2012) rates of lung cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B16(b): Survival and prevalence of lung cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	3,512	2,715	6,227
5-year prevalence	7,782	6,136	13,918
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	36.0	43.6	39.0
95% confidence interval	35.5–36.6	42.9–44.4	38.6–39.5
5-year relative survival at diagnosis (%)	12.5	17.1	14.3
95% confidence interval	12.1–13.0	16.5–17.7	14.0–14.7
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	31.6	36.4	33.6
95% confidence interval	29.0–34.2	33.7–39.1	31.7–35.6
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	67.6	73.2	70.0
95% confidence interval	64.9–70.3	70.6–75.8	68.1–71.9

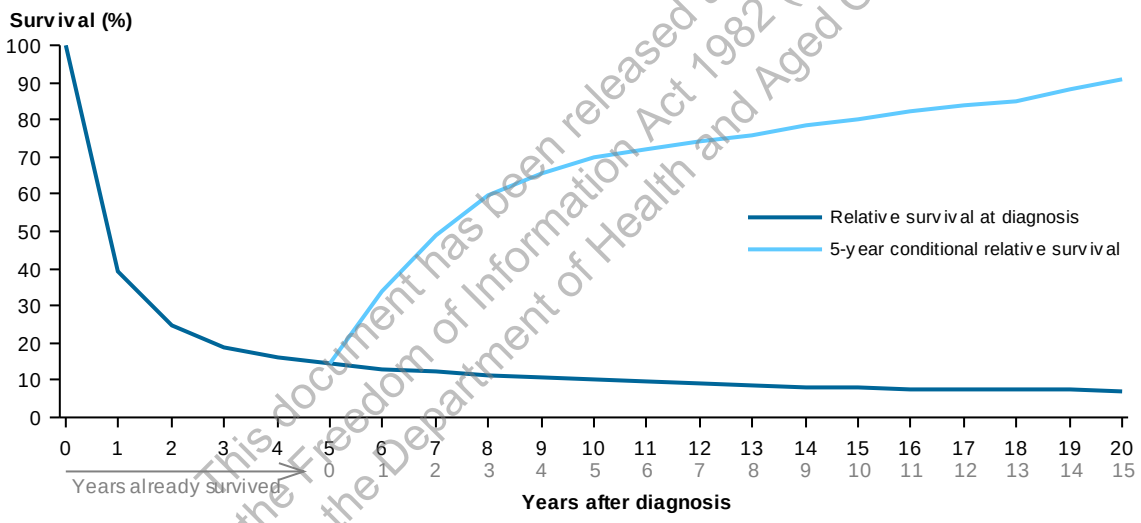


Figure B16(c): Relative survival at diagnosis and 5-year conditional survival from lung cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Melanoma of the skin (C43)

Risk factors[a]**:**

Table B17(a): Incidence and mortality of melanoma of the skin

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	6,734	4,835	11,570	1,039	476	1,515
Crude rate	60.6	43.1	51.8	9.2	4.2	6.7
ASR	58.5	39.0	48.0	9.0	3.4	5.9
Risk to age 75	1 in 23	1 in 33	1 in 27	1 in 187	1 in 456	1 in 266
Risk to age 85	1 in 14	1 in 24	1 in 18	1 in 84	1 in 240	1 in 129
Mean age	63.2	60.4	62.0	70.9	70.6	70.8
Estimated number for 2014, 2015 and 2016[c]						
2014	7,440	5,210	12,640	1,120	505	1,625
2015	7,640	5,320	12,960	1,160	515	1,675
2016	7,850	5,440	13,280	1,210	530	1,740

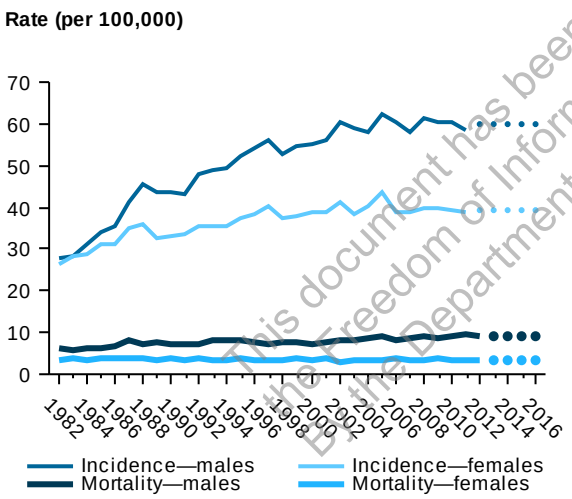


Figure B17(a): Incidence and mortality ASRs[b,c] **of melanoma of the skin, 1982–2016**

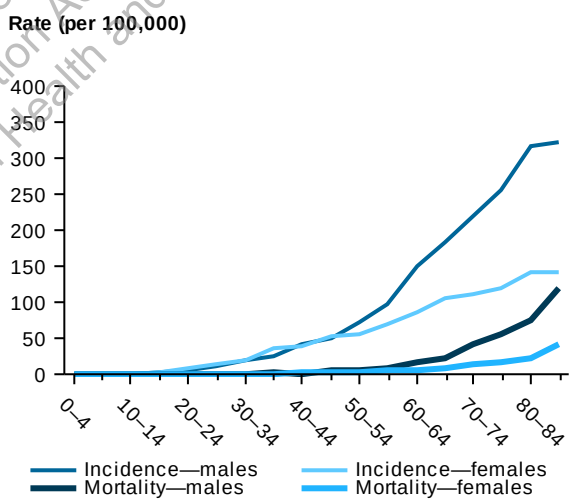


Figure B17(b): Incidence (2011) and mortality (2012) rates for melanoma of the skin, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B17(b): Survival and prevalence of melanoma of the skin

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	6,383	4,606	10,989
5-year prevalence	27,402	20,962	48,364
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	96.3	98.3	97.1
95% confidence interval	96.0–96.6	98.0–98.5	96.9–97.3
5-year relative survival at diagnosis (%)	88.2	93.5	90.4
95% confidence interval	87.6–88.7	92.9–94.0	90.0–90.8
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	90.4	94.5	92.2
95% confidence interval	89.9–90.9	94.0–94.9	91.8–92.5
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	95.8	97.6	96.6
95% confidence interval	95.3–96.3	97.2–98.1	96.3–97.0

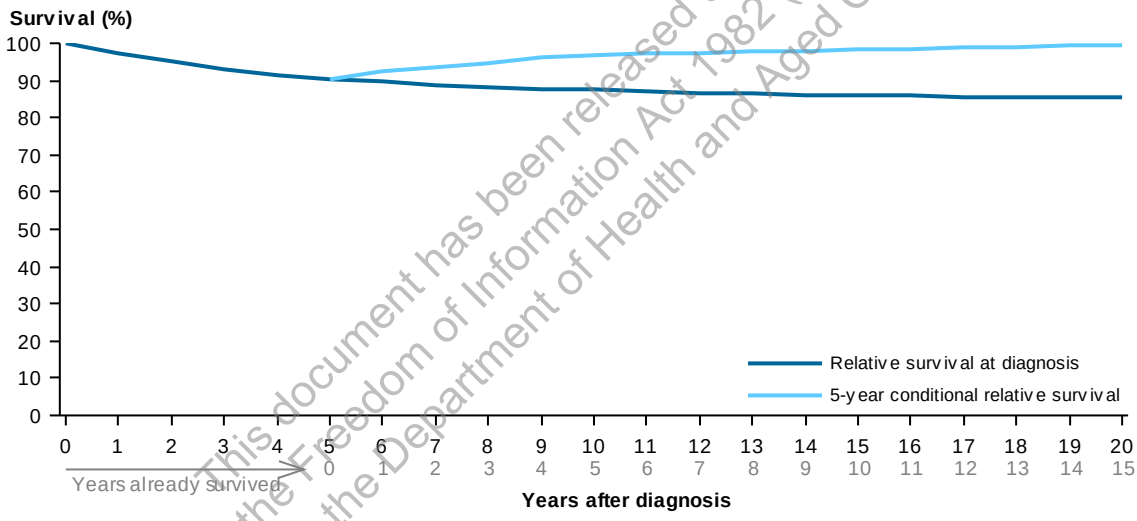


Figure B17(c): Relative survival at diagnosis and 5-year conditional survival from melanoma of the skin, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Mesothelioma (C45)

Risk factors[a]**:**

Table B18(a): Incidence and mortality of mesothelioma

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	573	117	690	538	100	638
Crude rate	5.2	1.0	3.1	4.8	0.9	2.8
ASR	5.1	0.9	2.8	4.6	0.7	2.5
Risk to age 75	1 in 302	1 in 1,505	1 in 507	1 in 382	1 in 2,057	1 in 650
Risk to age 85	1 in 130	1 in 842	1 in 238	1 in 140	1 in 970	1 in 259
Mean age	73.3	73.3	73.3	74.4	74.0	74.3
Estimated number for 2014, 2015 and 2016[c]						
2014	640	145	780	575	125	700
2015	655	150	805	595	130	725
2016	675	155	830	620	135	755

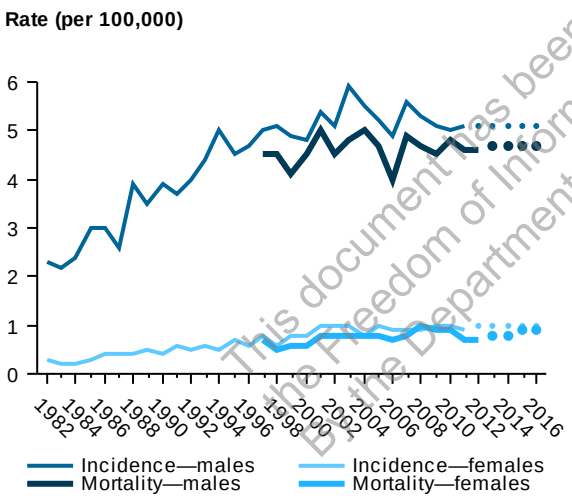


Figure B18(a): Incidence and mortality ASRs[b,c] **of mesothelioma, 1982–2016**

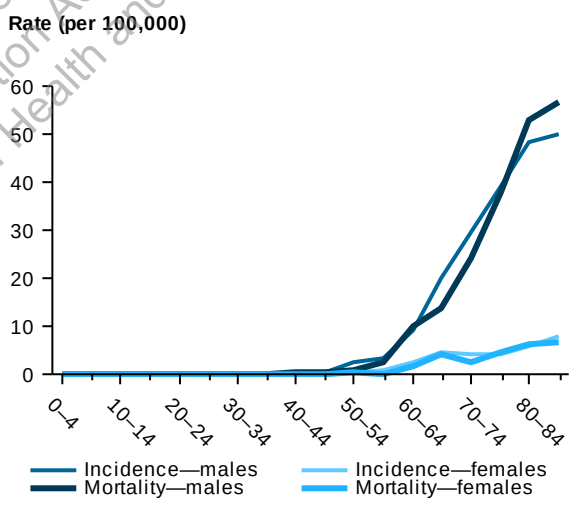


Figure B18(b): Incidence (2011) and mortality (2012) rates of mesothelioma, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B18(b): Survival and prevalence of mesothelioma

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	357	86	443
5-year prevalence	647	162	809
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	43.1	47.7	43.9
95% confidence interval	41.1–45.1	43.3–51.9	42.1–45.7
5-year relative survival at diagnosis (%)	5.2	8.4	5.8
95% confidence interval	4.4–6.2	6.2–11.0	4.9–6.7
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	n.p.[(c)]	n.p.[(c)]	n.p.[(c)]
95% confidence interval	n.p.[(c)]	n.p.[(c)]	n.p.[(c)]
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	44.8	41.7	45.1
95% confidence interval	21.5–68.2	10.5–72.9	27.4–62.8

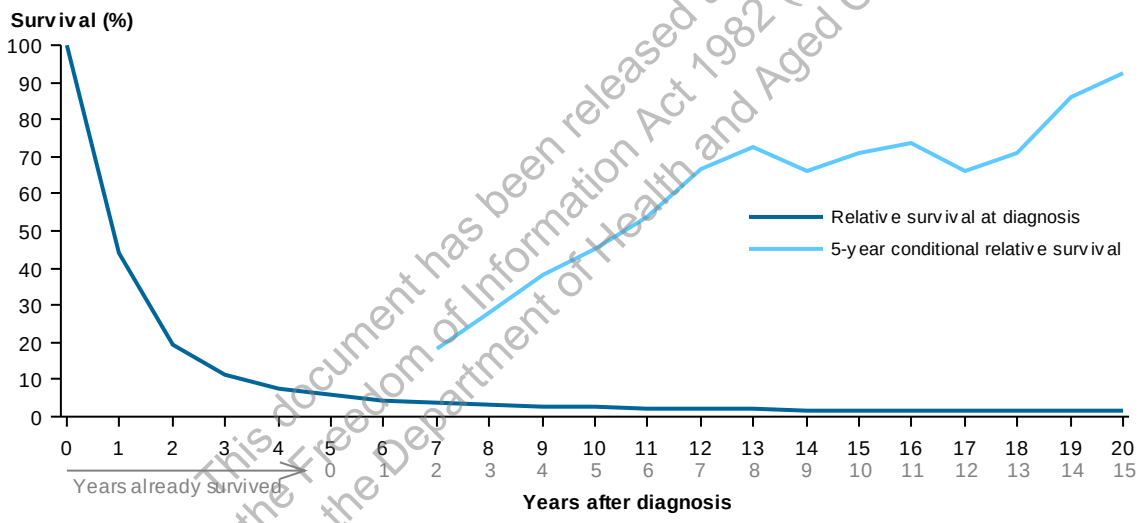


Figure B18(c): Relative survival at diagnosis and 5-year conditional survival from mesothelioma, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

(c) Survival estimates and confidence interval are not presented due to the high standard error.

Source: AIHW ACD 2011.

Mouth cancer (C03–C06)

Risk factors[a]**:**

Table B19(a): Incidence and mortality of mouth cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	356	215	571	76	43	119
Crude rate	3.2	1.9	2.6	0.7	0.4	0.5
ASR	3.0	1.6	2.3	0.6	0.3	0.5
Risk to age 75	1 in 392	1 in 760	1 in 518	1 in 1,714	1 in 6,239	1 in 2,707
Risk to age 85	1 in 272	1 in 483	1 in 350	1 in 1,293	1 in 3,819	1 in 1,960
Mean age	64.3	68.3	65.8	68.0	77.4	71.4
Estimated number for 2014, 2015 and 2016[c]						
2014	360	230	595	75	55	130
2015	370	235	605	75	55	130
2016	380	245	620	75	55	130

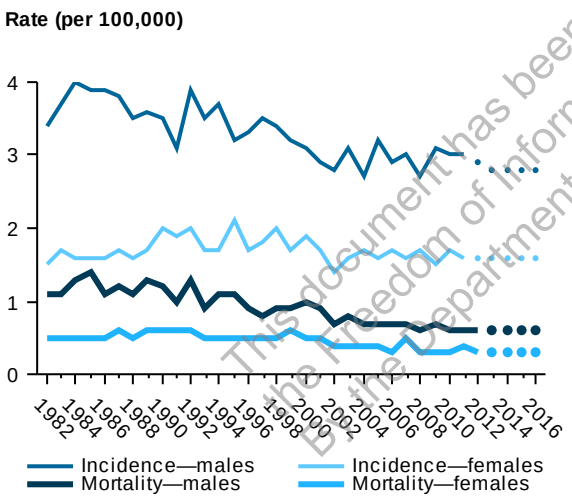


Figure B19(a): Incidence and mortality ASRs[b,c] **of mouth cancer, 1982–2016**

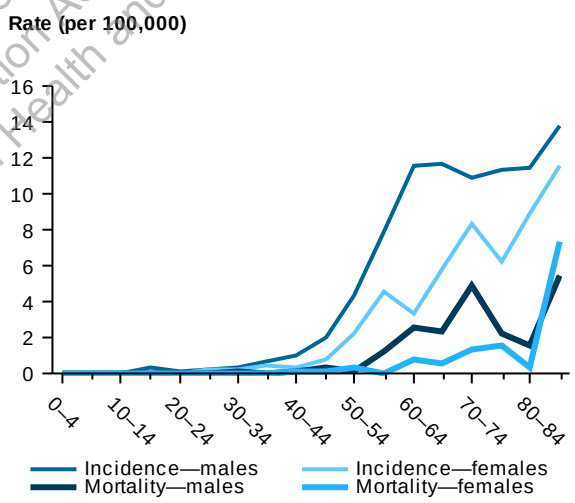


Figure B19(b): Incidence (2011) and mortality (2012) rates of mouth cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B19(b): Survival and prevalence of mouth cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	312	167	479
5-year prevalence	1,057	670	1,727
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	82.0	83.6	82.6
95% confidence interval	79.8–84.0	80.8–86.1	80.9–84.2
5-year relative survival at diagnosis (%)	57.0	63.7	59.6
95% confidence interval	54.2–59.8	60.0–67.3	57.3–61.8
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	65.8	74.0	69.0
95% confidence interval	61.8–69.8	69.7–78.3	66.0–71.9
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	72.1	81.8	76.1
95% confidence interval	67.4–76.8	77.1–86.5	72.8–79.5

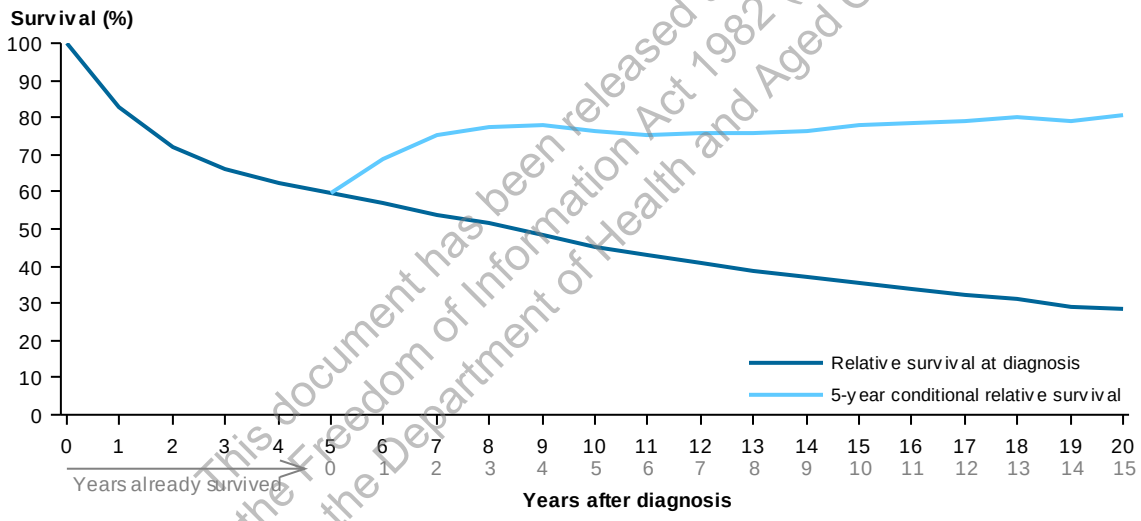


Figure B19(c): Relative survival at diagnosis and 5-year conditional survival from mouth cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Multiple primary cancers (C97)

Table B20(a): Mortality of multiple primary cancers

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2012 mortality[(a)]						
Number	. .	. .	. .	312	194	506
Crude rate	. .	. .	. .	2.8	1.7	2.2
ASR	. .	. .	. .	2.8	1.3	1.9
Risk to age 75	. .	. .	. .	1 in 990	1 in 1,259	1 in 1,110
Risk to age 85	. .	. .	. .	1 in 259	1 in 589	1 in 376
Mean age	. .	. .	. .	78.1	75.9	77.2
Estimated number for 2014, 2015 and 2016[(b)]						
2014	. .	. .	. .	415	230	645
2015	. .	. .	. .	430	240	670
2016	. .	. .	. .	445	245	690

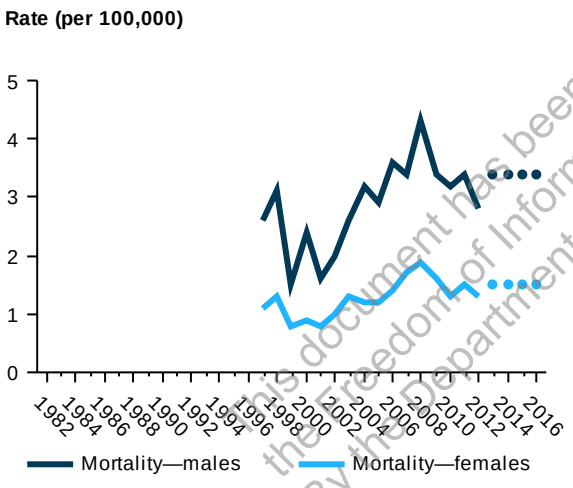


Figure B20(a): Mortality ASRs[(a,b)] of multiple primary cancers, 1982–2016

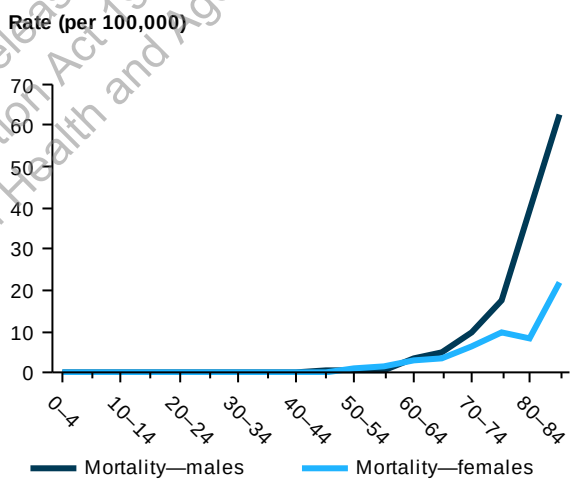


Figure B20(b): Mortality (2012) rates of multiple primary cancers, by age group

(a) Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Although a person can have more than one primary cancer, a diagnosis of 'multiple primary cancers' (ICD-10 code C97) is not used by cancer registries; rather, each of the person's cancers is coded separately. C97 only occurs in mortality data in cases when the certifying doctor cannot determine which of the cancers was the underlying cause of death. Because C97 is not a diagnosis used by cancer registries, prevalence and survival have not been calculated.

Myelodysplastic syndromes (D46)

Table B21(a): Incidence and mortality of myelodysplastic syndromes

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	829	480	1,309	268	156	424
Crude rate	7.5	4.3	5.9	2.4	1.4	1.9
ASR	7.6	3.4	5.2	2.4	1.0	1.6
Risk to age 75	1 in 304	1 in 532	1 in 388	1 in 1,889	1 in 3,296	1 in 2,407
Risk to age 85	1 in 95	1 in 203	1 in 134	1 in 323	1 in 942	1 in 506
Mean age	76.8	76.5	76.7	81.3	83.5	82.1
Estimated number for 2014, 2015 and 2016[b]						
2014	910	490	1,400	275	165	440
2015	945	495	1,440	280	170	450
2016	975	500	1,480	290	175	465

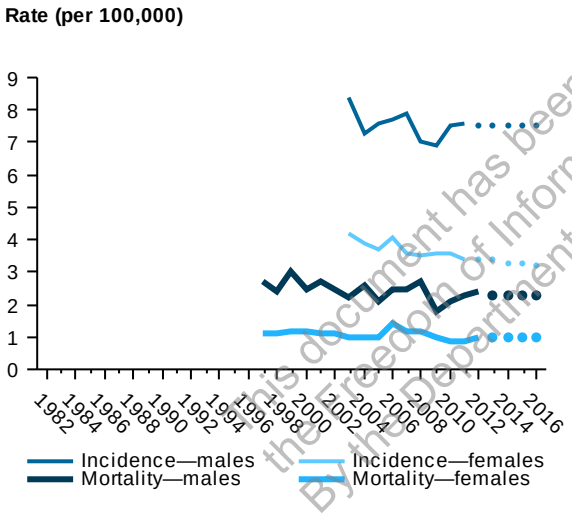


Figure B21(a): Incidence and mortality ASRs[a,b] of myelodysplastic syndromes, 1982–2016

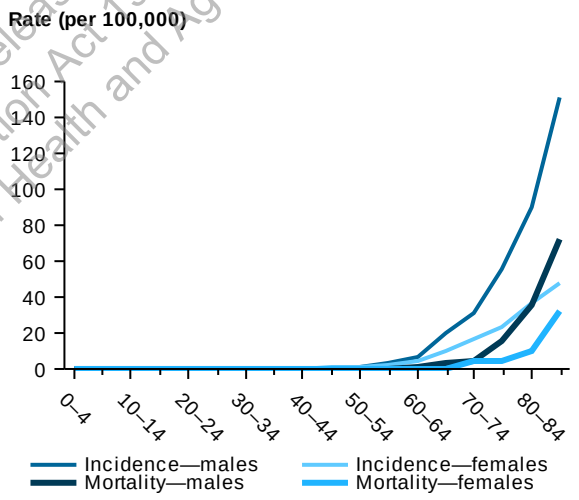


Figure B21(b): Incidence (2011) and mortality (2012) rates of myelodysplastic syndromes, by age group

(a) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2003–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B21(b): Survival and prevalence of myelodysplastic syndromes

	Males	Females	Persons
Prevalence as at the end of 2009[a]			
1-year prevalence	549	353	902
5-year prevalence	1,742	1,175	2,917
Relative survival in 2007–2011[b]			
1-year relative survival at diagnosis (%)	72.5	74.6	73.3
95% confidence interval	70.7–74.2	72.4–76.6	71.9–74.6
5-year relative survival at diagnosis (%)	36.5	40.3	38.0
95% confidence interval	34.5–38.6	37.8–42.8	36.4–39.6
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	43.4	45.9	44.4
95% confidence interval	38.2–48.5	40.3–51.6	40.6–48.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	49.7	57.6	53.4
95% confidence interval	40.8–58.6	49.5–65.6	47.4–59.4

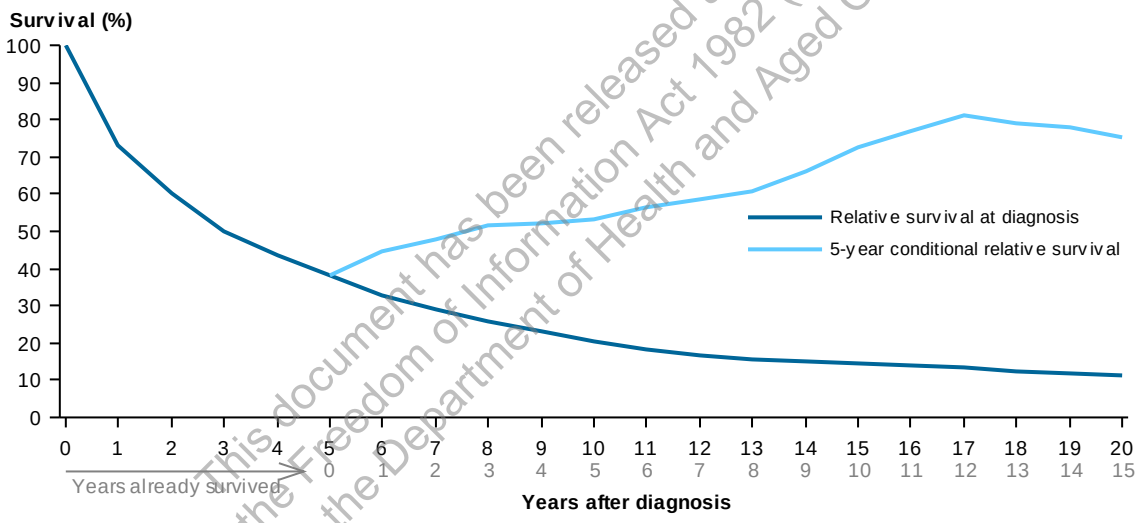


Figure B21(c): Relative survival at diagnosis and 5-year conditional survival from myelodysplastic syndromes, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Myeloma (C90)

Table B22(a): Incidence and mortality of myeloma

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	886	647	1,533	470	364	834
Crude rate	8.0	5.8	6.9	4.2	3.2	3.7
ASR	7.7	4.9	6.2	4.1	2.5	3.2
Risk to age 75	1 in 191	1 in 268	1 in 223	1 in 469	1 in 742	1 in 576
Risk to age 85	1 in 96	1 in 149	1 in 118	1 in 162	1 in 275	1 in 209
Mean age	70.1	71.3	70.6	74.3	77.5	75.7
Estimated number for 2014, 2015 and 2016[b]						
2014	975	700	1,680	535	405	940
2015	1,010	715	1,730	550	415	965
2016	1,050	735	1,780	570	425	995

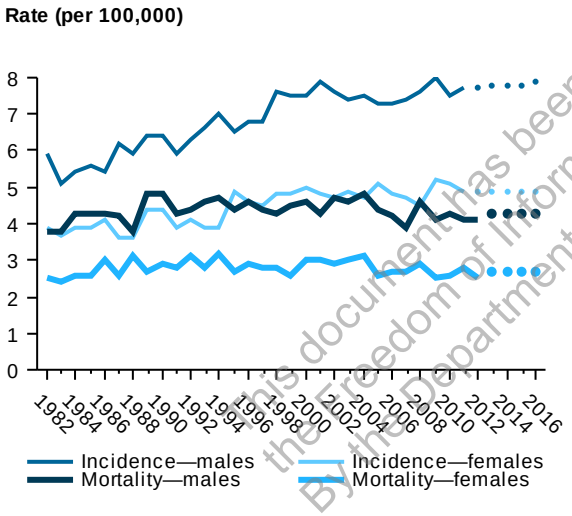


Figure B22(a): Incidence and mortality ASRs[a,b] of myeloma, 1982–2016

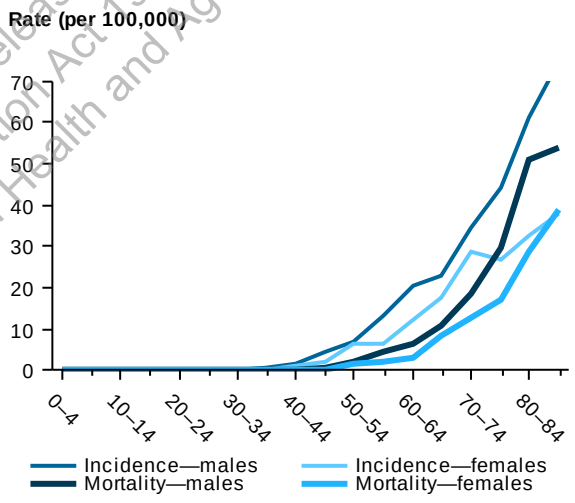


Figure B22(b): Incidence (2011) and mortality (2012) rates of myeloma, by age group

(a) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B22(b): Survival and prevalence of myeloma

	Males	Females	Persons
Prevalence as at the end of 2009[a]			
1-year prevalence	721	557	1,278
5-year prevalence	2,346	1,739	4,085
Relative survival in 2007–2011[b]			
1-year relative survival at diagnosis (%)	80.5	78.5	79.6
95% confidence interval	79.0–81.9	76.7–80.1	78.5–80.7
5-year relative survival at diagnosis (%)	45.4	43.9	44.8
95% confidence interval	43.5–47.3	41.8–46.0	43.4–46.2
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	48.9	48.5	48.8
95% confidence interval	45.1–52.7	44.3–52.7	46.0–51.6
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	55.7	57.2	56.4
95% confidence interval	50.5–61.0	51.6–62.8	52.6–60.2

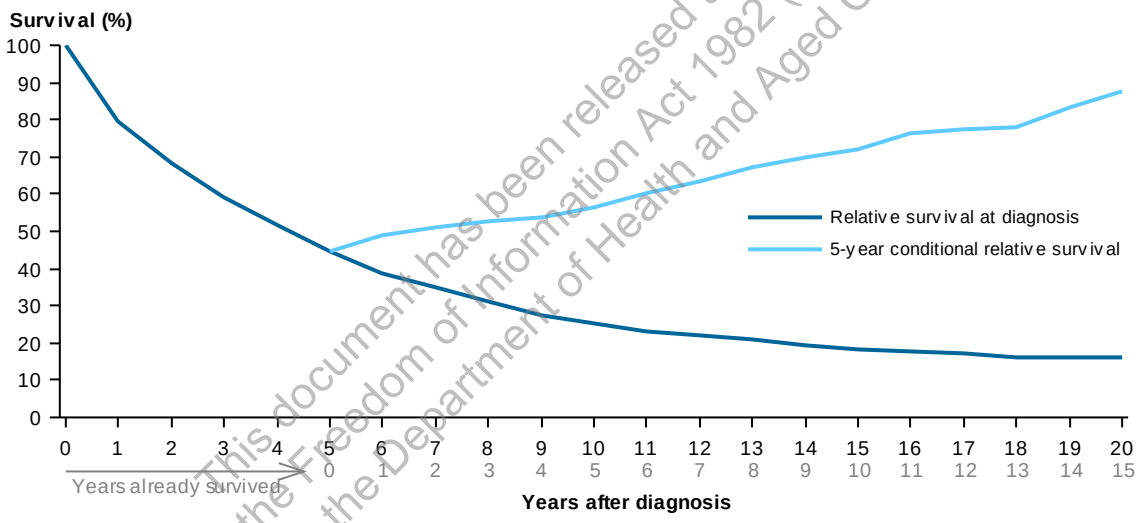


Figure B22(c): Relative survival at diagnosis and 5-year conditional survival from myeloma, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Myeloproliferative cancers excluding CML (C94.1, C94.3, C96.2, D45, D47.1, D47.3)

Table B23(a): Incidence and mortality of myeloproliferative cancers excluding CML

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	359	293	651	80	81	161
Crude rate	3.2	2.6	2.9	0.7	0.7	0.7
ASR	3.2	2.3	2.7	0.7	0.5	0.6
Risk to age 75	1 in 471	1 in 628	1 in 539	1 in 3,781	1 in 4,495	1 in 4,109
Risk to age 85	1 in 246	1 in 352	1 in 293	1 in 1,158	1 in 1,658	1 in 1,385
Mean age	65.1	65.6	65.3	77.4	82.4	79.9
Estimated number for 2014, 2015 and 2016[b]						
2014	320	300	625	95	95	190
2015	315	300	615	100	95	195
2016	310	300	610	100	100	200

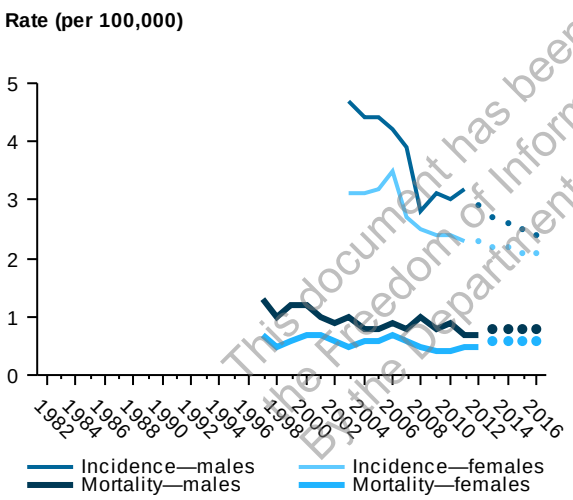


Figure B23(a): Incidence and mortality ASRs[a,b] of myeloproliferative cancers excluding CML, 1982–2016

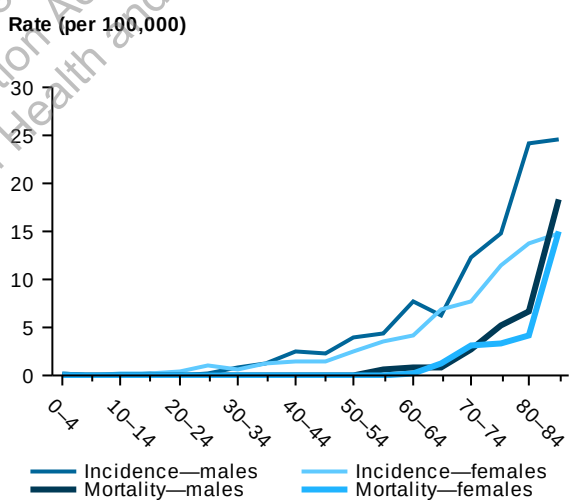


Figure B23(b): Incidence (2011) and mortality (2012) rates of other myeloproliferative cancers excluding CML, by age group

(a) 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2003–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B23(b): Survival and prevalence of myeloproliferative cancers excluding CML

	Males	Females	Persons
Prevalence as at the end of 2009[a]			
1-year prevalence	301	264	565
5-year prevalence	1,392	1,327	2,719
Relative survival in 2007–2011[b]			
1-year relative survival at diagnosis (%)	91.5	93.7	92.5
95% confidence interval	89.7–93.0	92.1–95.1	91.3–93.6
5-year relative survival at diagnosis (%)	71.8	81.7	76.4
95% confidence interval	69.2–74.3	79.0–84.1	74.5–78.2
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	74.6	82.7	78.4
95% confidence interval	71.6–77.6	80.0–85.4	76.4–80.4
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	77.1	80.1	78.5
95% confidence interval	73.2–80.9	76.3–83.8	75.8–81.2

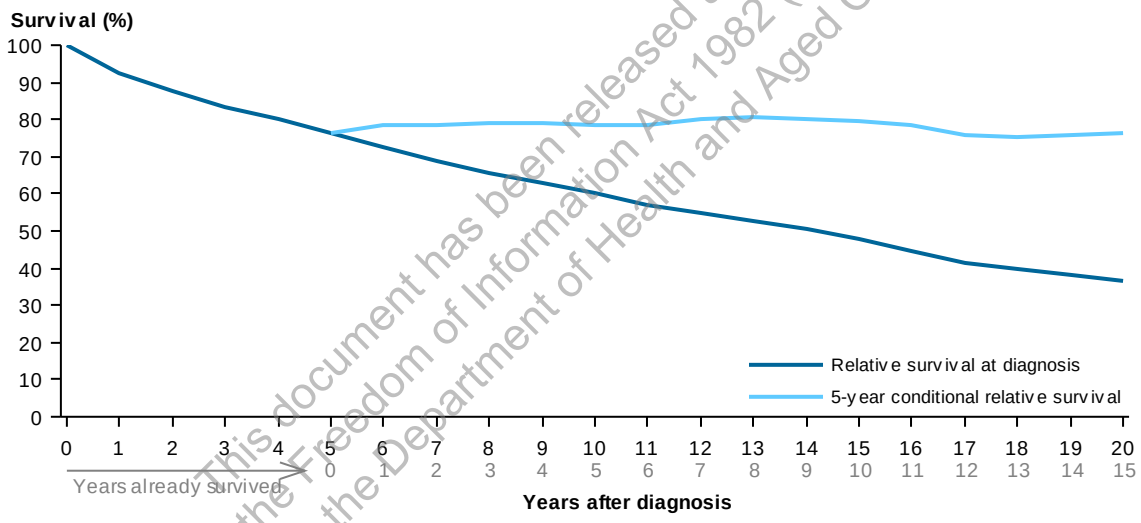


Figure B23(c): Relative survival at diagnosis and 5-year conditional survival from myeloproliferative cancers excluding CML, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Non-Hodgkin lymphoma (C82–C85)

Risk factor[a]**:** 

Table B24(a): Incidence and mortality of non–Hodgkin lymphoma

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	2,639	1,992	4,631	820	582	1,402
Crude rate	23.7	17.8	20.7	7.2	5.1	6.2
ASR	23.1	15.5	19.1	7.1	4.0	5.4
Risk to age 75	1 in 59	1 in 88	1 in 71	1 in 262	1 in 514	1 in 348
Risk to age 85	1 in 34	1 in 50	1 in 41	1 in 99	1 in 174	1 in 128
Mean age	64.3	66.8	65.4	73.7	76.3	74.7
Estimated number for 2014, 2015 and 2016[c]						
2014	2,780	2,170	4,940	830	605	1,435
2015	2,850	2,220	5,070	840	600	1,440
2016	2,930	2,270	5,200	850	595	1,445

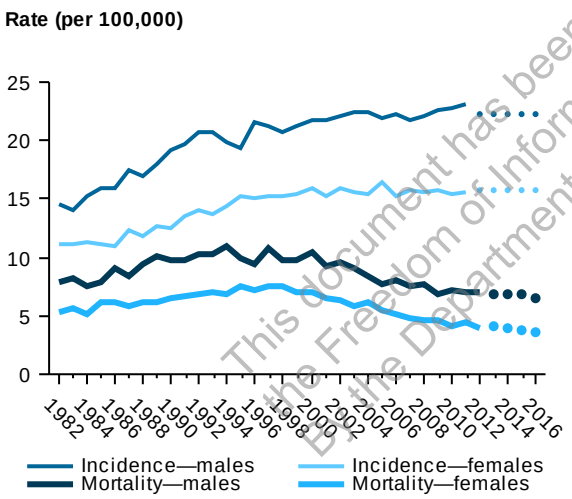


Figure B24(a): Incidence and mortality ASRs[b,c] **of non-Hodgkin lymphoma, 1982–2016**

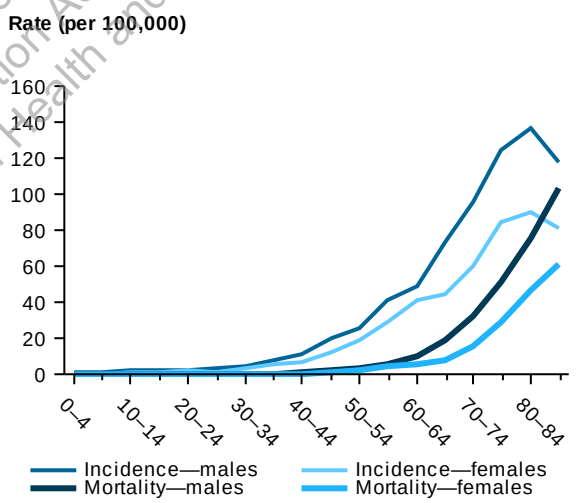


Figure B24(b): Incidence (2011) and mortality (2012) rates of non-Hodgkin lymphoma, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B24(b): Survival and prevalence of non–Hodgkin lymphoma

	Males	Females	Persons
Prevalence as at the end of 2009[(b)]			
1-year prevalence	2,191	1,671	3,862
5-year prevalence	8,440	6,851	15,291
Relative survival in 2007–2011[(c)]			
1-year relative survival at diagnosis (%)	84.3	83.9	84.1
95% confidence interval	83.6–85.1	83.0–84.7	83.6–84.7
5-year relative survival at diagnosis (%)	71.4	72.9	72.1
95% confidence interval	70.3–72.4	71.8–74.0	71.3–72.8
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	81.7	84.8	83.1
95% confidence interval	80.6–82.8	83.7–85.9	82.3–83.9
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	86.9	89.0	87.9
95% confidence interval	85.7–88.1	87.7–90.2	87.0–88.7

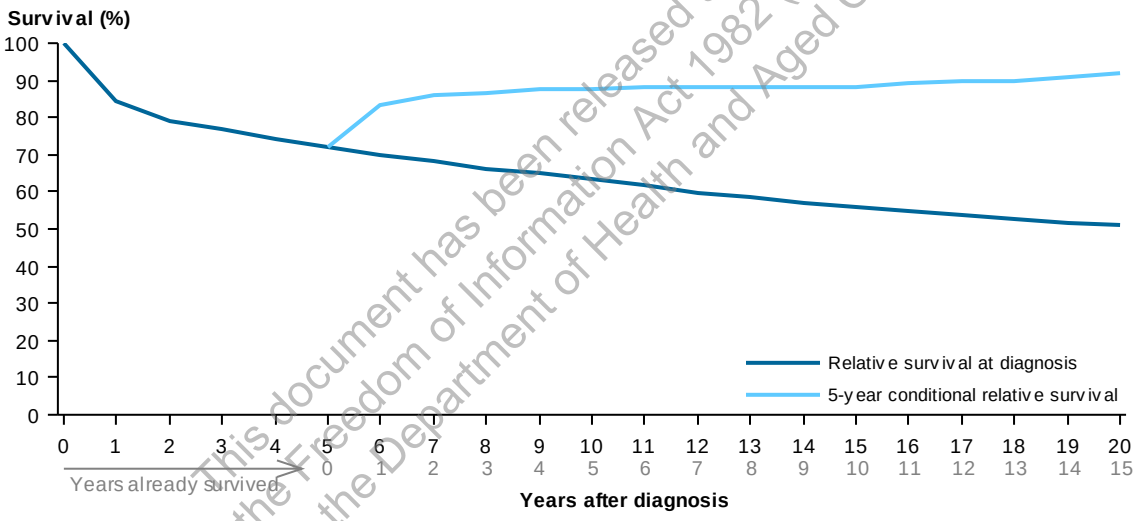


Figure B24(c): Relative survival at diagnosis and 5-year conditional survival from non–Hodgkin lymphoma, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Non-melanoma skin cancer (C44)

Risk factors[a]**:**

Table B25(a): Incidence and mortality of non-melanoma skin cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	487	282	769	362	159	521
Crude rate	4.4	2.5	3.4	3.2	1.4	2.3
ASR	4.4	2.1	3.1	3.2	1.0	1.9
Risk to age 75	1 in 421	1 in 763	1 in 544	1 in 715	1 in 3,521	1 in 1,197
Risk to age 85	1 in 170	1 in 368	1 in 239	1 in 265	1 in 889	1 in 424
Mean age	70.7	70.8	70.8	76.3	84.0	78.7
Estimated number for 2014, 2015 and 2016[c]						
2014	530	315	845	345	175	520
2015	545	325	870	355	180	535
2016	565	330	895	360	185	545

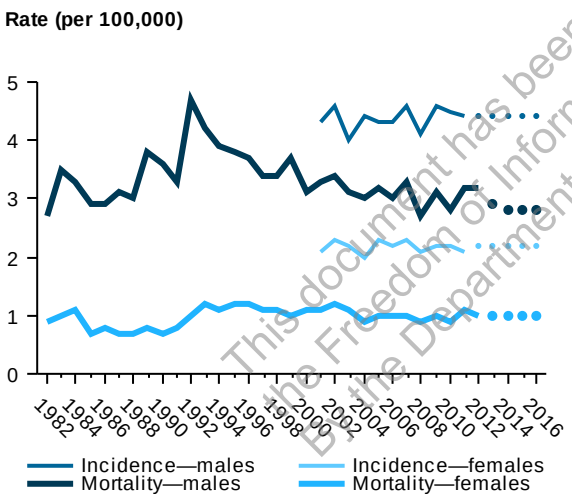


Figure B25(a): Incidence and mortality ASRs[b,c] **of non-melanoma skin cancer, 1982–2016**

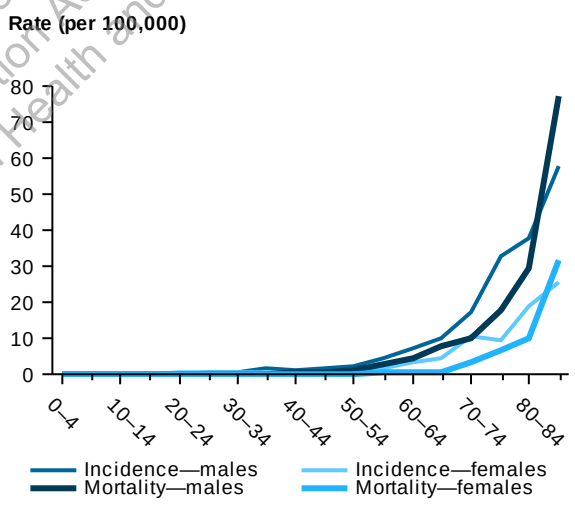


Figure B25(b): Incidence (2011) and mortality (2012) rates of non-melanoma skin cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) For incidence data, ICD-10 C44 codes that indicate a basal or squamous cell carcinoma of the skin are not included. The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B25(b): Survival and prevalence of non-melanoma skin cancer[a]

	Males	Females	Persons
Prevalence as at the end of 2009[b]			
1-year prevalence	437	255	692
5-year prevalence	1,557	993	2,550
Relative survival in 2007–2011[c]			
1-year relative survival at diagnosis (%)	89.3	88.2	88.9
95% confidence interval	87.6–90.9	85.9–90.2	87.5–90.1
5-year relative survival at diagnosis (%)	70.0	73.7	71.5
95% confidence interval	67.2–72.7	70.4–76.9	69.4–73.5
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	77.5	81.7	79.2
95% confidence interval	74.4–80.6	78.3–85.1	76.9–81.5
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	89.7	92.2	90.8
95% confidence interval	86.5–92.8	89.0–95.4	88.6–93.1

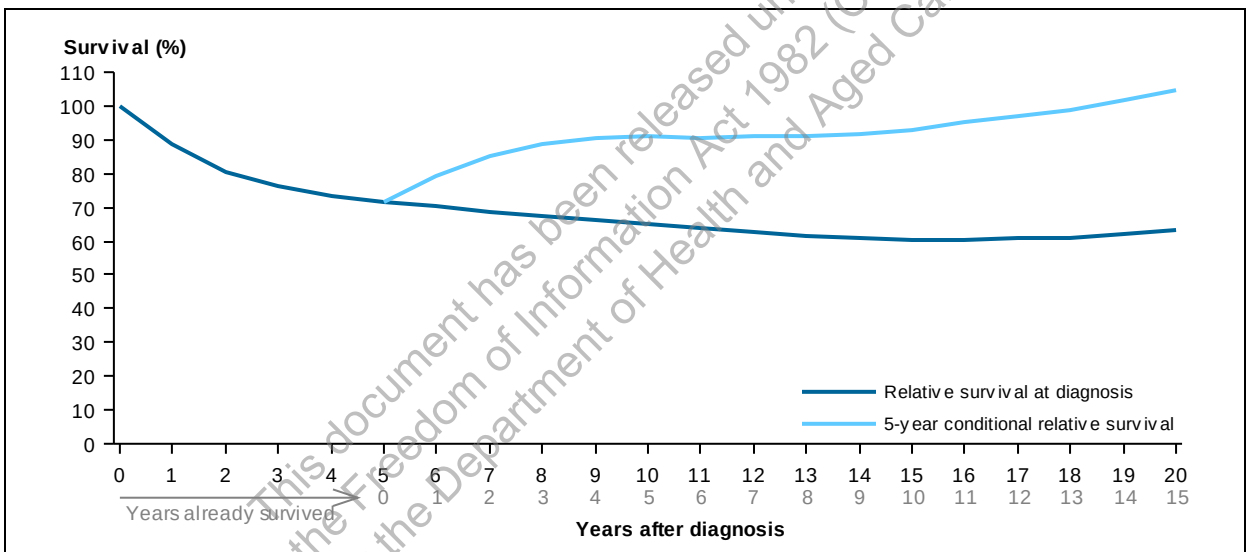


Figure B25(c): Relative survival at diagnosis and 5-year conditional survival from non-melanoma skin cancer, Australia, 2007–2011

(a) For survival and prevalence data, those ICD-10 C44 codes that indicate a basal or squamous cell carcinoma of the skin are not included.

(b) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(c) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Oesophageal cancer (C15)

Risk factors[a]:

Table B26(a): Incidence and mortality of oesophageal cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	991	404	1,395	879	324	1,203
Crude rate	8.9	3.6	6.2	7.8	2.8	5.3
ASR	8.6	3.0	5.6	7.4	2.2	4.7
Risk to age 75	1 in 159	1 in 559	1 in 249	1 in 201	1 in 876	1 in 329
Risk to age 85	1 in 85	1 in 230	1 in 127	1 in 97	1 in 339	1 in 155
Mean age	69.5	74.8	71.0	70.5	76.4	72.1
Estimated number for 2014, 2015 and 2016[c]						
2014	1,070	455	1,530	975	380	1,355
2015	1,110	465	1,570	1,000	385	1,385
2016	1,140	475	1,610	1,020	395	1,415

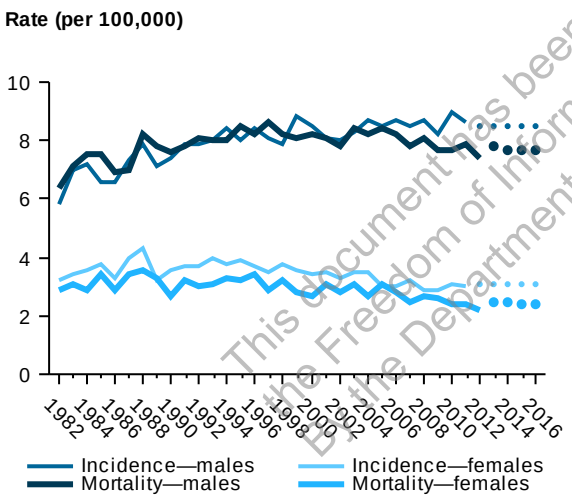


Figure B26(a): Incidence and mortality ASRs[b,c] **of oesophageal cancer, 1982–2016**

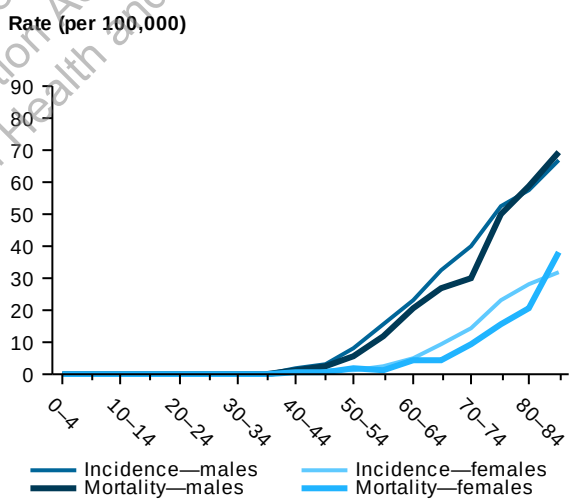


Figure B26(b): Incidence (2011) and mortality (2012) rates of oesophageal cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B26(b): Survival and prevalence of oesophageal cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	644	255	899
5-year prevalence	1,414	567	1,981
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	47.3	44.9	46.6
95% confidence interval	45.8–48.9	42.4–47.3	45.3–47.9
5-year relative survival at diagnosis (%)	17.3	18.0	17.5
95% confidence interval	16.1–18.6	16.1–20.0	16.5–18.6
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	34.3	38.4	35.6
95% confidence interval	28.4–40.2	30.2–46.7	30.7–40.4
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	77.6	77.6	77.5
95% confidence interval	72.4–82.7	70.8–84.5	73.4–81.7

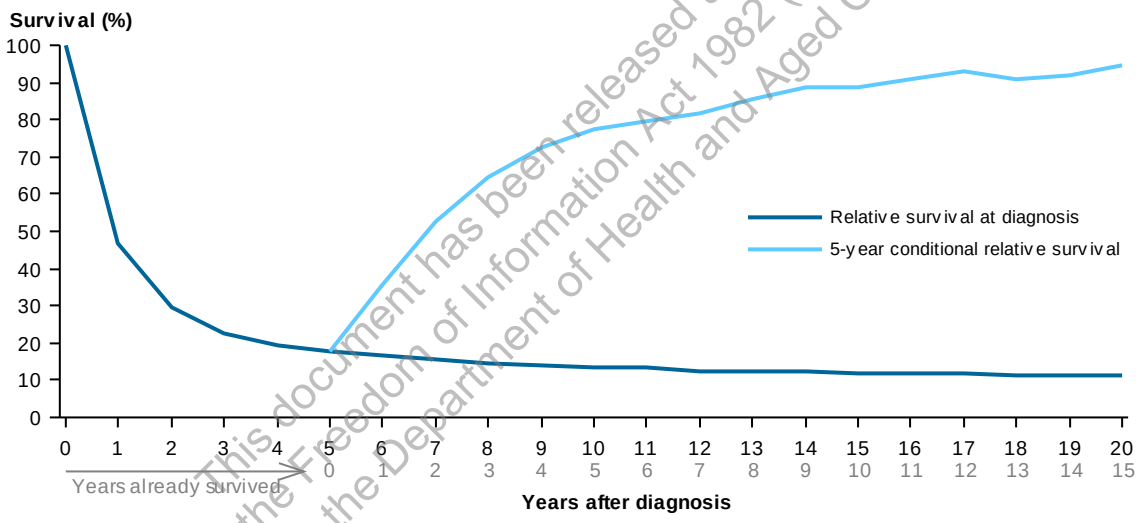


Figure B26(c): Relative survival at diagnosis and 5-year conditional survival from oesophageal cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Cancer of other digestive organs (C26)

Table B27(a): Incidence and mortality of cancer of other digestive organs

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	81	104	185	646	594	1,240
Crude rate	0.7	0.9	0.8	5.7	5.2	5.5
ASR	0.7	0.7	0.7	5.7	4.0	4.7
Risk to age 75	1 in 2,917	1 in 4,390	1 in 3,514	1 in 375	1 in 569	1 in 453
Risk to age 85	1 in 1,132	1 in 1,310	1 in 1,210	1 in 136	1 in 199	1 in 164
Mean age	74.5	80.8	78.1	74.8	78.4	76.5
Estimated number for 2014, 2015 and 2016[b]						
2014	85	110	195	740	680	1,420
2015	90	110	200	765	695	1,460
2016	95	115	205	790	715	1,505

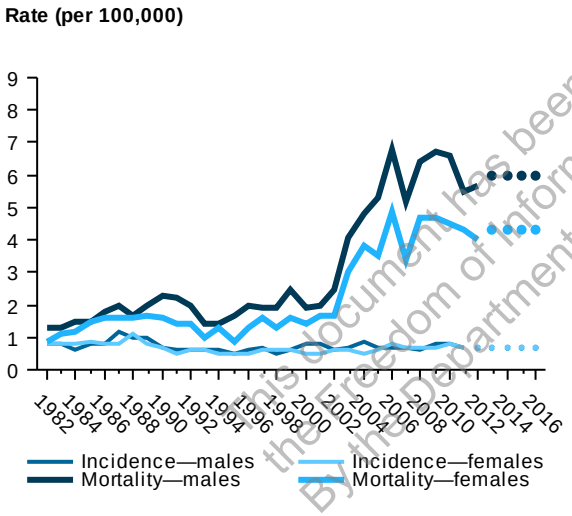


Figure B27(a): Incidence and mortality ASRs[a,b] of cancer of other digestive organs, 1982–2016

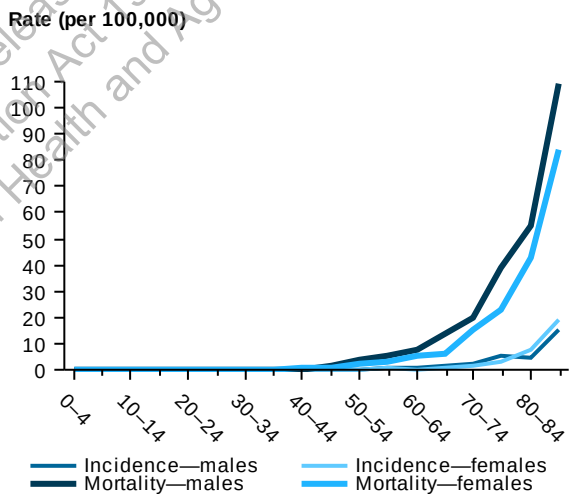


Figure B27(b): Incidence (2011) and mortality (2012) rates of cancer of other digestive organs, by age group

(a) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B27(b): Survival and prevalence of other digestive organs

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	32	31	63
5-year prevalence	76	70	146
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	21.3	19.4	20.3
95% confidence interval	16.4–26.7	15.1–24.3	17.0–23.8
5-year relative survival at diagnosis (%)	12.9	11.3	12.1
95% confidence interval	9.1–17.5	7.8–15.5	9.4–15.1
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	54.4	49.0	51.9
95% confidence interval	32.3–76.5	24.2–73.8	35.3–68.4
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	68.8	90.5	79.4
95% confidence interval	45.0–92.5	74.7–106.3	65.2–93.6

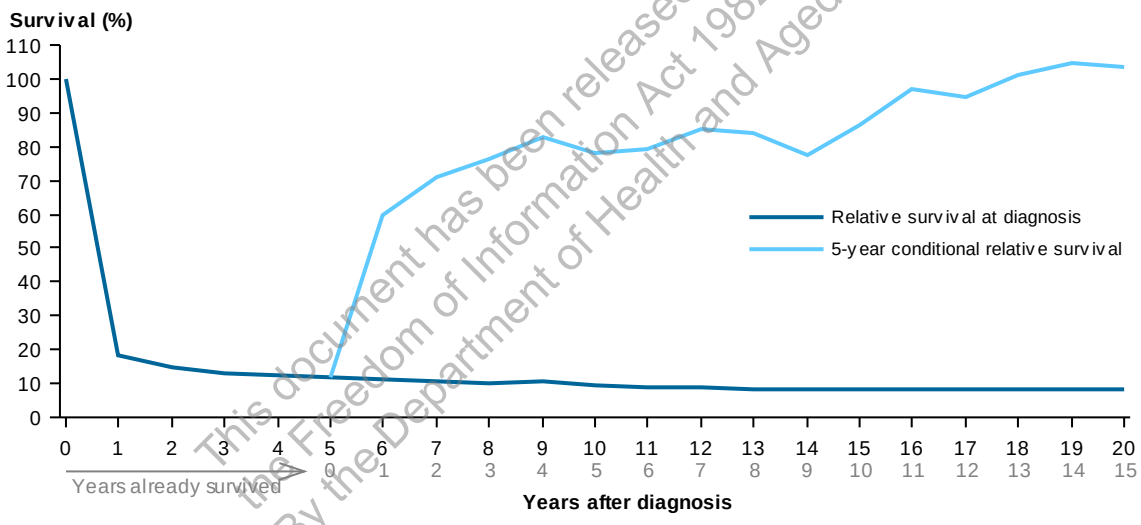


Figure B27(c): Relative survival at diagnosis and 5-year conditional survival from other digestive organs, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Other soft tissue cancers (C47, C49)

Table B28(a): Incidence and mortality of other soft tissue cancers

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[a]						
Number	372	270	641	133	132	265
Crude rate	3.3	2.4	2.9	1.2	1.2	1.2
ASR	3.3	2.2	2.7	1.2	1.0	1.1
Risk to age 75	1 in 449	1 in 625	1 in 523	1 in 1,785	1 in 1,483	1 in 1,617
Risk to age 85	1 in 270	1 in 412	1 in 330	1 in 578	1 in 784	1 in 682
Mean age	58.8	60.5	59.5	66.6	68.2	67.4
Estimated number for 2014, 2015 and 2016[b]						
2014	370	280	650	155	130	285
2015	380	285	665	155	135	290
2016	390	290	685	160	135	295

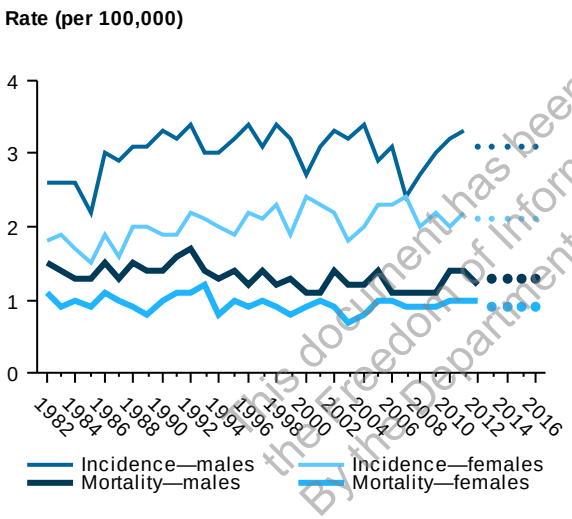


Figure B28(a): Incidence and mortality ASRs[a,b] of other soft tissue cancers, 1982–2016

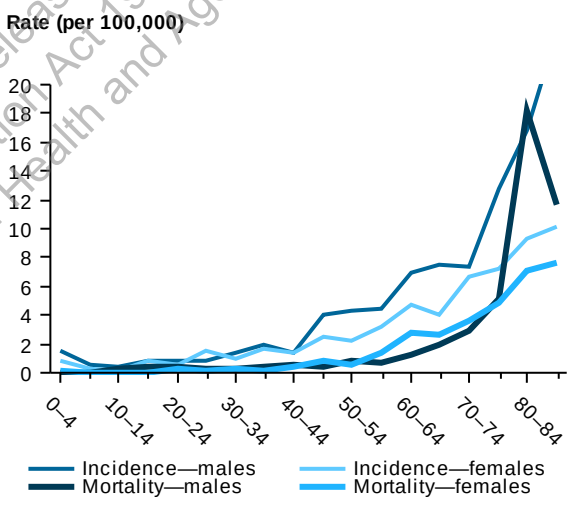


Figure B28(b): Incidence (2011) and mortality (2012) rates of other soft tissue cancers, by age group

(a) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(b) The 2012–2016 estimates for incidence are based on 2003–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B28(b): Survival and prevalence of other soft tissue cancers

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	283	241	524
5-year prevalence	1,038	944	1,982
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	83.0	84.9	83.9
95% confidence interval	80.8–85.0	82.6–87.0	82.3–85.4
5-year relative survival at diagnosis (%)	65.0	67.7	66.2
95% confidence interval	62.1–67.8	64.6–70.7	64.1–68.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	76.8	76.7	76.8
95% confidence interval	73.6–80.0	73.3–80.1	74.5–79.1
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	90.5	90.2	90.4
95% confidence interval	87.7–93.2	87.3–93.0	88.4–92.4

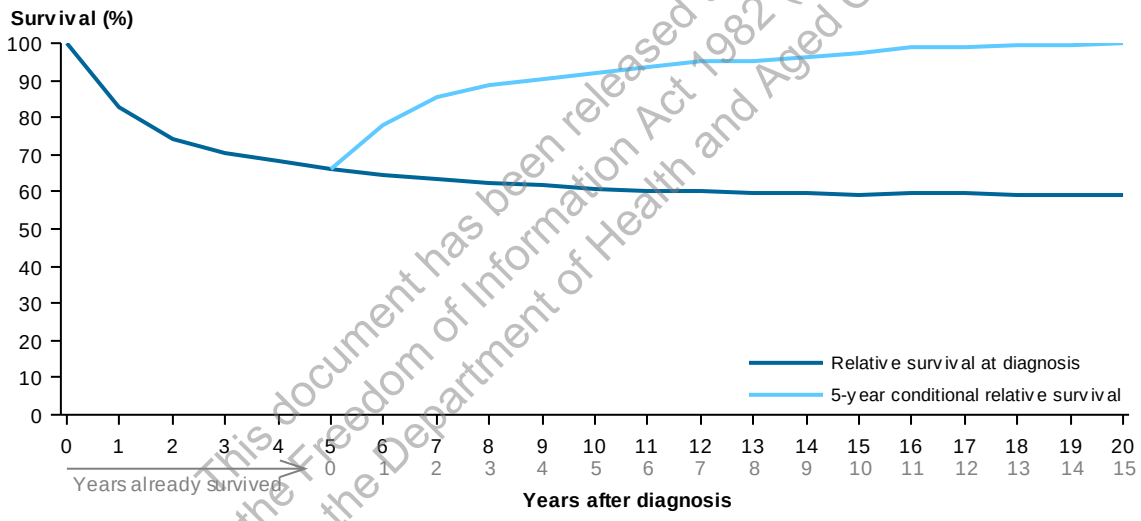


Figure B28(c): Relative survival at diagnosis and 5-year conditional survival from other soft tissue cancers, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Ovarian cancer (C56)

Risk factors[a]**:** 

Table B29(a): Incidence and mortality of ovarian cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	. .	1,330	1,330	. .	933	933
Crude rate	. .	11.9	. .	. .	8.2	. .
ASR	. .	10.4	. .	. .	6.7	. .
Risk to age 75	. .	1 in 125	. .	. .	1 in 208	. .
Risk to age 85	. .	1 in 81	. .	. .	1 in 111	. .
Mean age	. .	64.5	. .	. .	71.5	. .
Estimated number for 2014, 2015 and 2016[c]						
2014	. .	1,430	1,430	. .	1,000	1,000
2015	. .	1,460	1,460	. .	1,020	1,020
2016	. .	1,480	1,480	. .	1,040	1,040

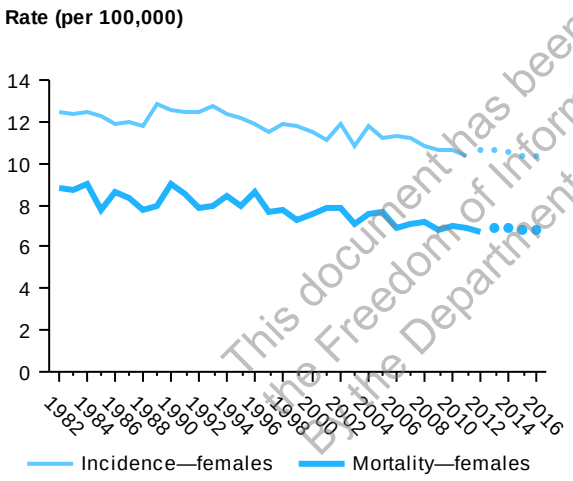


Figure B29(a): Incidence and mortality ASRs[b,c] **of ovarian cancer, 1982–2016**

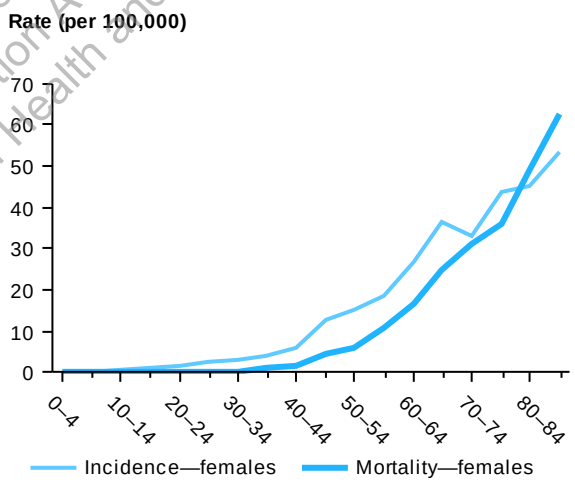


Figure B29(b): Incidence (2011) and mortality (2012) rates of ovarian cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B29(b): Survival and prevalence of ovarian cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	. .	1,054	1,054
5-year prevalence	. .	3,806	3,806
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	. .	76.0	76.0
95% confidence interval	. .	74.8–77.1	74.8–77.1
5-year relative survival at diagnosis (%)	. .	43.0	43.0
95% confidence interval	. .	41.7–44.3	41.7–44.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	. .	52.5	52.5
95% confidence interval	. .	50.0–55.0	50.0–55.0
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	. .	78.1	78.1
95% confidence interval	. .	76.0–80.2	76.0–80.2

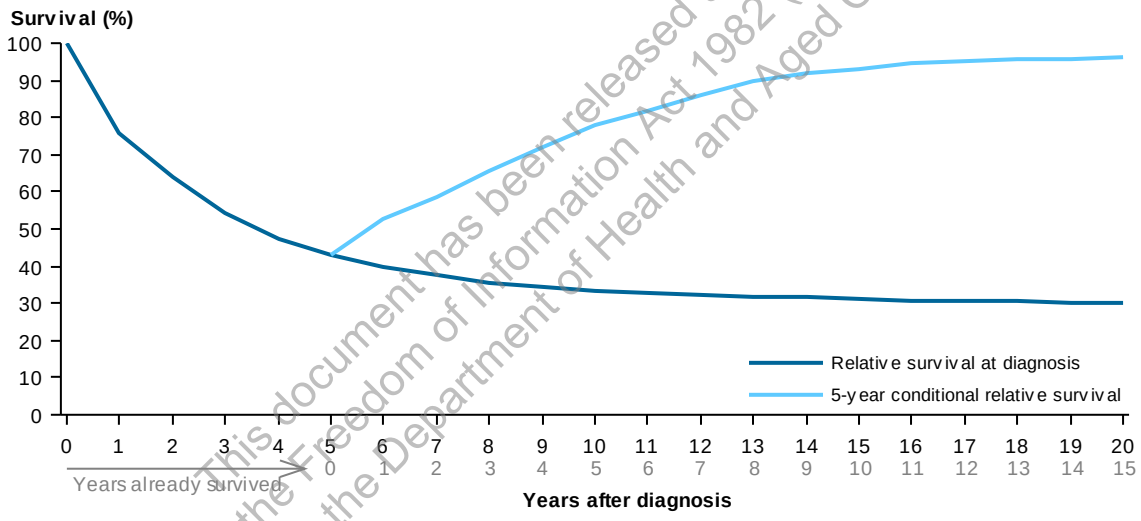


Figure B29(c): Relative survival at diagnosis and 5-year conditional survival from ovarian cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Pancreatic cancer (C25)

Risk factors[a]**:**

Table B30(a): Incidence and mortality of pancreatic cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	1,425	1,322	2,748	1,331	1,193	2,524
Crude rate	12.8	11.8	12.3	11.8	10.5	11.1
ASR	12.5	9.8	11.0	11.3	8.4	9.8
Risk to age 75	1 in 116	1 in 158	1 in 134	1 in 135	1 in 202	1 in 162
Risk to age 85	1 in 56	1 in 71	1 in 63	1 in 63	1 in 83	1 in 72
Mean age	70.6	73.5	72.0	71.6	74.9	73.2
Estimated number for 2014, 2015 and 2016[c]						
2014	1,530	1,410	2,940	1,360	1,280	2,640
2015	1,570	1,460	3,030	1,400	1,310	2,710
2016	1,620	1,500	3,120	1,450	1,350	2,800

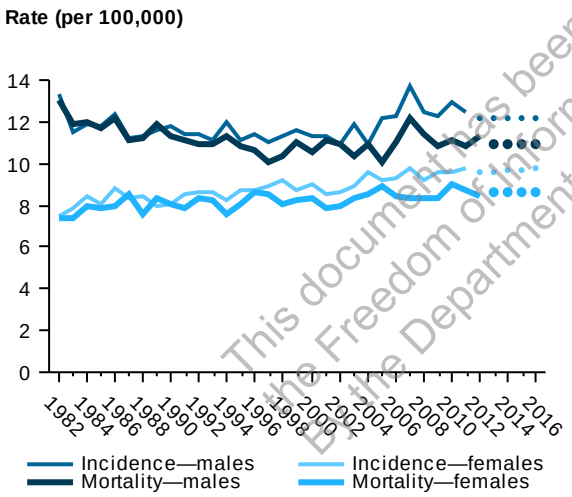


Figure B30(a): Incidence and mortality ASRs[b,c] **of pancreatic cancer, 1982–2016**

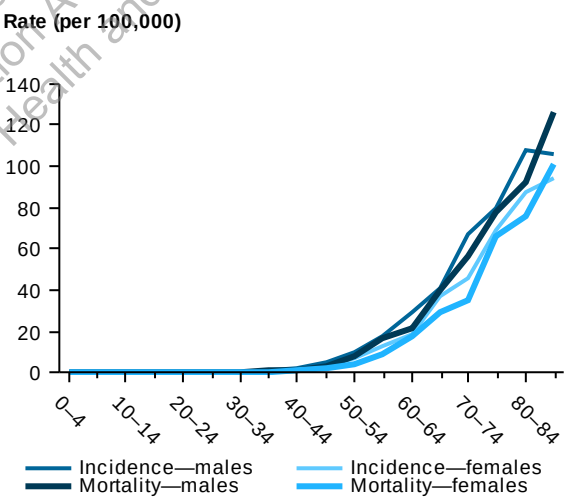


Figure B30(b): Incidence (2011) and mortality (2012) rates of pancreatic cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B30(b): Survival and prevalence of pancreatic cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	657	613	1,270
5-year prevalence	1,157	1,048	2,205
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	24.8	23.7	24.2
95% confidence interval	23.7–25.8	22.6–24.8	23.5–25.0
5-year relative survival at diagnosis (%)	6.0	6.2	6.1
95% confidence interval	5.3–6.6	5.5–6.9	5.6–6.6
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	22.7	23.7	23.2
95% confidence interval	14.1–31.3	15.0–32.5	17.0–29.3
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	75.6	75.4	75.5
95% confidence interval	67.7–83.5	67.8–83.0	70.0–81.0

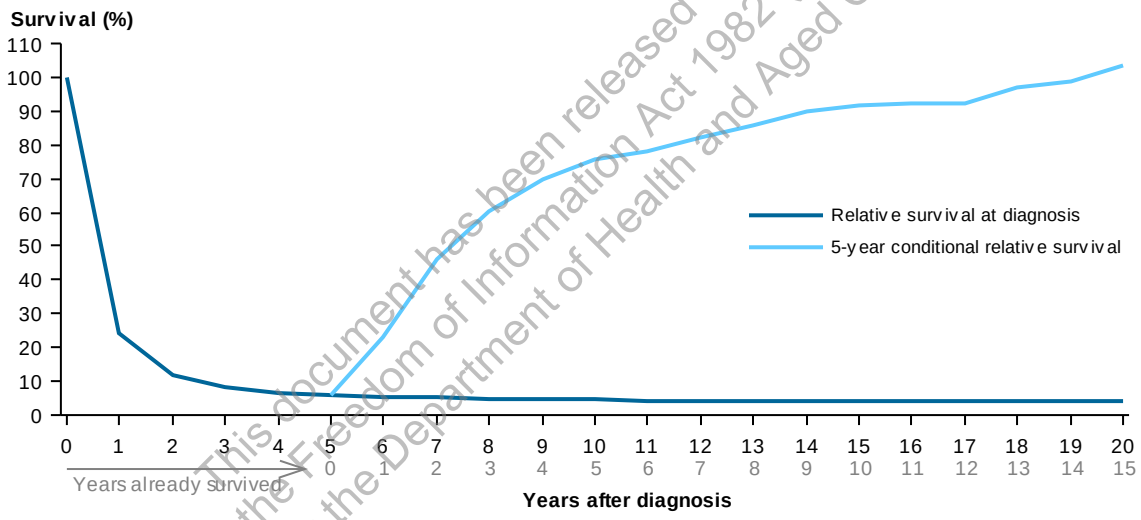


Figure B30(c): Relative survival at diagnosis and 5-year conditional survival from pancreatic cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Prostate cancer (C61)

Risk factors[a]**:**

Table B31(a): Incidence and mortality of prostate cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	19,993	. .	19,993	3,079	. .	3,079
Crude rate	179.8	. .	. .	27.2	. .	. .
ASR	167.3	. .	. .	27.6	. .	. .
Risk to age 75	1 in 7	. .	. .	1 in 119	. .	. .
Risk to age 85	1 in 5	. .	. .	1 in 28	. .	. .
Mean age	68.2	. .	. .	80.2	. .	. .
Estimated number for 2014, 2015 and 2016[c]						
2014	17,050	. .	17,050	3,390	. .	3,390
2015	17,250	. .	17,250	3,440	. .	3,440
2016	18,140	. .	18,140	3,500	. .	3,500

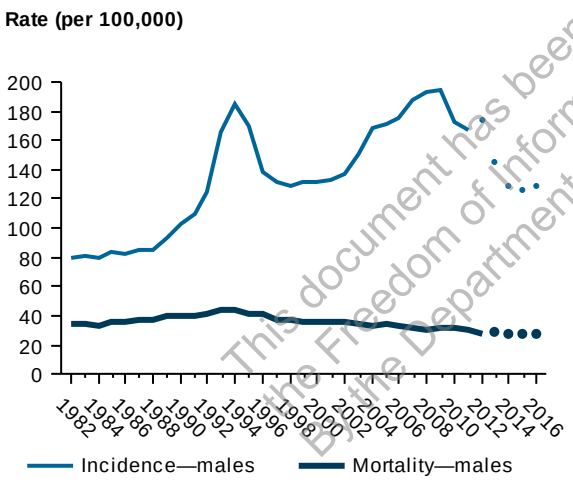


Figure B31(a): Incidence and mortality ASRs[b,c] **of prostate cancer, 1982–2016**

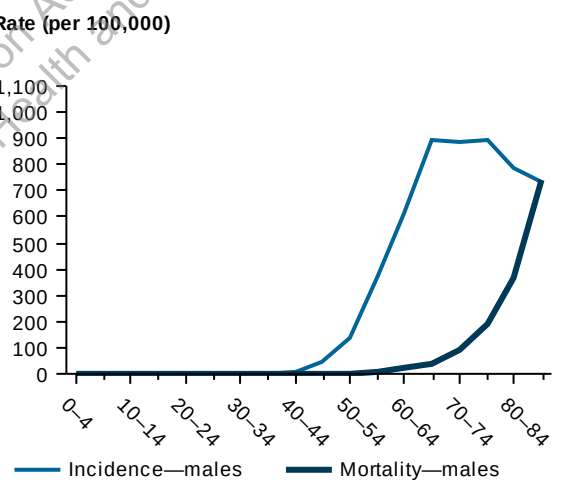


Figure B31(b): Incidence (2011) and mortality (2012) rates of prostate cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B31(b): Survival and prevalence of prostate cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	21,266	. .	21,266
5-year prevalence	86,207	. .	86,207
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	98.3	. .	98.3
95% confidence interval	98.1–98.4	. .	98.1–98.4
5-year relative survival at diagnosis (%)	93.2	. .	93.2
95% confidence interval	92.8–93.5	. .	92.8–93.5
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	93.6	. .	93.6
95% confidence interval	93.4–93.9	. .	93.4–93.9
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	92.6	. .	92.6
95% confidence interval	92.2–93.1	. .	92.2–93.1

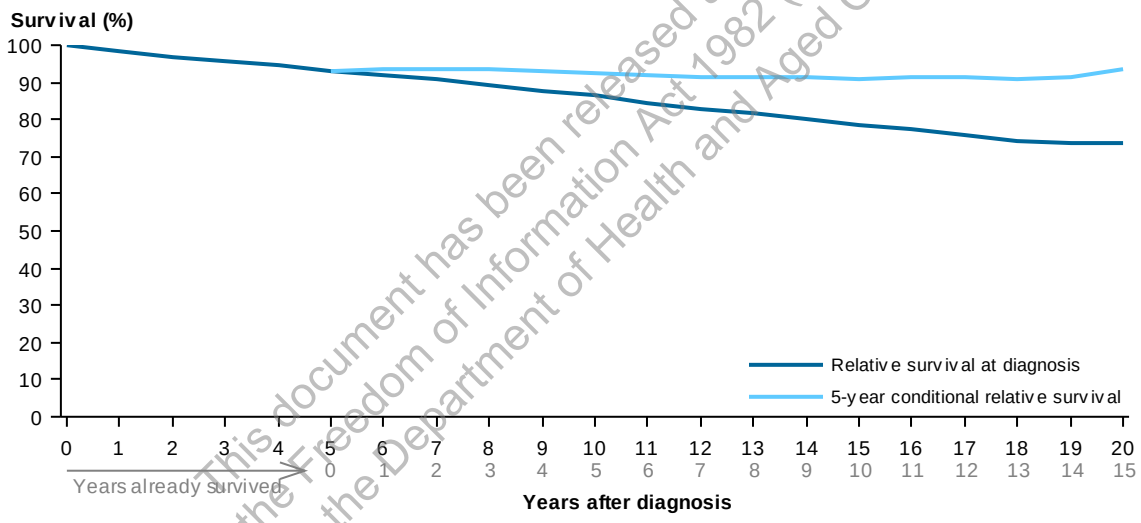


Figure B31(c): Relative survival at diagnosis and 5-year conditional survival from prostate cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Stomach cancer (C16)

Risk factors[a]**:**

Table B32(a): Incidence and mortality of stomach cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	1,357	736	2,093	707	436	1,143
Crude rate	12.2	6.6	9.4	6.3	3.8	5.0
ASR	11.9	5.5	8.5	6.1	3.1	4.5
Risk to age 75	1 in 125	1 in 268	1 in 171	1 in 261	1 in 610	1 in 367
Risk to age 85	1 in 60	1 in 138	1 in 86	1 in 123	1 in 248	1 in 168
Mean age	69.9	71.6	70.5	70.9	74.8	72.4
Estimated number for 2014, 2015 and 2016[c]						
2014	1,460	785	2,240	700	415	1,115
2015	1,480	800	2,280	695	415	1,110
2016	1,510	815	2,330	690	410	1,100

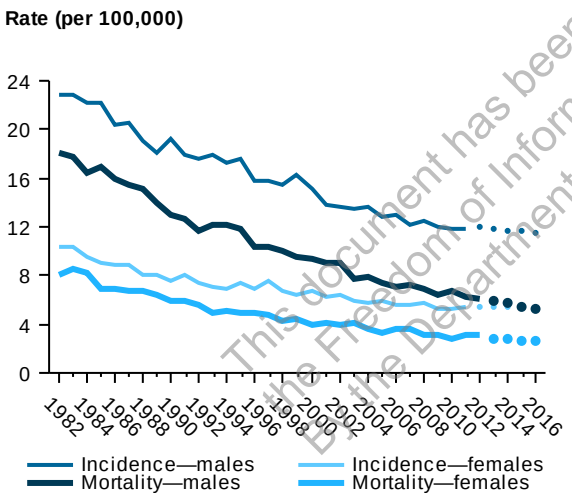


Figure B32(a): Incidence and mortality ASRs[b,c] **of stomach cancer, 1982–2016**

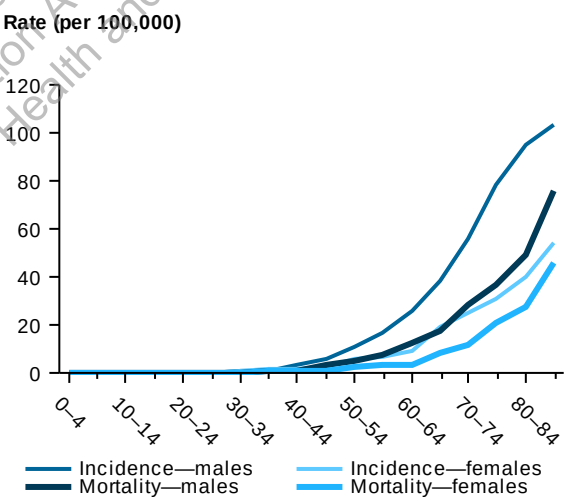


Figure B32(b): Incidence (2011) and mortality (2012) rates of stomach cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B32(b): Survival and prevalence of stomach cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	906	441	1,347
5-year prevalence	2,471	1,287	3,758
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	51.8	51.4	51.6
95% confidence interval	50.4–53.1	49.5–53.3	50.6–52.7
5-year relative survival at diagnosis (%)	26.4	28.3	27.0
95% confidence interval	25.1–27.6	26.6–30.1	26.0–28.0
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	49.2	53.7	50.7
95% confidence interval	45.7–52.7	49.3–58.0	48.0–53.5
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	87.4	90.7	88.6
95% confidence interval	84.6–90.3	87.5–93.9	86.5–90.8

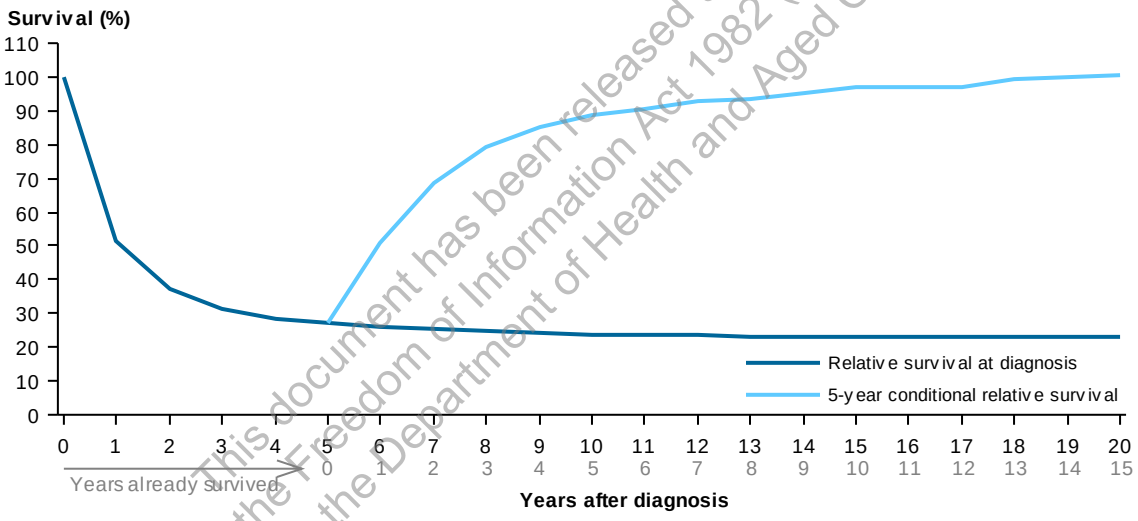


Figure B32(c): Relative survival at diagnosis and 5-year conditional survival from stomach cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Testicular cancer (C62)

Risk factor[a]**:**

Table B33(a): Incidence and mortality of testicular cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	732	. .	732	25	. .	25
Crude rate	6.6	. .	. .	0.2	. .	. .
ASR	6.7	. .	. .	0.2	. .	. .
Risk to age 75	1 in 215	. .	. .	1 in 6,334	. .	. .
Risk to age 85	1 in 208	. .	. .	1 in 5,440	. .	. .
Mean age	36.2	. .	. .	41.2	. .	. .
Estimated number for 2014, 2015 and 2016[c]						
2014	770	. .	770	5	. .	5
2015	780	. .	780	5	. .	5
2016	795	. .	795	5	. .	5

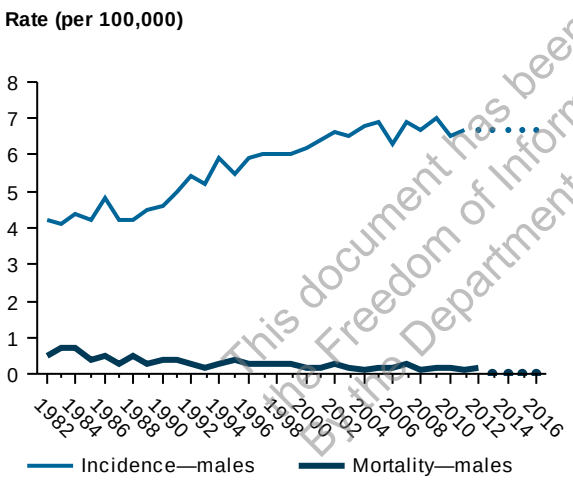


Figure B33(a): Incidence and mortality ASRs[b,c] **of testicular cancer, 1982–2016**

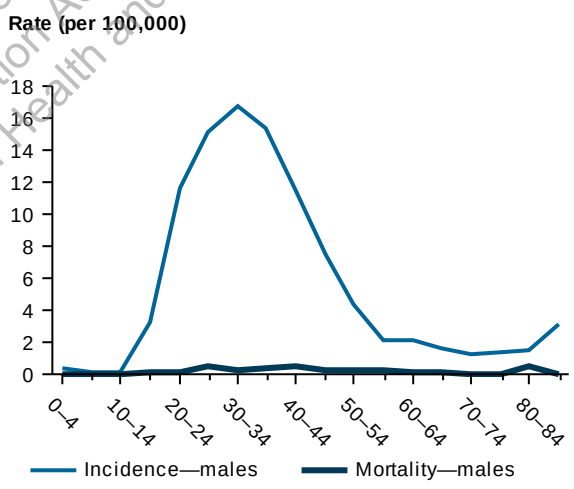


Figure B33(b): Incidence (2011) and mortality (2012) rates of testicular cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B33(b): Survival and prevalence of testicular cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	742		742
5-year prevalence	3,380		3,380
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	99.1	. .	99.1
95% confidence interval	98.6–99.4	. .	98.6–99.4
5-year relative survival at diagnosis (%)	97.9	. .	97.9
95% confidence interval	97.2–98.4	. .	97.2–98.4
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	98.8	. .	98.8
95% confidence interval	98.3–99.2	. .	98.3–99.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	99.7	. .	99.7
95% confidence interval	99.3–100.1	. .	99.3–100.1

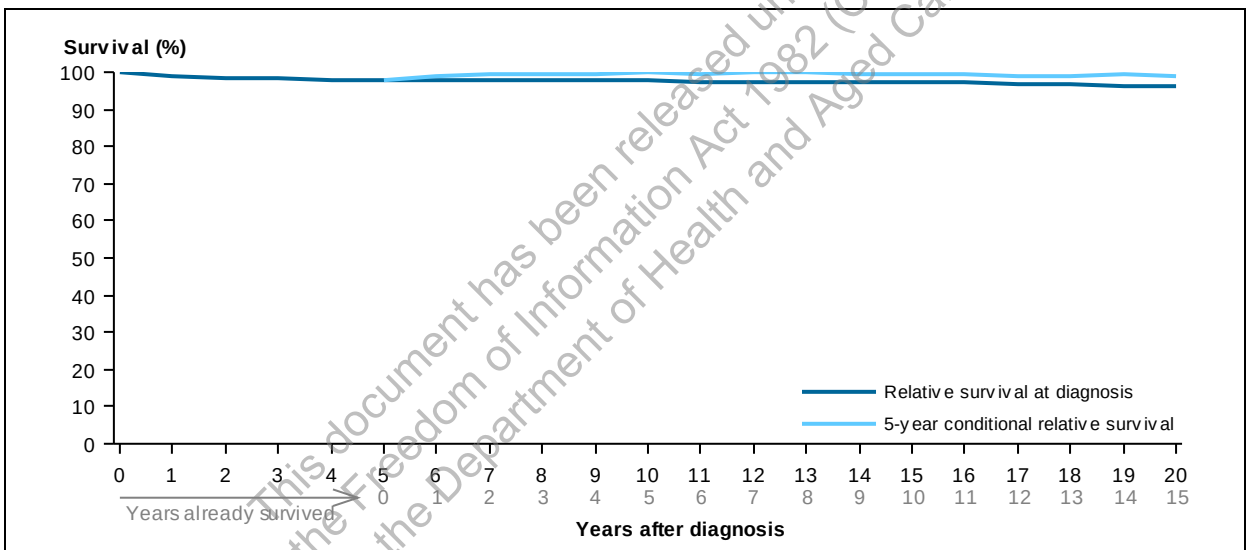


Figure B33(c): Relative survival at diagnosis and 5-year conditional survival from testicular cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Thyroid cancer (C73)

Risk factors[a]**:**

Table B34(a): Incidence and mortality of thyroid cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	580	1,518	2,098	67	59	126
Crude rate	5.2	13.5	9.4	0.6	0.5	0.6
ASR	5.1	13.1	9.1	0.6	0.4	0.5
Risk to age 75	1 in 246	1 in 97	1 in 139	1 in 3,311	1 in 4,750	1 in 3,909
Risk to age 85	1 in 190	1 in 85	1 in 117	1 in 1,215	1 in 1,801	1 in 1,469
Mean age	54.4	50.9	51.9	71.7	77.1	74.3
Estimated number for 2014, 2015 and 2016[c]						
2014	630	1,890	2,520	55	70	125
2015	660	1,980	2,640	55	70	125
2016	690	2,070	2,760	60	75	135

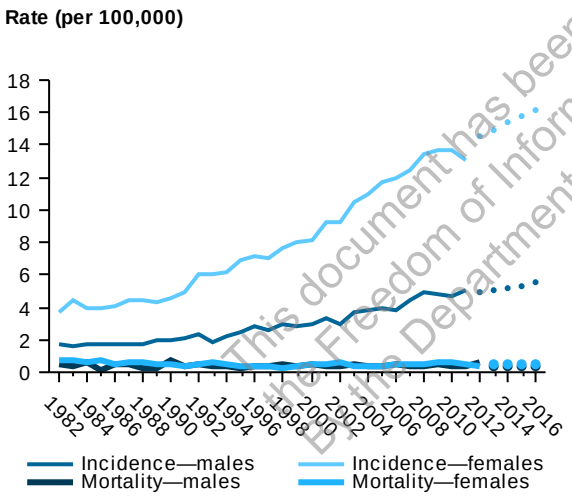


Figure B34(a): Incidence and mortality ASRs[b,c] **of thyroid cancer, 1982–2016**

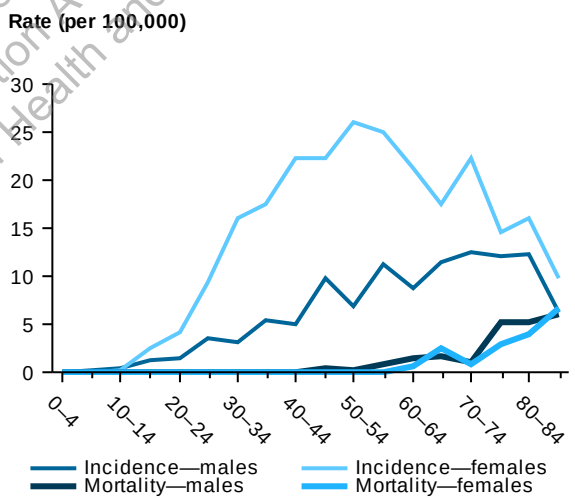


Figure B34(b): Incidence (2011) and mortality (2012) rates of thyroid cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B34(b): Survival and prevalence of thyroid cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	504	1,482	1,986
5-year prevalence	2,057	6,482	8,539
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	95.8	97.9	97.3
95% confidence interval	94.8–96.7	97.4–98.2	96.9–97.7
5-year relative survival at diagnosis (%)	92.1	97.0	95.8
95% confidence interval	90.5–93.6	96.3–97.5	95.2–96.3
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	95.1	98.9	98.0
95% confidence interval	93.8–96.4	98.5–99.4	97.6–98.5
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	96.0	99.4	98.6
95% confidence interval	94.5–97.6	98.8–99.9	98.1–99.1

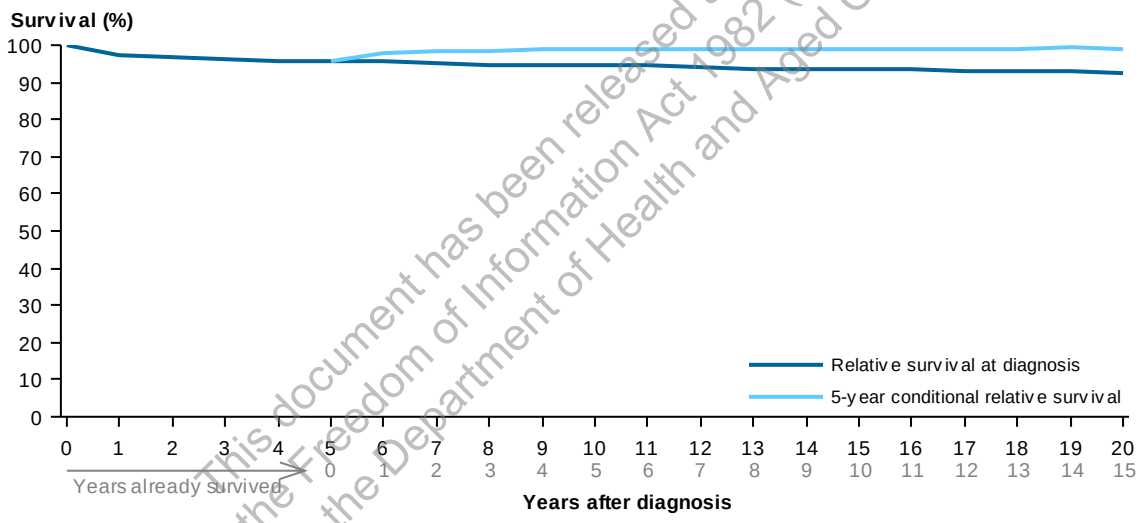


Figure B34(c): Relative survival at diagnosis and 5-year conditional survival from thyroid cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Tongue cancer (C01–C02)

Risk factors[a]**:**

Table B35(a): Incidence and mortality of tongue cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	474	215	689	128	82	210
Crude rate	4.3	1.9	3.1	1.1	0.7	0.9
ASR	4.0	1.7	2.8	1.1	0.6	0.8
Risk to age 75	1 in 288	1 in 859	1 in 433	1 in 1,201	1 in 2,405	1 in 1,608
Risk to age 85	1 in 210	1 in 474	1 in 293	1 in 646	1 in 1,201	1 in 850
Mean age	62.2	65.4	63.1	68.9	71.2	69.8
Estimated number for 2014, 2015 and 2016[c]						
2014	480	220	695	130	70	200
2015	490	225	715	135	75	210
2016	505	230	735	135	75	210

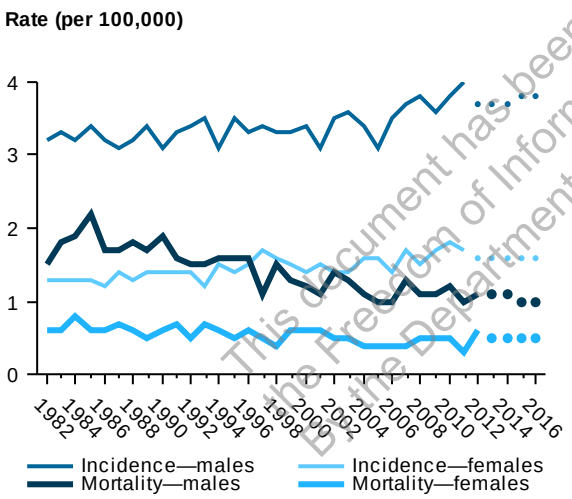


Figure B35(a): Incidence and mortality ASRs[b,c] **of tongue cancer, 1982–2016**

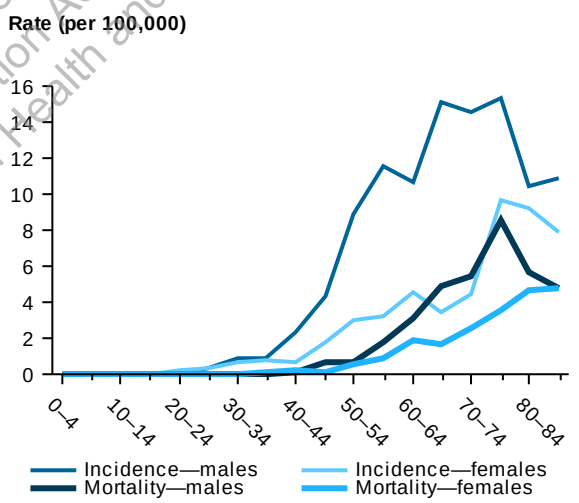


Figure B35(b): Incidence (2011) and mortality (2012) rates of tongue cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (see Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B35(b): Survival and prevalence of tongue cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	372	183	555
5-year prevalence	1,361	639	2,000
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	82.0	84.3	82.8
95% confidence interval	80.1–83.8	81.6–86.7	81.2–84.2
5-year relative survival at diagnosis (%)	61.9	66.0	63.2
95% confidence interval	59.4–64.4	62.3–69.5	61.2–65.2
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	72.8	74.6	73.4
95% confidence interval	69.6–75.9	70.3–78.9	70.8–75.9
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	80.8	85.4	82.4
95% confidence interval	77.2–84.5	80.9–89.8	79.6–85.2

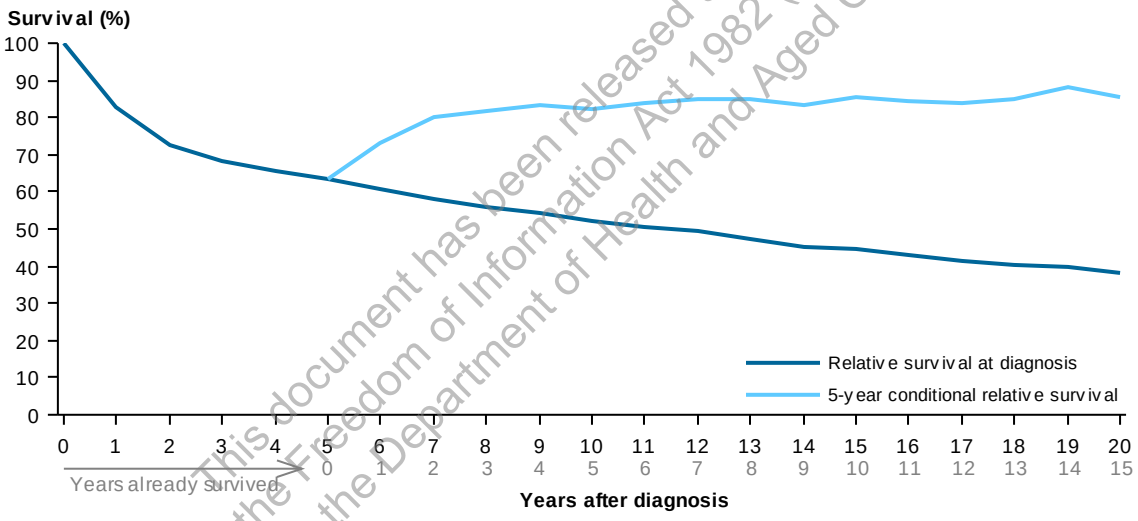


Figure B35(c): Relative survival at diagnosis and 5-year conditional survival from tongue cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Cancer of unknown primary site (C80)[a]

Table B36(a): Incidence and mortality of cancer of unknown primary site

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 incidence/2012 mortality[b]						
Number	1,495	1,307	2,802	1,089	1,044	2,133
Crude rate	13.4	11.6	12.5	9.6	9.1	9.4
ASR	13.4	9.2	11.1	9.4	7.0	8.1
Risk to age 75	1 in 142	1 in 216	1 in 172	1 in 221	1 in 311	1 in 259
Risk to age 85	1 in 57	1 in 82	1 in 68	1 in 79	1 in 112	1 in 94
Mean age	74.1	76.2	75.1	75.2	77.9	76.5
Estimated number for 2014, 2015 and 2016[c]						
2014	1,430	1,210	2,640	1,160	1,180	2,340
2015	1,430	1,190	2,620	1,140	1,190	2,330
2016	1,430	1,180	2,610	1,130	1,200	2,330

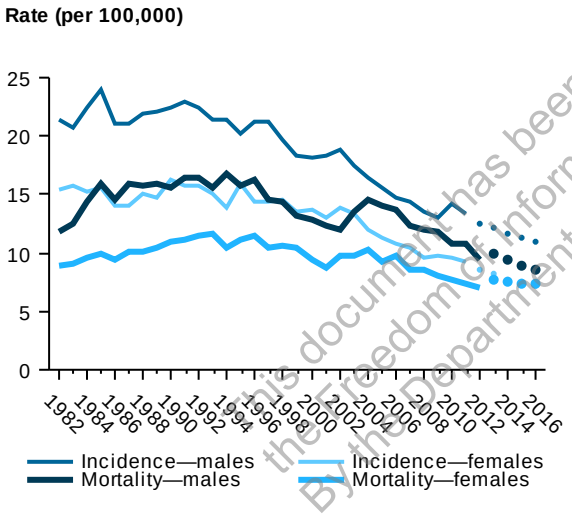


Figure B36(a): Incidence and mortality ASRs[b,c] of cancer of unknown primary site, 1982–2016

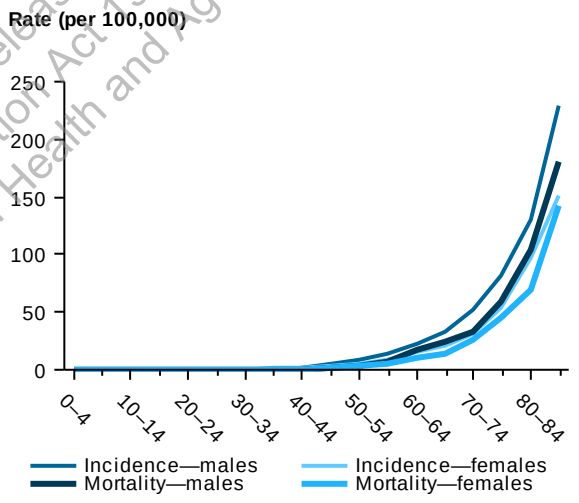


Figure B36(b): Incidence (2011) and mortality (2012) rates for cancer of unknown primary site, by age group

(a) For mortality data before 2008, the applicable codes are C77–C80.

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B36(b): Survival and prevalence of unknown primary site

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	564	504	1,068
5-year prevalence	1,682	1,329	3,011
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	24.6	18.8	21.8
95% confidence interval	23.5–25.7	17.7–19.8	21.1–22.6
5-year relative survival at diagnosis (%)	16.3	11.2	13.8
95% confidence interval	15.4–17.3	10.4–12.0	13.2–14.5
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	64.8	57.4	61.6
95% confidence interval	61.3–68.2	53.0–61.7	58.9–64.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	84.8	83.7	84.3
95% confidence interval	81.3–88.3	79.6–87.7	81.7–87.0

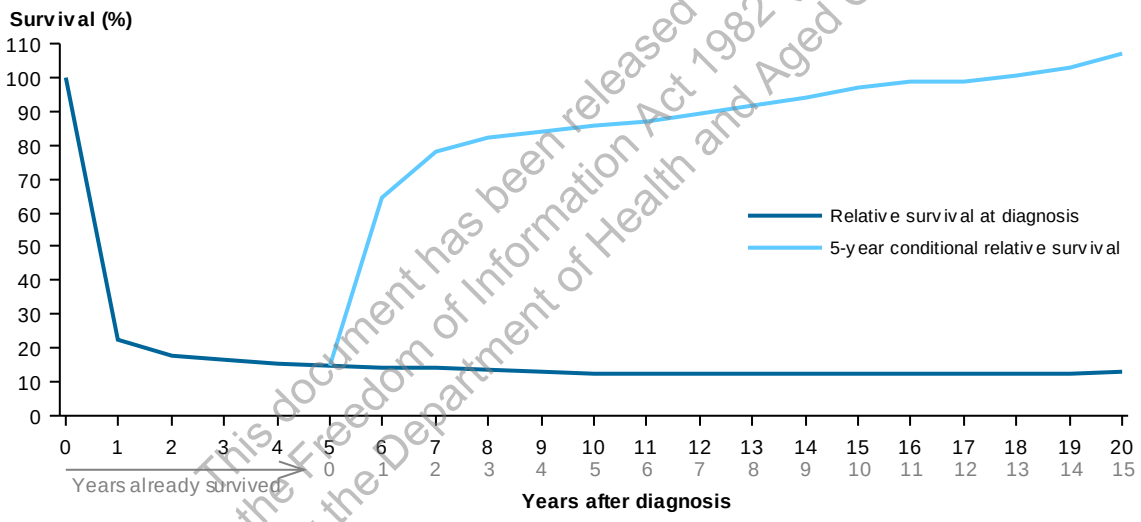


Figure B36(c): Relative survival at diagnosis and 5-year conditional survival from unknown primary site, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Uterine cancer (C54–C55)

Risk factor[a]**:**

Table B37(a): Incidence and mortality of uterine cancer

	Incidence			Mortality		
	Males	Females	Persons	Males	Females	Persons
2011 Incidence/2012 mortality[b]						
Number	. .	2,238	2,238	. .	421	421
Crude rate	. .	19.9	. .	. .	3.7	. .
ASR	. .	17.4	. .	. .	3.1	. .
Risk to age 75	. .	1 in 65	. .	. .	1 in 495	. .
Risk to age 85	. .	1 in 47	. .	. .	1 in 232	. .
Mean age	. .	65.0	. .	. .	72.4	. .
Estimated number for 2014, 2015 and 2016[c]						
2014	. .	2,490	2,490	. .	405	405
2015	. .	2,570	2,570	. .	415	415
2016	. .	2,650	2,650	. .	425	425

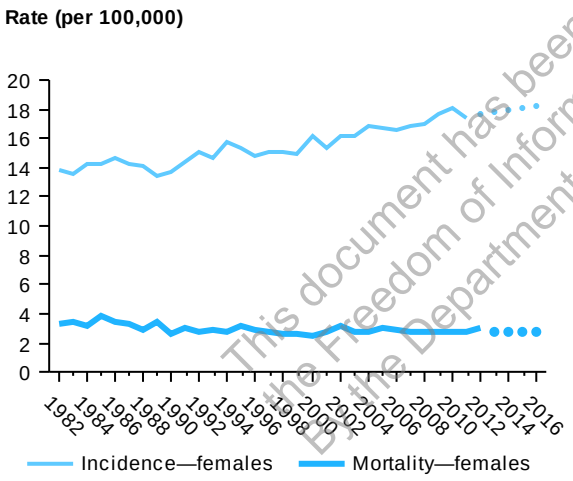


Figure B37(a): Incidence and mortality ASRs[b,c] **of uterine cancer, 1982–2016**

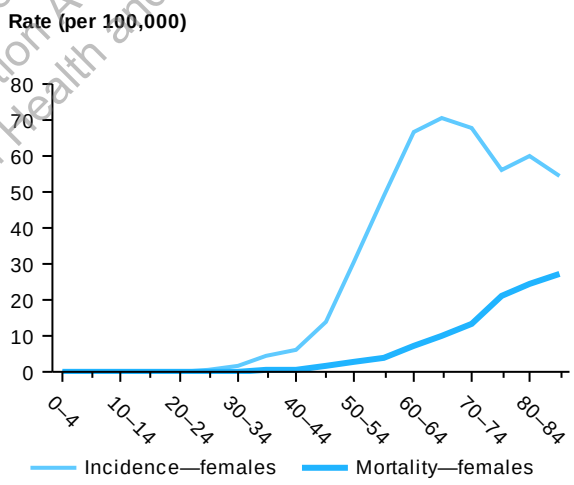


Figure B37(b): Incidence (2011) and mortality (2012) rates of uterine cancer, by age group

(a) Based on IARC (2014) and WCRF & AICR (2007) (See Chapter 2).

(b) The 2011 incidence data include estimates for NSW and the ACT. Mean age for 2011 incidence was calculated excluding NSW and the ACT (see Appendix F). Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS. ASRs were directly standardised to the Australian population as at 30 June 2001. Rates are expressed per 100,000 population.

(c) The 2012–2016 estimates for incidence are based on 2002–2011 incidence data. The 2013–2016 estimates for mortality are based on 2002–2012 mortality data (see Appendix G). They are rounded to the nearest 10. Estimates less than 1,000 are rounded to the nearest 5. The estimates for males and females may not add to estimates for persons due to rounding.

Sources: AIHW ACD 2011; AIHW NMD.

Table B37(b): Survival and prevalence of uterine cancer

	Males	Females	Persons
Prevalence as at the end of 2009[(a)]			
1-year prevalence	. .	2,040	2,040
5-year prevalence	. .	8,296	8,296
Relative survival in 2007–2011[(b)]			
1-year relative survival at diagnosis (%)	. .	93.6	93.6
95% confidence interval	. .	93.0–94.1	93.0–94.1
5-year relative survival at diagnosis (%)	. .	82.5	82.5
95% confidence interval	. .	81.5–83.4	81.5–83.4
5-year conditional relative survival for those already survived 1 year after diagnosis (%)	. .	87.3	87.3
95% confidence interval	. .	86.4–88.2	86.4–88.2
5-year conditional relative survival for those already survived 5 years after diagnosis (%)	. .	95.4	95.4
95% confidence interval	. .	94.6–96.3	94.6–96.3

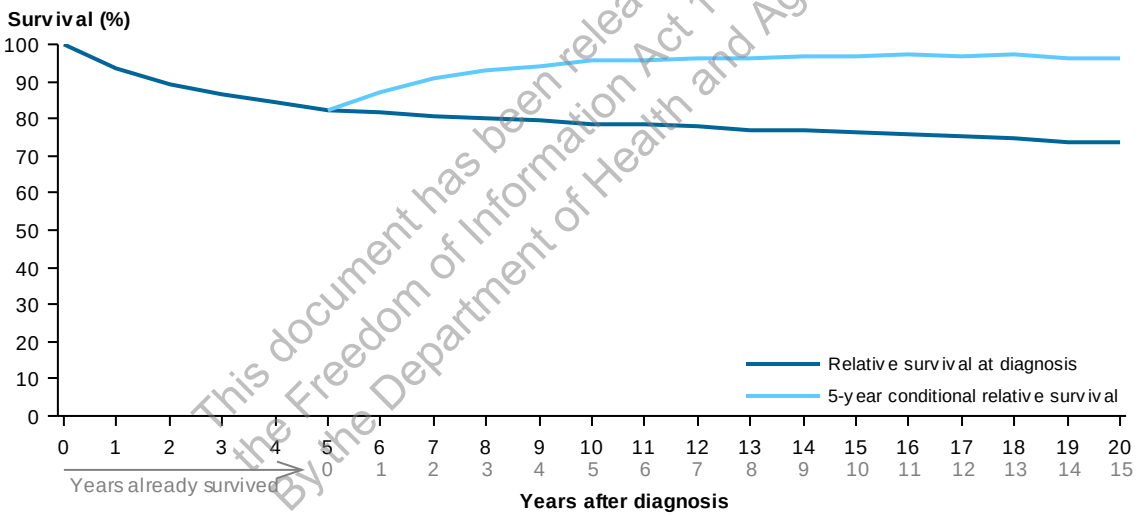


Figure B37(c): Relative survival at diagnosis and 5-year conditional survival from uterine cancer, Australia, 2007–2011

(a) Prevalence refers to the number of living people previously diagnosed with cancer, not the number of cancer cases.

(b) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

Source: AIHW ACD 2011.

Appendix C: Cancer incidence, mortality and survival for all cancer groupings

Table C1: Incidence (2011), mortality (2012) and 5-year relative survival (2007–2011) by cancer type, persons, Australia

	Incidence[a,b]		Mortality[c]		Survival[b,d]	
Cancer site/type (ICD-10 codes)	**Number**	**ASR[e]**	**Number**	**ASR[e]**	**RS (%)[f]**	**95% CI[g]**
Lip, oral cavity and pharynx						
Lip (C00)	912	3.8	12	0.1	93.4	92.1–94.7
Tongue (C01–C02)	689	2.8	210	0.8	63.2	61.2–65.2
Mouth (C03–C06)	571	2.3	119	0.5	59.6	57.3–61.8
Salivary glands (C07–C08)	287	1.2	89	0.3	71.5	68.4–74.4
Oropharynx (C09–C10)	456	1.9	144	0.6	61.3	58.9–63.6
Nasopharynx (C11)	120	0.5	43	0.2	70.0	65.8–73.8
Hypopharynx (C12–C13)	147	0.6	45	0.2	29.2	25.6–32.9
Other sites in pharynx, etc. (C14)	83	0.3	85	0.3	33.1	27.8–38.6
Digestive organs						
Oesophagus (C15)	1,395	5.6	1,203	4.7	17.5	16.5–18.6
Stomach (C16)	2,093	8.5	1,143	4.5	27.0	26.0–28.0
Small intestines (C17)	442	1.8	127	0.5	58.4	55.8–60.9
Colorectal (C18–C20)	15,151	61.5	3,980	15.4	66.9	66.4–67.3
Anus (C21)	369	1.5	71	0.3	64.5	61.7–67.3
Liver (C22)	1,446	5.9	1,490	5.9	16.0	15.0–17.0
Gallbladder and extrahepatic bile ducts (C23–C24)	771	3.1	254	1.0	18.5	17.1–20.1
Pancreas (C25)	2,748	11.0	2,524	9.8	6.1	5.6–6.6
Other digestive organs (C26)	185	0.7	1,240	4.7	12.1	9.4–15.1
Respiratory system and intrathoracic organs						
Nose, sinuses, etc. (C30–C31)	177	0.7	30	0.1	56.5	52.5–60.4
Larynx (C32)	590	2.4	208	0.8	62.3	60.2–64.4
Lung (C33–C34)	10,511	42.5	8,137	31.8	14.3	14.0–14.7
Other thoracic and respiratory organs (C37–C39)	102	0.4	58	0.2	52.8	47.6–57.8
Bone (C40–C41)	**229**	**1.0**	**112**	**0.5**	**66.9**	**63.6–70.1**
Skin						
Melanoma of the skin (C43)	11,570	48.0	1,515	5.9	90.4	90.0–90.8
Non-melanoma of the skin (C44)[b]	769	3.1	521	1.9	71.5	69.4–73.5
Mesothelial and soft tissue						
Mesothelioma (C45)	690	2.8	638	2.5	5.8	4.9–6.7
Kaposi sarcoma (C46)	69	0.3	2	0.0	85.3	78.9–90.8
Peritoneum (C48)	203	0.8	96	0.4	39.7	36.4–43.0

(continued)

Cancer site/type (ICD-10 codes)	Incidence[a,b] Number	Incidence[a,b] ASR[e]	Mortality[c] Number	Mortality[c] ASR[e]	Survival[b,d] RS (%)[f]	Survival[b,d] 95% CI[g]
Other soft tissue (C47, C49)	641	2.7	265	1.1	66.2	64.1–68.3
Breast in females (C50)	**14,465**	**116.0**	**2,795**	**20.6**	**89.6**	**89.3–89.9**
Female genital organs						
Vulva (C51)	318	1.3	90	0.3	74.2	71.1–77.2
Vagina (C52)	77	0.3	20	0.1	46.7	40.6–52.7
Cervix (C53)	801	3.5	226	0.9	71.9	70.2–73.4
Uterus (C54–C55)	2,238	9.0	421	1.6	82.5	81.5–83.4
Ovary (C56)	1,330	5.4	933	3.6	43.0	41.7–44.3
Other female genital organs and placenta (C57–C58)	155	0.6	44	0.2	58.0	53.1–62.7
Male genital organs						
Penis (C60)	108	0.4	14	0.1	70.6	64.4–76.2
Prostate (C61)	19,993	79.7	3,079	11.6	93.2	92.8–93.5
Testis (C62)	732	3.3	25	0.1	97.9	97.2–98.4
Other male genital organs (C63)	28	0.1	2	0.0	82.6	71.6–91.4
Urinary tract						
Kidney (C64)	2,847	11.7	907	3.5	73.4	72.4–74.3
Bladder (C67)	2,404	9.6	1,038	3.9	53.1	51.9–54.3
Other urinary organs (C65–C66, C68)	455	1.8	195	0.8	42.6	40.1–45.2
Eye, brain and other parts of the central nervous system						
Eye (C69)	266	1.1	30	0.1	79.1	76.3–81.8
Brain (C71)	1,724	7.3	1,241	5.0	21.6	20.7–22.6
Other central nervous system (C70, C72)	90	0.4	14	0.1	67.1	61.6–72.2
Thyroid and other endocrine glands						
Thyroid (C73)	2,098	9.1	126	0.5	95.8	95.2–96.3
Other endocrine glands (C74–C75)	99	0.4	51	0.2	60.1	55.4–64.5
Blood and lymphatic system						
Hodgkin lymphoma (C81)	606	2.7	78	0.3	87.2	85.7–88.6
Non-Hodgkin lymphoma (C82–C85)	4,631	19.1	1,402	5.4	72.1	71.3–72.8
Immunoproliferative cancers (C88)	89	0.4	33	0.1	74.0	68.1–79.5
Myeloma (C90)	1,533	6.2	834	3.2	44.8	43.4–46.2
Acute lymphoblastic leukaemia (ALL)(C91.0)	353	1.6	111	0.5	71.0	68.6–73.3
Chronic lymphocytic leukaemia (CLL)(C91.1)	1,174	4.7	342	1.3	76.7	75.1–78.2
Other and unspecified lymphoid leukaemia (C91.2–C91.9)	126	0.5	45	0.2	82.3	77.6–86.5
Acute myeloid leukaemia (AML)(C92.0, C92.3–C92.5, C93.0, C94.0, C94.2, C94.4, C94.5)	913	3.8	813	3.2	24.5	23.2–25.9
Chronic myelogenous leukaemia (CML)(C92.1)	334	1.4	102	0.4	76.1	73.2–78.8
Other and unspecified myeloid leukaemia (C92.2, C92.7, C92.9, C93.1–C93.9, C94.7)	315	1.3	95	0.4	35.9	32.7–39.2

(continued)

Cancer site/type (ICD-10 codes)	Incidence[a,b] Number	Incidence[a,b] ASR[e]	Mortality[c] Number	Mortality[c] ASR[e]	Survival[b,d] RS (%)[f]	Survival[b,d] 95% CI[g]
Myeloproliferative cancers excluding CML (C94.1, C94.3, C96.2, D45, D47.1, D47.3)	651	2.7	161	0.6	76.4	74.5–78.2
Myelodysplastic syndromes (D46)	1,309	5.2	424	1.6	38.0	36.4–39.6
Other cancers of blood and lymphatic system (C95, C96.0, C96.1, C96.3–C96.9)	90	0.4	143	0.5	30.5	25.1–36.2
Other						
Other and ill-defined sites (C76)	35	0.1	181	0.7	39.7	31.1–48.5
Unknown primary site (C80)[h]	2,802	11.1	2,133	8.1	13.8	13.2–14.5
Multiple primary (C97)[i]	. .	. .	506	1.9	. .	. .
All cancers combined (C00–C97[b, i], D45, D46, D47.1, D47.3)	**118,711**	**484.1**	**43,039**	**166.8**	**66.7**	**66.5–66.8**

(a) The 2011 incidence data include estimates for NSW and the ACT. See Appendix F for more details.

(b) For incidence and survival data, those C44 codes that indicate basal or squamous cell carcinoma of the skin are not included.

(c) Deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS.

(d) Relative survival was calculated with the period method, using the period 2007–2011 (Brenner & Gefeller 1996). Note that this period does not contain incidence data for 2010–2011 for NSW or the ACT (see Appendix F).

(e) The rates were age-standardised to the Australian population as at 30 June 2001 and expressed by 100,000 population.

(f) RS = relative survival.

(g) CI = confidence interval.

(h) For mortality data before 2008, the applicable codes are C77–C80.

(i) C97 is of relevance for mortality data only.

Sources: ABS 2014b; AIHW ACD 2011; AIHW NMD.

Appendix D: Guide to online supplementary tables

Additional tables are available as online Excel tables at <www.aihw.gov.au>. These tables contain detailed statistics, some of which are presented in summary form in the body of the report. Throughout the report, online additional tables are referred to with a prefix 'D'; for example, 'See online Table D3.1'.

There are 9 Excel files, each representing a chapter (or appendix) from the report:

- Chapter 2—Risk factors, early detection and prevention
- Chapter 3—Incidence of cancer
- Chapter 4—Hospitalisations and palliative care for cancer
- Chapter 5—Survival after a diagnosis of cancer
- Chapter 6—Prevalence of cancer
- Chapter 7—Mortality from cancer
- Chapter 8—Focus on key population groups
- Chapter 9—International comparisons
- Appendix B—Summary pages for selected cancers

Appendix E: Classifications

Remoteness Areas

The Remoteness Areas (RAs) divide Australia into broad geographic regions that share common characteristics of remoteness for statistical purposes. The Remoteness Structure divides each state and territory into several regions on the basis of their relative access to services. There are six classes of RA in the Remoteness Structure: *Major cities*, *Inner regional*, *Outer regional*, *Remote Australia*, *Very remote* and *Migratory*. The category *Major cities* includes Australia's capital cities, except for Hobart and Darwin, which are classified as Inner regional. RAs are based on the Accessibility and Remoteness Index of Australia (ARIA) produced by the Australian Population and Migration Research Centre at the University of Adelaide (ABS 2014a).

Each unit record in the ACD contains the 2006 Statistical Local Area (SLA) and 2011 Statistical Area Level 2 (SA2) but not the RA. In order to calculate the cancer incidence rates by RA discussed in Chapter 8, a correspondence was used to map the 2006 SLA to the 2006 RA (ABS 2011a). Similarly, the cancer mortality rates by RA in Chapter 8 were calculated by applying a correspondence from the 2011 SA2 to the 2011 RA (ABS 2012a).

Index of Relative Socio-economic Disadvantage

The Index of Relative Socio-economic Disadvantage (IRSD) is one of four Socio-Economic Indexes for Areas (SEIFAs) developed by the ABS (ABS 2011b). This index is based on factors such as average household income, education levels and unemployment rates. The IRSD is not a person-based measure; rather, it is an area-based measure of socioeconomic disadvantage in which small areas of Australia are classified on a continuum from disadvantaged to affluent. This information is used as a proxy for the socioeconomic disadvantage of people living in those areas and may not be correct for each person in that area.

Socioeconomic disadvantage quintiles were assigned to cancer cases according to the IRSD of the Statistical Local Area of residence at the time of diagnosis, and to deaths according to the Statistical Area Level 2 (SA2) of residence at the time of death.

In this report, the first socioeconomic status group (quintile 1) corresponds to geographical areas containing the 20% of the population with the greatest socioeconomic disadvantage according to the IRSD, and the fifth group (quintile 5) corresponds to the 20% of the population with the least socioeconomic disadvantage.

International Classification of Diseases for Oncology

Cancers were originally classified solely under the ICD classification system, based on topographic site and behaviour. However, during the creation of the Ninth Revision of the ICD in the late 1960s, working parties suggested creating a separate classification for cancers that included improved morphological information. The first edition of the ICD-O was subsequently released in 1976 and, in this classification, cancers were coded by both morphology (histology type and behaviour) and topography (site).

Since the first edition of the ICD-O, a number of revisions have been made, mainly in the area of lymphomas and leukaemias. The current edition, the Third Edition (ICD-O-3), was released in 2000 and is used by most state and territory cancer registries in Australia, as well as by the AIHW in regard to the ACD.

International Statistical Classification of Diseases and Related Health Problems

The International Statistical Classification of Diseases and Related Health Problems (ICD) is used to classify diseases and other health problems (including symptoms and injuries) in clinical and administrative records. The use of a standard classification system enables the storage and retrieval of diagnostic information for clinical and epidemiological purposes that is comparable between different service providers, across countries and over time.

In 1903, Australia adopted the ICD to classify causes of death and it was fully phased in by 1906. Since 1906, the ICD has been revised nine times in response to the recognition of new diseases (for example, Acquired Immunodeficiency Syndrome, or AIDS), increased knowledge of diseases, and changing terminology in the description of diseases. The version currently in use, the ICD-10 (WHO 1992), was endorsed by the 43rd World Health Assembly in May 1990 and officially came into use in WHO member states from 1994.

International Statistical Classification of Diseases and Related Health Problems, Australian Modification

The Australian modification of the ICD-10, referred to as the ICD-10-AM (NCCH 2010), is based on the ICD-10. The ICD-10 was modified for the Australian setting by the National Centre for Classification in Health, with assistance from clinicians and clinical coders. Despite the modifications, compatibility with the ICD-10 at the higher levels of the classification (that is, up to 4 character codes) has been maintained. The ICD-10-AM has been used to classify diagnoses in hospital records in all states and territories since 1999–00 (AIHW 2000).

Australian Classification of Health Interventions

The current version of the ICD does not incorporate a classification system for coding health interventions (that is, procedures). In Australia, a health intervention classification system was designed to be implemented at the same time as the ICD-10-AM in July 1998. The system was based on the Medicare Benefits Schedule (MBS) coding system and originally called MBS-Extended. The name was changed to the Australian Classification of Health Interventions (ACHI) with the release of the Third Revision of the ICD-10-AM in July 2002 (NCCH 2010). The ACHI and the ICD-10-AM are used together to classify morbidity, surgical procedures and other health interventions in Australian hospital records.

Appendix F: How estimated data in the 2011 Australian Cancer Database were calculated

The 2010 and 2011 incidence data for NSW and the ACT were not available for inclusion in the 2011 version of the ACD. The development of the new NSW Cancer Registries system has resulted in a delay in processing incidence data for 2010 onwards and therefore the most recent NSW data available for inclusion in the ACD are for 2009. Full details about this situation are given on the following web page: <http://www.cancerinstitute.org.au/data-and-statistics/accessing-our-data/availability-of-nsw-central-cancer-registry-data>.

As the coding of ACT cancer notifications is contracted to the NSW Cancer Registry, the most recent data available for the ACT are also for 2009. The 2010 and 2011 incidence data for NSW and the ACT were estimated by the AIHW (see below for detail of procedure). These estimates were combined with the actual data supplied by the other six state and territory cancer registries to form the 2011 ACD.

Estimating 2010 and 2011 cancer incidence for NSW and the ACT, excluding prostate cancer

To estimate 2010 and 2011 cancer incidence for NSW and the ACT, except for prostate cancer (detailed below), the most recent 10 years of incidence count data, from 2000 to 2009, were divided into time series, stratified as follows:

- jurisdiction: NSW, ACT
- sex: male, female
- age group: 5-year age groups, 0–4, …, 80–84, and 85+
- 4-character ICD-O-3 topography code: C00.0, …, C80.9
- 4-digit ICD-O-3 histology code: 8000, …, 9989.

For each series, the following steps were undertaken to estimate cancer incidence:

- The incidence numbers were divided by the sex- and age-specific mid-year populations to obtain the age-specific incidence rates from 2000 to 2009.
- If any of the rates in the series was zero (0), the mean of the 10 rates was used as the estimate of the 2010 and 2011 rates.
- If none of the rates were zero (0), least squares linear regression was used to find the straight line of best fit through the time series.
- A 5% level of significance was used to test the hypothesis that the slope of the line was different from zero (0).
- If the slope was not found to be significantly different from zero (0), the mean of the 10 rates was used as the estimate of the 2010 and 2011 rates.
- If the slope was found to be positive, the straight line of best fit was extrapolated to obtain the estimates of the 2010 and 2011 rates.

- If the slope was negative, the time series was fitted with a log-linear model (that is, the logs of the rates were fitted with a straight line) and the estimated rates for 2010 and 2011 were found by extrapolating this line.
- The estimated incidence rates for 2010 and 2011 were then multiplied by the Estimated Resident Populations for 2010 and 2011 to obtain the estimated incidence numbers.

There were a small number of series that did not have a history of 10 years of incidence data. These were the non-melanoma skin cancers, for which the series begin at 2001, and the myelodysplastic and/or myeloproliferative cancers (histology codes 9950, 9960–9962 and 9980–9989), for which the series begin at 2003.

Estimating 2010 and 2011 prostate cancer incidence for NSW and the ACT

Due to the effect of PSA testing, prostate cancer incidence rates have fluctuated considerably over time, making the above methodology unreliable for estimating the incidence of prostate cancer. Instead, the estimates of 2010 and 2011 prostate cancer incidence for NSW and the ACT were based on the actual data for 2010 and 2011 for the other six states and territories combined.

Prostate cancer in those aged under 35 is very rare (just 12 cases in Australia in the period 2000–2009). Therefore, the number of cases estimated for 2010 and 2011 for NSW and the ACT was zero (0). For those aged 35 and over, the time series for 2000–2009 of prostate cancer incidence counts were stratified as follows:

- jurisdiction: NSW, ACT, SIX, where 'SIX' stands for the other six jurisdictions combined. Note that the series for SIX extends to 2011
- age group: 5-year age groups, 35–39, …, 80–84, and 85+.

The general procedure for calculating the estimates is illustrated by the following example for NSW and any fixed age group:

- Convert the count data to age-specific incidence rates, using the relevant age- and jurisdiction-specific populations.
- For each year from 2000 to 2009, divide the age-specific incidence rate for NSW by the corresponding age-specific incidence rate for SIX.
- Calculate the average of the 10 ratios computed in the previous step.
- Multiply the average ratio calculated in the previous step by the age-specific incidence rate for SIX in 2010, and likewise for 2011. This gives the estimated age-specific incidence rates for NSW for 2010 and 2011.
- Convert these incidence rates to incidence counts by multiplying by the relevant populations.

Estimating 2009 provisional death-certificate-only cases for NSW and the ACT

The 2009 incidence data for NSW and the ACT provided to the AIHW excluded the provisional death-certificate-only cases. The reason the provisional death-certificate-only (DCO) cases were not available is explained on the following web page: <http://www.cancerinstitute.org.au/data-and-statistics/accessing-our-data/availability-of-

nsw-central-cancer-registry-data>. The AIHW has estimated the number of provisional DCO cases in 2009 for each cancer, sex and age group based on the numbers observed for 2004–2008. Overall, about 1.7% of NSW cases and 1.9% of ACT cases in 2009 are estimated provisional DCO cases.

The procedure for estimating the number of provisional DCO cases for NSW and the ACT in 2009 was as follows:

- For each jurisdiction separately, divide the total number of provisional DCO cases in 2004–2008 (years combined) by the total number of cases in 2004–2008 that were not provisional DCO.
- Multiply the ratio computed in the previous step by the total number of cases in 2009 that were not provisional DCO (which is simply the total number of cases supplied for 2009). This gives the estimated total number of provisional DCO cases in 2009.
- Allocate the estimated total computed in the previous step to each combination of sex, age group, topography code and histology code according to the same distribution as was observed in 2004–2008.

Appendix G: Methodology for cancer projections

Incidence projections, excluding prostate cancer

Estimates of incidence in 2012–2016 were calculated using the same approach as used to estimate 2010 and 2011 incidence for NSW and the ACT (Appendix F). Note the following:

- Estimates were made for Australia as a whole, not for individual jurisdictions.
- Instead of using the topography and histology codes to define the cancer groups, the 'Cancer in Australia' reporting groups were used; that is, lip, tongue, mouth, and so on (see Appendix C).
- The incidence estimates already made for 2009–2011 for NSW and the ACT were treated as real data for the purposes of estimating Australian incidence for 2012–2016.
- The 10 years of incidence data used as the baseline were 2002–2011, except for the myelodysplastic and/or myeloproliferative cancers (histology codes 9950, 9960–9962 and 9980–9989) for which there was only a 9-year series, 2003–2011.
- For populations, the ABS preliminary Estimated Resident Populations were used for 2012–2013, and the ABS population projection series 29(B) for 2014–2016 (ABS 2013).

Estimating the incidence of prostate cancer

As explained in Appendix F, MBS item 66655 (PSA test) enables testing activity for prostate cancer to be quantified. At the time this analysis was undertaken, the number of services of item 66655 was available up to and including June 2014. The total number of services for 2014 was estimated using the following data:

- year of test: 2004, …, 2013
- MBS age group: 0–4, then 10-year age groups 5–14, …, 75–84, and 85+
- total number of services of item 66655 from January to June inclusive
- total number of services of item 66655 from January to December inclusive.

The ratio 'January to June total' divided by 'January to December total' was computed for each unit record in the above data set to form a time series from 2004 to 2013. The same approach as is described in Appendix F was used to estimate the ratios for 2014. Applying these ratios to the known 'January to June' totals for 2014 produced the estimated number of services for the whole of 2014. This number is used below.

It has been noted previously that there is a positive correlation between the number of services of item 66655 and the incidence of prostate cancer (AIHW & AACR 2012). During the present analysis, it was noticed that this correlation is stronger when the reference year for the MBS data is 1 year behind that for the incidence data. This relationship is employed in the following explanation of how the estimates of prostate cancer incidence for 2012–2015 were derived. The data used were:

- year: 2003, …, 2011. Note that a 10-year time series would be preferable but 2002 cannot be used because the PSA data are incomplete for 2001
- MBS age group: 0–4, then 10-year age groups 5–14, …, 75–84, and 85+

- prostate cancer incidence: number of cases of prostate cancer in that year
- PSA tests: number of services of item 66655 for the *previous* year, downloaded from <www.medicareaustralia.gov.au/statistics/mbs_item.shtml>. Thus, the years used for the PSA data were 2002–2010.

The ratio 'number of cases' divided by 'number of tests' was computed for each stratum in the above data set to form a time series of ratios from 2003 to 2011. For each of these time series, the method explained in Appendix F was used to estimate the ratios for 2012–2015. The estimated incidence counts for 2012–2015 were then obtained by multiplying the estimated ratios for 2012–2015 by the number of services of item 66655 for 2011–2014, respectively. (Note that the method for estimating the number of services for 2014 is explained above.)

The final step was to convert the estimated incidence counts for the 10-year MBS age groups to 5-year age groups, consistent with incidence data. The data used in this step were as follows:

- year of diagnosis: 2002, …, 2011
- MBS age group: 10-year age groups 5–14, …, 75–84 (0–4 and 85+ not required)
- 5-year age group within the 10-year age group. For example, in the MBS age group 5–14 there would be the 'younger' age group 5–9 and the 'older' age group 10–14
- prostate cancer incidence: number of cases of prostate cancer in each 5-year age group.

The 'younger ratio' is defined to be 'number of cases of prostate cancer in younger age group' divided by 'number of cases of prostate cancer in corresponding 10-year age group', and the 'older ratio' is the analogous ratio. Note that the older ratio can also be defined as 1 minus the younger ratio. The following steps were then undertaken:

- The younger ratios were computed for each stratum in the above data set to form a time series of ratios from 2002 to 2011.
- If any of the ratios in the series was zero (0), the mean of the 10 ratios was used as the estimates of the 2012–2015 younger ratios.
- If none of the ratios were zero (0), least squares linear regression was used to find the straight line of best fit through the time series.
- A 5% level of significance was used to test the hypothesis that the slope of the line was different from zero (0).
- If the slope was not found to be significantly different from zero (0), the mean of the ratios was used as the estimates of the 2012–2015 younger ratios.
- If the slope was found to be significantly different from zero (0), note that the slope of the younger ratio time series will be equal in magnitude but of opposite sign to the slope of the older ratio time series. Therefore, one will have a negative slope and the other a positive slope.
- The series with negative slope was fitted with a log-linear model and the estimated ratios for 2012–2015 were found by extrapolating this line.
- For each 2012–2015 ratio that was determined above (by either the mean or a log-linear model), the other ratios for 2012–2015 were computed to be 1 minus the ratio determined. There is now a complete set of estimated younger and older ratios for 2012–2015.

- The estimated number of cases for each 5-year age group for 2012–2015 were then obtained by multiplying the estimated number of cases for the corresponding 10-year age group by the appropriate ratio (that is, younger or older) for 2012–2015.

At this point there are incidence estimates for each 5-year age group for each year from 2012 to 2015. The estimates for 2016 cannot be obtained by the same method because there are no PSA data for 2015 yet. The 2016 prostate cancer incidence estimates were obtained by using the method explained in Appendix F on the 2006–2015 time series (treating the 2012–2015 data as real).

Mortality projections model

Simple linear or log-linear ordinary least squares linear regression models of age-specific rates generally provide a good fit to the data while giving reasonably accurate predictions over a short to medium time span The accepted (conservative) approach among statisticians preparing projections of this nature is to assume a linear model for increasing rates, and a log-linear model for decreasing rates to prevent projecting incidence rates below zero (0). Where there is no significant trend, the mean rate over the most recent trend is used.

Following this approach, a national model was developed for each cancer (by sex) using the following 4-step method:

1. assess the historical trend in annual mortality for 1968 to 2012
2. test the significance of the historical trend
3. extrapolate that trend to predict annual rates for the years 2013 to 2024
4. apply those rates to projected populations to derive projected mortality counts.

These steps are described in more detail below.

Step 1—assess the historical trend in annual mortality for 1968 to 2012

Joinpoint analysis was used to assess the significance of the historical trend in annual cancer mortality for each cancer by sex and 5-year age group using national cancer mortality data.

The most recent significant trend was used as the observation window from which to extrapolate the future trend (Step 2). The cancer- and sex-specific observation windows are presented in Table G1.

Table G1: Cancer- and sex-specific observation windows

	Observation window (start year)		
Cancer site/type	**Males**	**Females**	**Persons**
Acute myeloid leukaemia (AML)	1968	1993	1995
Bladder	1985	1968	1985
Brain	1996	1990	1994
Breast	1968	1999	1968
Cervix	2013	2004	2013
Chronic lymphocytic leukaemia (CLL)	1994	1988	1994
Chronic myelogenous leukaemia (CML)	1993	1992	1992
Colorectal	1997	2006	2006
Hodgkin lymphoma	1968	1968	1968
Kidney	1999	1993	1995
Liver	2004	1993	2004
Lung	1994	1999	1989
Melanoma of the skin	1987	1986	1998
Mesothelioma	1997	1997	1997
Non-Hodgkin lymphoma	1994	1998	2000
Non-melanoma of the skin	1992	1994	1992
Oesophagus	1998	1995	1997
Ovary	2013	1994	2013
Pancreas	1997	1968	1998
Prostate	1993	2013	2013
Stomach	1985	1993	1968
Uterus	2013	1992	2013
Anus	1968	1980	1982
Gallbladder and extrahepatic bile ducts	2005	1997	2004
Larynx	1991	1968	1991
Lip	1979	1968	1984
Mouth	1979	1991	1991
Myeloma	1986	1988	1988
Tongue	1987	1968	1988
Unknown primary site	2005	1993	2006
Leukaemias	1985	1992	1993
Lymphomas	1997	1998	1997
Bone	1968	1968	2000

Step 2—test the significance of the historical trend

An ordinary least squares (OLS) linear regression model was developed for each 5-year age-sex group using national mortality rates from the most recent trend, as defined by the observation window derived in Step 1. The significance of each age-sex trend for each

cancer was tested, with one of three possible outcomes: significant increase, significant decrease, no significant trend.

Step 3—extrapolate the trend to predict annual mortality rates for 2013 to 2016

The historical trend within the observation window was extrapolated using one of three methods (see below), as determined by the outcome of the significance testing in Step 2:

1. An OLS linear regression model was applied to significant increasing trends, so as not to overstate future mortality.
2. An OLS linear regression model with log transformation (log-linear) was applied to significant decreasing trends, so as not to project mortality below zero (0).
3. An intercept-only model (mean) was applied to non-significant trends.

Step 4—derive projected mortality counts for 2013 to 2016

The projected rates derived from Step 3 were applied to projected population data to estimate the future number of deaths for each cancer by age and sex. These projected counts were then summed to obtain the total number of deaths (and total ASR) for each cancer type.

Assumptions

It should be noted that there is a fundamental assumption in this approach that the factors that affect cancer mortality (for example, risk factors, cancer detection, and treatment) evolve in an approximately linear or log-linear way with time for each age group. This assumption should hold as long as there are no major quantitative changes in trends, as might occur, for example, from increased risk factors, or from treatment or screening breakthroughs.

These assumptions are as follows:

- Trends in age-sex-cancer specific mortality rates are the same across Australia.
- The most recent trend will continue into the future.
- The trend for the 5-year age group is representative of the trends of each single year of age within that group.
- An appropriate model is chosen to describe both the historical data and expected future trend.
- Projected populations, based on current trends in fertility, life expectancy at birth and net overseas migration, are indicative of future populations.

Appendix H: Statistical methods and technical notes

Age-specific rates

Age-specific rates provide information on the incidence of a particular event in an age group relative to the total number of people at risk of that event in the same age group. It is calculated by dividing the number of events occurring in each specified age group by the corresponding 'at-risk' population in the same age group and then multiplying the result by a constant (for example, 100,000) to derive the rate. Age-specific rates are often expressed per 100,000 population.

Age-standardised rates

A crude rate provides information on the number of, for example, new cases of cancer or deaths from cancer by the population at risk in a specified period. No age adjustments are made when calculating a crude rate. Since the risk of cancer is heavily dependent on age, crude rates are not suitable for looking at trends or making comparisons across groups in cancer incidence and mortality.

More meaningful comparisons can be made by the use of ASRs, with such rates adjusted for age in order to facilitate comparisons between populations that have different age structures—for example, between Indigenous people and other Australians. This standardisation process effectively removes the influence of age structure on the summary rate.

There are two methods commonly used to adjust for age: direct and indirect standardisation. In this report, the direct standardisation approach presented by Jensen and colleagues (1991) is used. To age-standardise using the direct method, the first step is to obtain population numbers and numbers of cases (or deaths) in age ranges—typically 5-year age ranges. The next step is to multiply the age-specific population numbers for the standard population (in this case, the Australian population as at 30 June 2001) by the age-specific incidence rates (or death rates) for the population of interest (such as those in a certain socioeconomic status group or those who lived in *Major cities*). The next step is to sum across the age groups and divide this sum by the total of the standard population to give an ASR for the population of interest. Finally, this is expressed per 1,000 or 100,000 as appropriate.

Mortality-to-incidence ratio

Both mortality-to-incidence ratios (MIRs) and relative survival ratios can be used to estimate survival from a particular disease, such as cancer, for a population. Although MIRs are the cruder of the two ratios, they do not have the same comparability and interpretation problems associated with them when trying to make international comparisons (see Chapter 9). Thus, the MIR is considered to be a better measure when comparing survival between countries.

The MIR is the number of deaths in a given year divided by the number of new cases in the same year. It is a number between 0 and 1 although it can exceed 1 in certain circumstances.

The MIR is a measure of the fatality of the cancer in question: if no-one ever died of the cancer, the MIR would be 0; if everyone died on the same day they were diagnosed, the MIR would be 1. Low values of the MIR indicate longer survival while high values indicate shorter survival. In general, if the MIR is decreasing over time, we can conclude that survival is improving over time.

The MIR gives a valid measure of the survival experience in a population only if:

- cancer registration and death registration are complete or nearly so, and
- the incidence rate, mortality rate and survival proportion are not undergoing rapid change.

The incidence and mortality data used to calculate the MIRs in Chapter 9 were extracted from the 2012 GLOBOCAN database (Ferlay et al. 2013).

Prevalence

Limited-duration prevalence is expressed as *N-year prevalence* throughout this report. *N-year prevalence* on a given index date (31 December 2009)—where *N* is any number 1, 2, 3 and so on—is defined as the number of people alive at the end of that day who had been diagnosed with cancer in the past *N* years. For example:

- 1-year prevalence is the number of living people who were diagnosed in the past year to 31 December 2009
- 5-year prevalence is the number of living people who were diagnosed in the past 5 years to 31 December 2009. This includes the people defined by 1-year prevalence.

Note that prevalence is measured by the number of people diagnosed with cancer, not the number of cancer cases. An individual who was diagnosed with two separate cancers will contribute separately to the prevalence of each cancer. However, this individual will contribute only once to prevalence of all cancers combined. For this reason, the sum of prevalence for individual cancers will not equal the prevalence of all cancers combined.

Prevalence can be expressed as a proportion of the total population as at the index date. In this report, the prevalence proportion is expressed per 10,000 population due to the relative size of the numerator and denominator. These are crude rates and have not been standardised.

Differences in limited-duration prevalence are presented according to age in the report. Note that while age for survival and incidence statistics refers to the age at diagnosis, prevalence age refers to the age at the point in time from which prevalence was calculated, or 31 December 2009 in this report. Therefore, a person diagnosed with cancer in 1982 when they turned 50 that year would be counted as age 75 in the prevalence statistics (as at the end of 2009).

Relative survival

Relative survival is a measure of the survival of people with cancer compared with that of the general population. It is the standard approach used by cancer registries to produce population-level survival statistics and is commonly used as it does not require information on cause of death. Instead, relative survival reflects the net survival (or excess mortality)

associated with cancer by adjusting the survival experience of those with cancer for the underlying mortality that they would have experienced in the general population.

Relative survival is calculated by dividing observed survival by expected survival, where the numerator and denominator have been matched for age, sex and calendar year.

Observed survival refers to the proportion of people alive for a given amount of time after a diagnosis of cancer; it is calculated from population-based cancer data. Expected survival refers to the proportion of people in the general population alive for a given amount of time and is calculated from life tables of the entire Australian population, assumed to be cancer free.

A simplified example of how relative survival is interpreted is shown in Figure H1. Given that 6 in 10 people with cancer are alive 5 years after their diagnosis (observed survival of 0.6) and that 9 in 10 people from the general population are alive after the same 5 years (expected survival of 0.9), the relative survival of people with cancer would be calculated as 0.6 divided by 0.9, or 0.67. This means that individuals with cancer are 67% as likely to be alive for at least 5 years after their diagnosis compared with their counterparts in the general population.

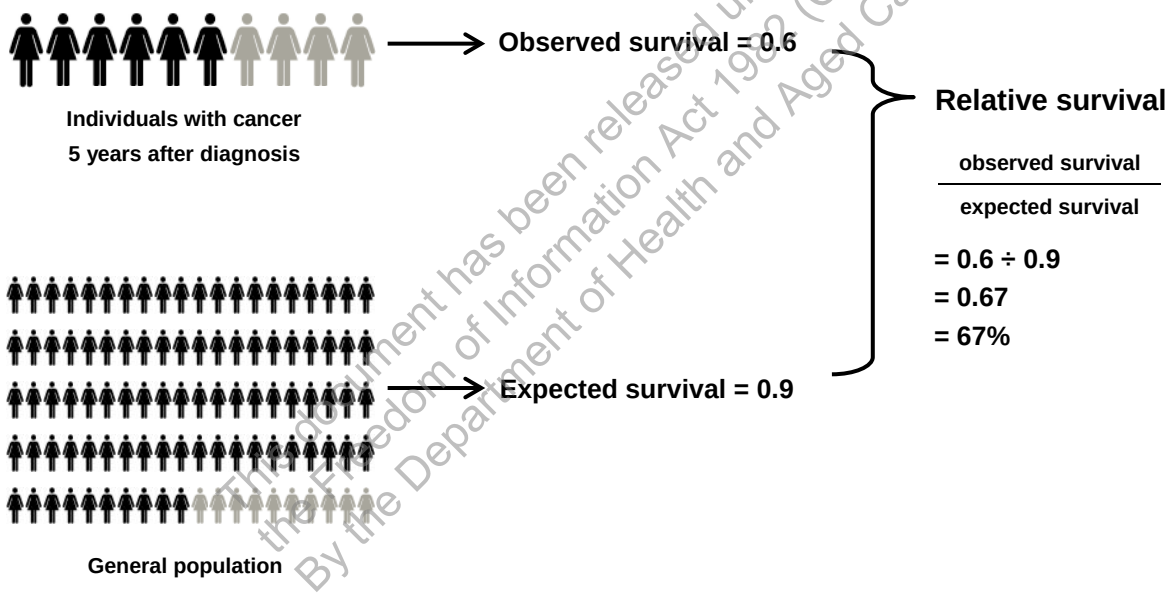


Figure H1: Simplified example of how relative survival is calculated

All observed survival was calculated from data in the ACD. Expected survival was calculated from the life tables of the entire Australian population, as well as the Australian population stratified by remoteness area and socioeconomic status quintile. The Ederer II method was used to determine how long people in the general population are considered 'at risk'. It is the default approach, whereby matched people in the general population are considered to be at risk until the corresponding cancer patient dies or is censored (Ederer & Heise 1959).

The survival analysis was based on records of primary and invasive cancers diagnosed between 1982 and 2011. At the time of analysis, these cases had been followed for deaths (from any cause) to the end of 2011. Therefore, the censor date selected for survival analysis was 31 December 2011.

The period method was used to calculate the survival estimates in this report (Brenner & Gefeller 1996), in which estimates are based on the survival experience during a given at-risk or follow-up period. Time at risk is left truncated at the start of the period and right censored at the end so that anyone who is diagnosed before this period and whose survival experience overlaps with this period would be included in the analysis.

The main follow-up period in this report was for the 5-year period 2007–2011, which was used for the most up-to-date estimates of survival by age, histological subtype, remoteness and socioeconomic status.

Trends are also analysed by six periods of follow-up: 1982–1986, 1987–1991, 1992–1996, 1997–2001, 2002–2006 and 2007–2011. In each period, 5 or 6 years of follow-up have been combined to draw upon a greater number of cases to produce more precise estimates.

All survival statistics in this report were produced using SAS statistical software and calculated using software written by Dickman (2004).

Calculation of conditional relative survival

Conditional survival is the probability of surviving j more days, given that an individual has already survived i days. It was calculated using the formula

$$S(j|i) = \frac{S(i+j)}{S(i)}$$

where

$S(j|i)$ indicates the probability of surviving at least j more days given survival of at least i days

$S(i+j)$ indicates the probability of surviving at least i+j days

$S(i)$ indicates the probability of surviving at least i days.

Confidence intervals for conditional survival were calculated using a variation of Greenwood's (1926) formula for variance (Skuladottir & Olsen 2003):

$$\mathrm{Var}[S(j|i)] = \sum_{k=i+1}^{i+j} \frac{d_k}{r_k(r_k - d_k)}$$

where

d_k is the number of deaths

r_k is the number at risk during the kth interval.

The 95% confidence intervals were constructed assuming that conditional survival estimates follow a normal distribution.

Risk to age 75 or 85

The calculations of risk shown in this report are measures that approximate the risk of developing (or dying from) cancer before the age of 75 or 85, assuming that the risks at the

time of estimation remained throughout life. It is based on a mathematical relationship with the cumulative rate.

The cumulative rate is calculated by summing the age-specific rates for all specific age groups:

$$\text{Cumulative rate} = \frac{5 \times (\text{Sum of the age-specific rates}) \times 100}{100{,}000}$$

The factor of 5 is used to indicate the 5 years of life in each age group and the factor of 100 is used to present the result as a percentage. As age-specific rates are presented per 100,000 population, the result is divided by 100,000 to return the age-specific rates to a division of cases by population. Cumulative risk is related to cumulative rate by the expression:

$$\text{Cumulative risk} = 1 - e^{-rate/100}$$

Where the rate is expressed as a percentage.

The risk is expressed as a '1 in *n*' proportion by taking the inverse of the above formula:

$$n = \frac{1}{\left(1 - e^{-rate/100}\right)}$$

For example, if *n* equals 3, the risk of a person in the general population being diagnosed with cancer before the age of 75 (or 85) is 1 in 3. Note that these figures are average risks for the total Australian population. An individual person's risk may be higher or lower than the estimated figures, depending on their particular risk factors.

Appendix I: Data sources

To provide a comprehensive picture of national cancer statistics in this report, a range of data sources were used, including AIHW and external data sources. These data sources are described in this appendix.

AIHW Australian Cancer Database

All forms of cancer, except basal and squamous cell carcinomas of the skin, are notifiable diseases in each Australian state and territory. This means there is legislation in each jurisdiction that requires hospitals, pathology laboratories and various other institutions to report all cases of cancer to their central cancer registry. An agreed subset of the data collected by these cancer registries is supplied annually to the AIHW, where it is compiled into the ACD. The ACD currently contains data on all cases of cancer diagnosed from 1982 to 2009 for all states and territories, and for 2010 and 2011 for all except NSW and the ACT (see Appendix F).

Cancer reporting and registration is a dynamic process, and records in the state and territory cancer registries may be modified if new information is received. As a result, the number of cancer cases reported by the AIHW for any particular year may change slightly over time and may not always align with state and territory reporting for that same year.

The Data Quality Statement for the ACD 2011 can be found on the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/586979 >.

AIHW National Mortality Database

The AIHW National Mortality Database (NMD) contains information provided by the Registries of Births, Deaths and Marriages and the National Coronial Information System—and coded by the ABS—for deaths from 1964 to 2012. Registration of deaths is the responsibility of the state and territory Registrars of Births, Deaths and Marriages. These data are then collated and coded by the ABS and are maintained at the AIHW in the NMD.

In the NMD, both the year of occurrence of the death and the year in which the death was registered are provided. For the purposes of this report, actual mortality data are shown based on the year of occurrence of the death, except for the most recent year (namely 2012) where the number of people whose death was registered is used. Previous investigation has shown that the year of death and its registration coincide for the most part. However, in some instances, deaths at the end of each calendar year may not be registered until the following year. Thus, year of death information for the latest available year is generally an underestimate of the actual number of deaths that occurred in that year.

In this report, deaths registered in 2010 and earlier are based on the final version of cause of death data; deaths registered in 2011 and 2012 are based on revised and preliminary versions, respectively, and are subject to further revision by the ABS.

A statement on data quality relating to the AIHW NMD is available at the following ABS website: Quality declaration summary, *Causes of death, 2012*, ABS cat. no. 3303.0 <http://www.abs.gov.au/AUSSTATS/abs@.nsf/Latestproducts/3303.0Quality%20Declaration02012?opendocument&tabname=Notes&prodno=3303.0&issue=2012&num=&view=>.

AIHW National Hospital Morbidity Database

The AIHW National Hospital Morbidity Database (NHMD) is compiled from data supplied by the state and territory health authorities. It is a collection of electronic confidentialised summary records for episodes of admitted patient care (separations or hospitalisations) in essentially all public and private hospitals in Australia. The data include demographic, administrative and clinical information, including patient diagnoses and other procedures.

For more information on the specific use of the NHMD in cancer reporting, see Appendix J.

The Data Quality Statement for the AIHW NHMD 2012–13 can be found at the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/568730>.

National Death Index

The National Death Index (NDI) is a database, housed at the AIHW, that contains records of all deaths occurring in Australia since 1980. The data are obtained from the Registrars of Births, Deaths and Marriages in each state and territory. The NDI is designed to facilitate the conduct of epidemiological studies and its use is strictly confined to medical research.

Cancer incidence records from the ACD were linked to the NDI and used to calculate the survival and prevalence data presented in this report.

The Data Quality Statement for the NDI can be found at the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/480010>.

AIHW Disease Expenditure Database

The AIHW Disease Expenditure Database contains estimates of expenditure by disease category, age group and sex for each of the following areas of expenditure: admitted patient hospital services, out-of-hospital medical services, prescription pharmaceuticals, optometrical and dental services, community mental health services and public health cancer screening.

For more information on the AIHW Disease Expenditure Database, see *Health system expenditures on cancer and other neoplasms in Australia: 2008–09* (AIHW 2013b).

The Data Quality Statement for the Disease Expenditure Database can be found on the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/512599>.

BreastScreen Australia Program data

Data from BreastScreen Australia were used in Chapter 2 to indicate the number of women who had had a screening mammogram and the number of women with invasive breast cancer and DCIS (detected through BreastScreen Australia). These data are supplied annually to the AIHW by state and territory BreastScreen programs for monitoring purposes. They are compiled by the AIHW and reports are produced annually (AIHW 2014b).

The latest Data Quality Statement for the BreastScreen Australia data can be found at the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/560075>.

National Bowel Cancer Screening Program data

Data from the National Bowel Cancer Screening Register were used in Chapter 2 to indicate the number of persons who participated in the National Bowel Cancer Screening Program as well as to indicate the number of bowel cancers detected through the program. These data are supplied twice a year to the AIHW by the Department of Human Services (formerly Medicare Australia) for monitoring purposes. They are compiled by the AIHW and reports are produced annually (AIHW 2014c).

The latest Data Quality Statement for the National Bowel Cancer Screening Program data can be found on the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/569056>.

National Cervical Screening Program data

Data from the National Cervical Screening Program were used in Chapter 2 to indicate the number of women who participated in the program, and the number of women with a high-grade cervical abnormality detected through the program. These data are supplied annually to the AIHW by state and territory cervical screening programs for monitoring purposes. They are compiled by the AIHW and reports are produced annually (AIHW 2014b).

The latest Data Quality Statement for the National Cervical Screening Program data can be found on the AIHW website at <http://meteor.aihw.gov.au/content/index.phtml/itemId/539449>.

GLOBOCAN

The GLOBOCAN database, prepared by the IARC, contains cancer incidence and mortality data from cancer registries around the world (Ferlay et al. 2013). The IARC uses these data to produce estimates for a 'common year'. The most recent GLOBOCAN estimates are for 2012 and are based on incidence data from 3 to 5 years earlier.

Population data

Throughout this report, population data were used to derive rates of, for example, cancer incidence and mortality. The population data were sourced from the ABS using the most up-to-date estimates available at the time of analysis.

To derive their estimates of the resident populations, the ABS uses the 5-yearly Census of Population and Housing data and adjusts it as follows:

- All respondents in the Census are placed in their state or territory, Statistical Local Area and postcode of usual residence; overseas visitors are excluded.
- An adjustment is made for persons missed in the Census.
- Australians temporarily overseas on Census night are added to the usual residence Census count.

Estimated resident populations are then updated each year from the Census data, using indicators of population change such as births, deaths and net migration. More information is available from the ABS website at <www.abs.gov.au>.

For the Indigenous comparisons in this report (Chapter 8), the most recently released Indigenous experimental estimated resident populations as released by the ABS were used (ABS 2014c). Those estimates were based on the 2011 Census of Population and Housing.

Appendix J: Definition of cancer-related hospitalisations

Data on hospitalisations include principal diagnosis—this is the reason determined to be chiefly responsible for the person's hospitalisation. The principal diagnosis recorded is usually a disease (or health-related condition), but can also be a specific treatment of an already diagnosed condition, such as chemotherapy for cancer. These treatments are usually coded using Z-codes defined in the ICD-10-AM Chapter 21 'Factors influencing health status and contact with health services' (NCCH 2010).

Due to the method in which the principal diagnosis for hospitalisations of cancer patients is coded, it is insufficient to simply select those hospitalisations for which cancer was recorded as the principal diagnosis—it must also include those hospitalisations where a treatment relating to cancer was recorded as the principal diagnosis.

Some cancer-related interventions recorded as a principal diagnosis (such as Z08 'Follow-up examination after treatment for malignant neoplasms) are specific only to the investigation for, or treatment of, cancer. However, some (such as Z51.0 'Radiotherapy session') are not entirely cancer specific; that is, they may be provided to a small number of non-cancer patients, although the majority of these interventions are cancer related. Some (such as Z45.1 'Adjustment and management of infusion pump' and Z45.2 'Adjustment and management of vascular access device') apply to a number of disease types.

For some cancer-related interventions (such as same-day chemotherapy), the Australian Coding Standards (NCCH 2010) stipulate that the principal diagnosis is to be coded to reflect the treatment, with the type(s) of cancer listed as an additional diagnosis. This standard does not apply, however, to all interventions that may be cancer related. Thus, for the purposes of examining the number of admitted patient hospitalisations that arose due to invasive cancer, or that were directly related to the investigation, treatment or care for cancer, 'cancer-related hospitalisations' were identified in this report as those hospitalisations in which:

- the principal diagnosis was cancer (ICD-10 AM codes C00–C97, D45, D46, D47.1 and D47.3)

or

- the principal diagnosis was related to health services or treatment for cancer. This includes a principal diagnosis of one of the following cancer-specific ICD-10-AM Z codes:
  - Z08 Follow-up examination after treatment for malignant neoplasms
  - Z12 Special screening examination for neoplasm
  - Z40.0 Prophylactic surgery for risk-factors related to malignant neoplasms
  - Z51.0 Radiotherapy session
  - Z51.1 Pharmacotherapy session for neoplasm
  - Z54.1 Convalescence following radiotherapy
  - Z54.2 Convalescence following chemotherapy
  - Z80 Family history of malignant neoplasm
  - Z85 Personal history of malignant neoplasm

or

- a principal diagnosis of one of the following non-cancer specific ICD-10-AM Z codes, with an additional diagnosis of cancer (ICD-10 AM codes C00–C97, D45, D46, D47.1 and D47.3):
  - Z29.1 Prophylactic immunotherapy
  - Z29.2 Other prophylactic chemotherapy
  - Z42.0 Follow-up care involving plastic surgery of head and neck
  - Z42.1 Follow-up care involving plastic surgery of breast
  - Z45.1 Adjustment and management of infusion pump
  - Z45.2 Adjustment and management of vascular access device.

Note that, based on the definition of cancer-related hospitalisations, data presented in this report may have included a small number of some treatments and services provided to non-cancer patients. However, the proportion of these over counts is less than 0.01% of the data presented in this report.

Identifying palliative care separations

Information on the provision of palliative care is captured by two NHMD data items: 'Care type' and 'Diagnoses'. If either (or both) has a code of *Palliative care*, that separation is included as being in scope.

A 'Care type' is assigned for each admitted patient separation, with any one separation equal to either a total hospital stay (from admission to discharge, transfer or death) or to a portion of a hospital stay starting or ending in a change of care type (for example, from a 'Care type' of *acute care* to a 'Care type' of *palliative care*).

In addition, information on palliative care is also recorded in the NHMD under the 'Diagnosis' data items. While diagnosis codes usually describe a disease, injury or poisoning, they can also be used in certain instances to indicate the specific care or service provided for a current condition or other reasons for hospitalisation. This is the case when *Palliative care* is recorded as a diagnosis code 'Z51.5'.

For the purpose of this report, a palliative care separation is defined as a separation for which palliation was a substantial component of the care provided, and those in which the principal clinical intent of the care was palliation during part or all of the separation, as evidenced by a code of *Palliative care* for the 'Care type' and/or diagnosis data items in the NHMD. Further information on this can be found in the AIHW report *Palliative care services in Australia 2014* (AIHW 2014d).

Glossary

Aboriginal or Torres Strait Islander: A person of Aboriginal and/or Torres Strait Islander descent who identifies as an Aboriginal and/or Torres Strait Islander. See also *Indigenous*.

Additional diagnosis: A condition or complaint either coexisting with the principal diagnosis or arising during the episode of care.

Administrative databases: Observations about events that are routinely recorded or required by law to be recorded. Such events include births, deaths, hospital separations and cancer incidence. Administrative databases include the Australian Cancer Database, the National Mortality Database and the National Hospital Morbidity Database.

Admitted patient: A person who undergoes a hospital's formal admission process to receive treatment and/or care. Such treatment or care can occur in hospital and/or in the person's home (as a 'hospital-in-home' patient).

Age-specific rate: A rate for a specific age group. The numerator and denominator relate to the same age group.

Age-standardisation: A method of removing the influence of age when comparing populations with different age structures. This is usually necessary because the rates of many diseases vary strongly (usually increasing) with age. The age structures of the different populations are converted to the same 'standard' structure, then the disease rates that would have occurred with that structure are calculated and compared.

Asymptomatic: Without symptoms.

Average length of stay: The average (mean) number of patient days for *admitted patient* episodes. Patients admitted and separated on the same date are allocated a length of stay of 1 day.

Benign: Term that describes non-cancerous tumours that may grow larger but do not spread to other parts of the body.

Body Mass Index: The most commonly used method of assessing whether a person is normal weight, underweight, overweight or obese. It is calculated by dividing the person's weight (in kilograms) by their height (in metres) squared; that is, kg/m^2. For both men and women, underweight is a BMI below 18.5, acceptable weight is from 18.5 to less than 25, overweight is 25 and above (includes obese), and obese is 30 and over.

Burden of disease and injury: Term referring to the quantified impact of a disease or injury on an individual or population, using the *disability-adjusted life year* measure.

Cancer (malignant neoplasm): A large range of diseases in which some of the body's cells become defective, begin to multiply out of control, can invade and damage the area around them, and can also spread to other parts of the body to cause further damage.

Carcinoma: A cancer that begins in the lining layer (epithelial cells) of organs such as the ovaries.

Chemotherapy: The use of drugs (chemicals) to prevent or treat disease, with the term being applied for treatment of cancer rather than for other uses.

Cohort method: A method of calculating *survival* that is based on a cohort of people diagnosed with cancer in a previous time period and followed over time.

Colonoscopy: A procedure to examine the bowel using a special scope (colonoscope) usually carried out in a hospital or day clinic.

Colorectal (bowel) cancer: Comprises cancer of the colon, cancer of the rectosigmoid junction and cancer of the rectum (ICD-10 codes C18–C20), collectively known as colorectal cancer.

Confidence interval (CI): A statistical term describing a range (interval) of values within which we can be 'confident' that the true value lies, usually because it has a 95% or higher chance of doing so.

Crude rate: The number of events in a given period divided by the size of the population at risk in a specified time period.

Death due to cancer: A death where the underlying cause is indicated as cancer.

Ductal carcinoma in situ (DCIS): A non-invasive tumour of the mammary gland (breast) arising from cells lining the ducts.

Expected survival: A measure of *survival* that reflects the proportion of people in the general population alive for a given amount of time. Expected survival estimates are crude estimates calculated from *life tables* of the general population by age, sex and calendar year.

FOBT (faecal occult blood test): A test used to detect tiny traces of blood in a person's faeces that may be a sign of bowel cancer. The immunochemical FOBT is a central part of Australia's National Bowel Cancer Screening Program.

Heath system expenditure: Includes expenditure on health goods and services (for example, medications, aids and appliances, medical treatment, public health, research, collectively termed current expenditure) and on health-related investment (often referred to as capital expenditure).

Histology: The microscopic characteristics of cellular structure and composition of tissue.

Hospitalisation: See *Separation*.

Incidence: The number of new cases (of an illness or event, and so on) in a given period.

Indigenous: A person of Aboriginal and/or Torres Strait Islander descent who identifies as an Aboriginal and/or Torres Strait Islander. See also *Aboriginal or Torres Strait Islander*.

International Statistical Classification of Diseases and Related Health Problems: The World Health Organization's internationally accepted classification of death and disease. The Tenth Revision (ICD-10) is currently in use. The ICD-10-AM is the Australian modification of the ICD-10; it is used for diagnoses and procedures recorded for patients admitted to hospitals (see Appendix E).

Invasive: See *Malignant*.

Length of stay: Duration of hospital stay, calculated by subtracting the date the patient was admitted from the day of separation. All leave days, including the day the patient went on leave, are excluded. A same-day patient is allocated a length of stay of 1 day.

Life tables: Tables of annual probabilities of death in the general population.

Limited-duration prevalence: The number of people alive at a specific time who have been diagnosed with cancer over a specified period (such as the previous 5 or 25 years).

Malignant: A tumour with the capacity to spread to surrounding tissue or to other sites in the body. See *Invasive*.

Mammogram: A radiographic depiction of the breast.

Metastasis: See *Secondary cancer*.

Mortality due to cancer: The number of deaths that occurred during a specified period (usually a year) for which the underlying cause of death was recorded as cancer.

Mortality-to-incidence ratio: The ratio of the age-standardised mortality rate for cancer to the age-standardised incidence rate for cancer.

Neoplasm: An abnormal ('neo' = new) growth of tissue. Can be *benign* (not a cancer) or *malignant* (a cancer) (see also *Invasive*). Also known as a tumour.

New cancer case: See *Incidence*.

Non-Indigenous: People who have declared that they are not of *Aboriginal or Torres Strait Islander* descent.

Observed survival: A measure of *survival* that reflects the proportion of people alive for a given amount of time after a diagnosis of cancer. Observed survival estimates are crude estimates calculated from population-based cancer data.

Other Australians: Includes people who have declared that they are not of *Aboriginal or Torres Strait Islander* descent as well as those who have not stated their Indigenous status.

Overnight patient: An *admitted patient* who receives hospital treatment for a minimum of 1 night (that is, is admitted to, and separates from, hospital on different dates).

Palliative care hospitalisations: For the purposes of this report, those *hospitalisations* for which palliative care was a substantial component of the care provided. Such separations were identified as those for which the principal clinical intent of the care was palliation during part or all of the separation, as evidenced by a code of *palliative care* for the 'Care type' and/or 'Diagnosis' data items in the National Hospital Morbidity Database.

Pap smear (Pap test): Papanicolaou smear, a procedure to detect cancer and pre-cancerous conditions of the female genital tract.

Patient days: The number of full or partial days of stay for patients who were admitted for an episode of care and who underwent *separation* during the reporting period. A patient who is admitted and separated on the same day is allocated 1 patient day.

Period method: A method of calculating *survival* that is based on the survival experience during a recent *at-risk* or *follow-up* time period.

Population estimates: Official population numbers compiled by the Australian Bureau of Statistics at both state and territory and Statistical Local Area levels by age and sex, as at 30 June each year. These estimates allow comparisons to be made between geographical areas of differing population sizes and age structures (see Appendix E).

Prevalence (or **complete prevalence**)**:** The total number of people alive at a specific date who have ever been diagnosed with a particular disease such as cancer.

Primary cancer: A tumour that is at the site where it first formed (see also *Secondary cancer*).

Principal diagnosis: The diagnosis listed in hospital records to describe the problem that was chiefly responsible for the patient's episode of care in hospital.

Procedure: A clinical intervention that is surgical in nature, carries a procedural risk, carries an anaesthetic risk, requires specialised training and/or requires special facilities or equipment available only in the acute care setting.

Projection: Longer-term extrapolation of recent trend data using unknown parameters such as expected future populations.

Relative survival: The ratio of *observed survival* of a group of persons diagnosed with cancer to *expected survival* of those in the corresponding general population after a specified interval following diagnosis (such as 5 or 10 years).

Risk factor: Any factor that represents a greater risk of a health disorder or other unwanted condition or event. Some risk factors are regarded as causes of disease, others are not necessarily so. Along with their opposites, namely protective factors, risk factors are known as 'determinants'.

Same-day patient: A patient who is admitted to, and separates from, hospital on the same date.

Secondary site cancer: A tumour that originated from a cancer elsewhere in the body. Also referred to as a *metastasis*.

Separation: An episode of care for an *admitted patient* which may include a total hospital stay (from admission to discharge, transfer or death) or a portion of a hospital stay that begins or ends in a change of type of care (for example, from acute to rehabilitation). In this report, separations are also referred to as *hospitalisations*.

Stage: The extent of a cancer in the body. Staging is usually based on the size of the tumour, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body.

Statistical significance: An indication from a statistical test that an observed difference or association may be significant or 'real' because it is unlikely to be due just to chance. A statistical result is usually said to be 'significant' if it would occur by chance only once in 20 times or less often (see Appendix B for more information about statistical significance).

Survival: A general term indicating the probability of being alive for a given amount time after a particular event, such as a diagnosis of cancer.

Symptom: Any indication of a disorder that is apparent to the person affected.

Tumour: An abnormal growth of tissue. Can be *benign* (not a cancer) or *malignant* (a cancer).

Underlying cause of death: The disease or injury that initiated the sequence of events leading directly to death.

Valid FOBT test result: Faecal occult blood test result that is either positive or negative. Inconclusive results are excluded from analysis.

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List of tables

List of figures

List of boxes

Cancer in Australia: an overview 2014 presents the latest available information on national population screening programs, cancer incidence, hospitalisations, survival, prevalence and mortality. It is estimated that the most commonly diagnosed cancers in 2014 will be prostate cancer, colorectal cancer and breast cancer (excluding basal and squamous cell carcinoma of the skin, as these cancers are not notifiable diseases in Australia). For all cancers combined, the incidence rate is expected to increase by 22% from 1982 to 2014, but the mortality rate is estimated to decrease by 20%. Cancer survival has improved over time. Cancer outcomes differ by Aboriginal and Torres Strait Islander status and remoteness area.

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Clinical Practice Guidelines

FOR THE DIAGNOSIS AND MANAGEMENT OF LYMPHOMA

APPROVED BY

Australian Government
National Health and Medical Research Council

Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma

APPROVED BY THE NHMRC ON 8 DECEMBER 2005

Australian Government
National Health and Medical Research Council

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NHMRC approval

These guidelines were approved by the National Health and Medical Research Council at its 159th Session on 8 December 2005, under section 14A of the National Health and Medical Research Council Act 1992. Approval for the guidelines by the NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with the Australian Cancer Network for any reviews or updates of these guidelines.

Disclaimer

This document is a general guide to appropriate practice, to be followed only subject to the clinician's judgement in each individual case.

The guidelines are designed to provide information to assist in decision making and are based on the best information available at the date of compilation (August 2004).

Conflict of interest

The development of these clinical practice guidelines has been by a non-remunerated working party of the Australian Cancer Network, with further support from The Cancer Council Australia and the Clinical Oncological Society of Australia.

Some members of the working party have received sponsorship to attend scientific meetings; been supported in the conducting of clinical trials; or been involved in an advisory capacity by pharmaceutical and biochemical companies.

Periodic updates

New information arising in areas considered to be of importance will be posted periodically on the ACN website (www.cancer.org.au/guidelines). This information will not yet have been approved by the NHMRC but will be included as appropriate in future editions of the document.

These guidelines can be downloaded from the Australian Cancer Network website at www.cancer.org.au/guidelines or from the National Health and Medical Research Council website: www.nhmrc.gov.au

Copies of this Guideline document can be ordered through the Australian Cancer Network on (02) 9036 3120 or email: acn@cancer.org.au

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CONTENTS

APPENDICES

Tables

Figures

PREAMBLE

Malignant lymphomas provide model strategies for cancer management. The sequential issues of sophisticated diagnostic and staging procedures, definition of therapeutic goals and integration of multimodality management are all present.

These guidelines emphasise the need for appropriate biopsy techniques to allow accurate diagnosis and subtyping according to the WHO scheme. Technical advances, particularly in molecular biology, will further refine diagnosis and generate prognostic information. These advances will allow treatment to be more tailored to individuals. In all types of lymphoma staging, using appropriate radiological techniques further refines prognosis and treatment selection. Emerging data from PET scanning offer additional promise.

Treatment across the spectrum of the lymphomas requires careful consideration of the integration of chemotherapy and/or radiotherapy. The availability of products of biotechnology (monoclonal antibodies and growth factors) in conjunction with chemotherapy offers improvements in treatment outcome. The entry of patients into appropriate clinical trials is recommended to improve evidence-based management policies.

The diagnostic and staging procedures define treatment decisions with either curative or palliative intent, depending on the subtype and stage of the lymphoma. The guidelines stress the need for the development of multimodality teams to guide the patient's journey from diagnosis through what are sometimes complex and difficult treatments.

Summary of guidelines and recommendations

Guidelines and key points	Level of evidence		Refs		Page
Chapter 2 – Epidemiology and aetiology	**NHL**	**Ref**	**HL**	**Ref**	
Guidelines: Immunodeficiency risk Post-transplant immunosuppression is a strong risk factor for lymphoma and a weak risk factor for Hodgkin lymphoma.	III-2	26	III-2	27	42
Immunodeficiency in HIV/AIDs infection is a strong risk factor.	III-2	28	III-2	29	42
Congenital immune deficiency is a strong risk factor.	IV	30	IV	2	42
Acquired autoimmune disease is a moderate risk factor.	III-2	31	III-2	31	42
Guidelines: Infectious organism risk Epstein-Barr virus (EBV) infection is a weak risk factor for lymphoma in the general population, a strong risk factor for lymphoma in the immune deficient, and a strong risk factor for Hodgkin lymphoma.	III-2	33	III-2	42	44
Helicobacter pylori (H *pylori*) infection is a moderate risk factor for gastric lymphoma.	III-2	43	-		44
Human T-lymphotrophic virus types I (HTLV-I) infection is a moderate risk factor for adult T-cell leukaemia/lymphoma (ATL).	IV	33	-		44
Human herpesvirus-8 (HHV8) infection is a moderate risk factor for primary effusion lymphoma (PEL).	IV	44	-		44
Proxy measures of delayed exposure to childhood infection are a moderate risk factor for Hodgkin lymphoma.	-		III-2	2	44
Guidelines: Occupational risk Exposure to pesticides or herbicides is a weak risk factor for lymphoma.	III-2	61	-		46
Farming as an occupation is a weak risk factor.	III-2	62	III-2	63	46
Work in a wood-related industry is a moderate risk factor for Hodgkin lymphoma.	-		III-2	64	46
Guidelines: Medical and comorbidity risk Childhood appendectomy is a moderate risk factor for lymphoma.	III-2	73	-		47
Skin cancer is a strong risk factor for lymphoma.	III-2	20	-		47
Diabetes is a weak risk factor for lymphoma.	III-2	74	-		47
Tuberculosis is a moderate risk factor for lymphoma.	III-2	75	-		47
Infectious mononucleosis is a moderate risk factor for Hodgkin lymphoma.	-		III-2	2	47
Guidelines: Lifestyle risk Cigarette smoking doubles risk of follicular lymphoma and Hodgkin lymphoma.	III-2	84	III-2	82	49
Use of vitamin supplements does not affect risk of lymphoma.	III-2	55	-		49

Guidelines and key points	Level of evidence	Refs	Page
Chapter 6 — Molecular techniques **Key points** Molecular tests should be performed by laboratories that have the required expertise and participate in relevant quality assurance programs. The results should always be correlated with clinical, morphological, immunophenotypic and other laboratory data, and should never be considered in isolation. At present, there is no Medicare funding to cover molecular studies. Strategies to overcome this issue should be addressed so that cost does not act as a disincentive.			101
Guideline: Assay — quality assurance Southern blot (SB) protocols should be optimised in each laboratory. At least three informative restriction enzymes should be used for each assay.	IV	9–12	103
Guideline: Assigning clonality Interpretation of Southern blot (SB) data and assignment of clonality should be according to widely accepted guidelines.	IV	11, 12, 14	103
Guideline: Preferred approach to molecular diagnosis Polymerase chain reaction (PCR)-based assays are the preferred first-line approach to the molecular diagnosis of lymphomas.	IV	3, 15–19	103
Guidelines: Assays — quality assurance PCR assays should be optimised in each laboratory, using accepted guidelines for performance and interpretation of results, and with knowledge of the sensitivity and limitations of each assay.	IV	14, 20, 21	105
In particular, new high-resolution automated assays, including multiplexed assays using comprehensive primer sets, will require a reappraisal of test sensitivities and specificities.	IV	22–26	105
PCR assays should be performed using a range of target DNA concentrations to avoid misinterpreting as monoclonal any discrete oligoclonal bands resulting from selective amplification of oligoclones in samples containing small numbers of lymphocytes.	IV	20, 27, 28	106
Where there is doubt over assignment of monoclonality, PCR assays should be repeated to ensure that a clone is reproducible.	IV	3, 29–31	106
Chapter 7 — Molecular and cytogenetic studies — diagnostic applications **Guidelines: Interpretation of assay results** PCR results for IgH clonality testing should: (i) be interpreted in the context of a detailed knowledge of the nature of the assay used, its qualitative and analytical sensitivities, and predictive value (ii) recognise that the most commonly employed CDR3 assays using consensus primers may have a significant false negative rate, particularly in follicular, marginal zone and diffuse large B-cell lymphomas.	IV	2–7	115
PCR analysis of TCRγ gene rearrangements is the recommended first-line approach for T-cell clonality testing. The results should be interpreted in the context of a detailed knowledge of the qualitative and analytical sensitivities, and the predictive value of the assay used.	IV	7, 10–19	116

Guidelines and key points	Level of evidence	Refs	Page
An appropriate laboratory should be informed before the biopsy, and specimens should be sent fresh and expeditiously.	IV	1, 2	144
Chapter 11 — Hodgkin lymphoma			
Guideline: Staging procedures			
All patients should undergo CT scans of at least the neck, chest, abdomen and pelvis.	IV	21, 22	151
Bone marrow biopsy is recommended in at least those cases with stage >IIA.	IV	23	151
FDG-PET scanning or, if unavailable, gallium scanning, are recommended for staging in all cases. Positron emission tomography (PET) is superior to gallium.	IV	24–27	151
Guideline: Approach to treatment			
Early-stage Hodgkin lymphoma with favourable characteristics should be treated by a combination of involved-field radiotherapy and systemic chemotherapy.	II	66	157
All subgroups of early Hodgkin lymphoma should be treated with a regimen that covers the spleen, supra-diaphragmatic and para-aortic lymph nodes, such as chemotherapy and involved-field radiotherapy, or subtotal nodal irradiation.	I	34	157
Guidelines: Hodgkin lymphoma (favourable) — chemo and radiation therapy			
Early-stage Hodgkin lymphoma with Favourable characteristics should be treated by a combination of involved-field radiotherapy and systemic chemotherapy.	II	34	158
Chemotherapy should consist of four cycles of ABVD. [This recommendation may change following completion of current studies investigating the use of two or three cycles of ABVD plus involved-field radiotherapy.]	II	74	158
Involved-field radiation therapy should be delivered to all the sites that were involved by Hodgkin lymphoma at diagnosis	II	34	158
Guidelines: Hodgkin lymphoma (unfavourable) — chemo and radiation therapy			
Early-stage Hodgkin lymphoma with unfavourable characteristics should be treated by a combination of Involved-field radiotherapy and systemic chemotherapy.	II	75, 76	159
Chemotherapy should consist of six cycles of ABVD.	II	75, 76	159
Involved-field radiation therapy should be delivered to all the sites that were involved by Hodgkin lymphoma at diagnosis.	II	75, 76	159
Guideline: Advanced disease			
Chemotherapy should be used for all patients with advanced Hodgkin lymphoma.	III	78, 79	159
Guideline: Advanced disease — chemotherapy regimen			
ABVD chemotherapy is recommended as a standard chemotherapy regimen for advanced Hodgkin lymphoma patients with an international prognostic score <4.	II-IV	64, 65	161
ABVD is superior to alternating MOPP/ABVD or MOPP/ABV hybrid because of lower toxicity.	II	64, 65	161
Chemotherapy should be given for a minimum of six cycles.	IV	65, 66	161

Guidelines and key points	Level of evidence	Refs	Page
A minimum of two further cycles of chemotherapy should be given after a complete response as been attained.	IV	64, 65	161
Guideline: Prognostic score – stem cell use			
BEACOPP (standard dose) should be considered in patients younger than 65 with advanced Hodgkin lymphoma and a prognostic score ≥4.	II	80	162
There is no group of patients that can be prospectively identified with a prognosis so poor that high-dose chemotherapy and haematopoietic stem cell transplantation can only be recommended for relapsed patients as primary treatment.	IV	82	162
Guideline: Hodgkin lymphoma — optimal radiotherapy			
Radiotherapy is not recommended after modern chemotherapy as routine treatment to non-bulky sites in advanced Hodgkin lymphoma that have attained complete response.	II	85	162
In bulky sites and in sites that fail to achieve complete remission after chemotherapy, radiotherapy can improve freedom from progression in advanced Hodgkin lymphoma	II	83, 84	162
Guideline: Hodgkin lymphoma — bulky mediastinal mass			
Consolidative involved-field radiotherapy is recommended after chemotherapy for patients with bulky mediastinal masses.	IV	83	162
Chemotherapy should be given for a minimum of six cycles.	II	83, 84	162
Guideline: Nodular lymphocyte predominant Hodgkin lymphoma			
Nodular lymphocyte predominant Hodgkin lymphoma Stage I–IIA nodular lymphocyte predominant Hodgkin lymphoma should be treated with radiotherapy	IV	86, 89	163
Involved-field radiotherapy should be used for non-bulky stage IA nodular lymphocyte predominant Hodgkin lymphoma.	IV	86, 89	163
Guidelines: Hodgkin lymphoma — CT and PET scanning			
Functional imaging is recommended in addition to CT scanning to assess definitive response to treatment.	IV	26, 32, 105, 110,	166
PET scanning rather than gallium scanning is recommended for response assessment after treatment for Hodgkin lymphoma.	IV	25, 110, 111	166
Guideline: Primary refractory Hodgkin lymphoma			
Patients with primary refractory Hodgkin lymphoma should be treated with high-dose chemotherapy and autologous stem cell transplantation.	IV	126	168
Key point:			
Biopsy is recommended to confirm first recurrence in all cases.			168
Chapter 12 — Low-grade lymphoma			
Guidelines: Staging — pre-radiotherapy			
Before embarking on potentially curative radiation therapy for patients with clinical stage I–III 'low-grade' lymphoma, staging should include functional imaging with PET or thallium scanning.	III	8, 9	184
Before embarking on potentially curative radiation therapy for patients with clinical stage I–III 'low-grade' lymphoma, staging should include careful examination of multiple levels of a bone marrow biopsy specimen ≥ 2.0 cm in length.	III	5, 6	184

Guidelines and key points	Level of evidence	Refs	Page
Guidelines: Staging — optimal treatment Treatment for adult patients with clinical stage I or II 'low-grade' follicular lymphoma should include involved-field radiation therapy of 30–36 Gy.	III	12	186
Patients with stage I 'low-grade' follicular lymphoma who are rendered apparently disease free after the diagnostic biopsy and have a life expectancy of less than five years may be observed without further therapy.	IV	21	186
Combined modality treatment with both IF XRT and combination chemotherapy based on alkylating agents is a reasonable option for adult patients with clinical stage I or II 'low-grade' follicular lymphoma.	III	26	186
Guideline: Lymphatic irradiation — haematopoietic progenitor Wide-field 'comprehensive lymphatic irradiation' should be considered for patients with clinical stage III disease after careful and complete staging.	III	35	188
Key point: Collection and storage of autologous haematopoietic progenitor cells should be considered before the delivery of pelvic irradiation.			188
Guideline: Low-grade lymphoma FLIPI — measure and record At the time of diagnosis, the factors constituting the FLIPI should be measured and recorded in all patients.	IV	39	188
Key point All patients with symptomatic advanced-stage follicular lymphoma should be offered therapy.			189
Guidelines: Low-grade lymphoma — 'watch and wait' criteria Where a 'watch and wait' approach is applied in the initial management of a patient with advanced-stage follicular lymphoma, regular monitoring and active surveillance for disease progression is mandatory.	IV	42	190
Patients who are initially managed by a 'watch and wait' policy and who either develop symptomatic disease, or have disease that progresses beyond the criteria for 'low tumour burden', should commence therapy.	IV	42	190
Asymptomatic patients who do not fulfil the criteria for 'low tumour burden' follicular lymphoma, using either of the validated criteria, should commence treatment at the time of diagnosis.	IV	42, 43	190
Guidelines: Therapy for advanced-stage follicular lymphoma Single-agent alkylating agents with or without corticosteroids (using published schedules) are a suitable treatment for patients with advanced-stage follicular lymphoma.	II	42, 46, 47, 49, 51	191
Combination chemotherapy regimens (e.g. CVP or CHOP) may be used where a shorter treatment duration or more rapid disease response is desired, although these regimens are not consistently associated with any long-term improvement in quality or duration of disease response, or overall survival.	II	46, 47, 49, 51	191
Guideline: Advanced disease response and radiotherapy (clinical trial) Where a patient with advanced-stage follicular lymphoma has achieved a compete response to initial therapy, irradiation to nodal sites of disease (initially bulky or otherwise) is not recommended outside of the context of a clinical trial.	II	48	191

Guidelines and key points	Level of evidence	Refs	Page
Guideline: 'Aggressive' treatment Pending the availability of further data from phase III studies, where motivated and informed patients have been made fully aware of the promising but inconclusive data regarding potential overall survival benefits of initial aggressive treatment approaches and wish to pursue such a strategy, initial therapy attempting to achieve maximal cytoreduction (potentially guided by molecular assessment of minimal residual disease) is a reasonable approach in carefully selected cases.	II	60–64	192
Guideline: Criteria for therapy with interferon The use of interferon-α maintenance after anthracycline -based initial therapy (e.g. CHOP) may be considered on an individual patient basis.	II	55, 53, 73	193
Guideline: Recurrent disease and fludarabine Where patients have initially been treated with an alkylating agent and have recurrent disease requiring systemic chemotherapy, therapy containing fludarabine should be considered.	II	76	194
Guideline: Therapy in relapsed follicular lymphoma In patients with relapsed follicular lymphoma, the addition of rituximab to fludarabine-based combination chemotherapy is associated with improved outcomes, including better overall survival.	II	65	194
Guideline: Radioimmunotherapy criteria For patients who fulfil specific criteria (specifically <25% bone marrow infiltration), the use of radioimmunotherapy is associated with a higher rate of disease control and should be considered in preference to single-agent rituximab.	II	77	195
Key point Where it can be safely performed, re-biopsy of the dominant or clinically suspicious disease site should be performed in patients with relapsed or refractory follicular lymphoma to investigate possible histologic transformation to aggressive lymphoma.			196
Guideline: Auto HCST — indication Auto-HSCT may be indicated in patients who have failed at least one conventional chemotherapeutic regimen. The use of auto-HSCT as part of up-front treatment remains controversial.	II III, IV	83 84, 85	197 197
Guidelines: Auto-HCST and NST considerations Conventional sibling allogeneic HSCT should be limited to young patients with poor prognosis follicular lymphoma who have limited comorbidities. NST can be considered in patients with poor prognosis follicular lymphoma, but should optimally be performed in the context of approved clinical trials.	IV III, IV	86-88 89–91, 92	197 197
Guideline: Extra-gastric marginal zone lymphoma — pathogen treatment urgency Where an identified pathogen is associated with extra-gastric marginal zone lymphoma, and there is no clinical urgency to obtain immediate disease regression, eradication therapy directed against the identified pathogen is recommended.	III	95, 96	199

Guidelines and key points	Level of evidence	Refs	Page
Guideline: Extra-gastric marginal zone lymphoma — durable local control			
Where there is no associated infective agent identified, successful eradication of the agent is not associated with disease regression, or there is clinical urgency to achieve disease regression, localised irradiation using 25–35 Gy is highly effective in achieving durable local control for extra-gastric marginal zone lymphoma (nodal and non-nodal).	III	93, 101, 102	200
Guidelines: Extra-gastric marginal zone lymphoma — therapeutic options			
Patients with asymptomatic disseminated marginal zone lymphoma may be observed without initial therapy.	III	110	201
Patients with symptomatic or progressive disseminated marginal zone lymphoma should be treated with single-agent chemotherapy (alkylating agents/nucleoside analogues/rituximab have similar levels of activity).	III	104–107	201
There is no apparent benefit from the use of combination chemotherapy regimens (e.g. CHOP) as initial therapy.	III	99, 109, 110	201
There is no benefit from the addition of anthracylines to alkylating agents (e.g. chlorambucil).	II	108	201
Guideline: Waldenstrom's lymphoma — therapeutic options			
Patients with asymptomatic Waldenstrom's macroglobulinemia may be observed without initial therapy.	IV	113	203
Patients with symptomatic or progressive Waldenstrom's macroglobulinemia may be treated with plasmapheresis.	III	115, 116	203
Guidelines: Waldenstrom's lymphoma — response to therapy			
In patients with relapsed Waldenstrom's macroglobulinemia, a nucleoside analogue (2-CdA or fludarabine) is associated with a higher response rate and more durable disease control than alkylating agent/anthracycline therapy.	II	122	204
Rituximab has useful activity as a single-agent in relapsed/refractory Waldenstrom's macroglobulinemia.	III	123–125	204
The combination of fludarabine and rituximab has high levels of activity in relapsed/refractory Waldenstrom's macroglobulinemia.	III	126	204
Key points			
Splenic Marginal Zone Lymphoma			205
There are no prospective studies available to guide recommendations in this area. All available data are derived from retrospective cohort series. Within these limitations, the following recommendations can be made:			
1 It is reasonable to follow, without active intervention, patients who are asymptomatic with stable lymphocytosis and minor, stable and asymptomatic cytopenias.		130,131	205
2 It is recommended that patients be screened for hepatitis C. Where active hepatitis C is the underlying immunological precipitant for their lymphoma, specific treatment of the hepatitis C can be associated with significant regression of the lymphoma.		7	205

Guidelines and key points	Level of evidence	Refs	Page
3 Where patients have progressive or symptomatic splenomegaly, even in the context of significant marrow infiltration, splenectomy is the preferred therapy, where this can be performed safely.[130–132] Splenectomy results in favourable clinical response in ~90% of patients. About50% will never require any further therapy. Patients who are initially treated with splenectomy are reported to have a superior likelihood of survival than those initially treated with chemotherapy, although selection bias cannot be excluded in these retrospective comparisons.[130]		130–132 as indicated	205
4 Where systemic chemotherapy is required for disease progression following splenectomy, or for symptomatic extra-splenic disease, either single-agent alkylating agents such as chlorambucil[131] or fludarabine[133,134] are reasonable choices, based on limited non-comparative data. CHOP does not appear superior to simpler alkylating agent therapy.[132]		132–134 as indicated	206
Chapter 13 — Aggressive lymphoma			
Guideline: Recommended treatment for localised aggressive lymphoma			
Patients with non-bulky stage I, with normal LDH and ECOG PS ≤1, should be treated with three cycles of CHOP and involved-field radiation therapy to a dose of 30–40 Gy.	II-III	19–24	221
Patients with bulky stage I, stage II, high LDH, ECOG ≥2 and/or three or more disease sites should be treated with 6–8 cycles of CHOP followed by involved-field radiation to 30–40 Gy.	II	15, 16	221
Radiotherapy may be unnecessary in elderly patients with localised aggressive lymphoma.	II	17	221
Patients with low-risk localised aggressive lymphoma may be treated with more intensive sequential chemotherapy, omitting radiation therapy.	II	18	221
Guideline: Recommended treatment for advanced-stage DLBCL			
CHOP chemotherapy is equivalent in outcome to other chemotherapy regimens with decreased toxicity.	II	19–24	222
The addition of rituximab to CHOP is superior to CHOP in patients older than 60 years.	II	25–31	223
Guideline: CHOP chemotherapy			
Dose escalation of CHOP or CHOP-like regimens does not improve overall survival.	II	32	223
Guideline: CHOP chemotherapy and etoposide			
Etoposide added to CHOP therapy in low-risk patients younger than 60 years is superior in time to treatment failure than CHOP	II	35	224
Key point			
It is difficult to offer a definitive guideline given the rapidly emerging new information about the adoption of dose-dense CHOP-like regimens with haemopoietic growth factor support. Participation is recommended in clinical trials where possible, or development of treatment policies in specialised units as new information becomes available.			224

Guidelines and key points	Level of evidence	Refs	Page
Key points: *Special populations — the aged* Prophylactic G-CSF should be considered in elderly patients and also in patients thought to be at high-risk, which is defined as: • pre-existing neutropenia due to disease • extensive previous chemotherapy or significant previous radiation therapy • history of recurrent febrile neutropenia while receiving chemotherapy of similar or lower-dose intensity • at risk for serious infection (e.g. poor performance status, decreased immune function, open wounds, or active tissue infection) Careful consideration should be given in the use of anthracyclines in this group of patients with potential cardiac dysfunction.			226
Guideline: Front-line high-dose therapy with stem cell support Up-front, high-dose therapy with autologous stem cell transplantation cannot be recommended outside of a clinical trial.	II	47–52	227
Key points *Mantle cell lymphoma* Identification of indolent subgroups of mantle cell lymphoma using appropriate indices and markers is emerging as an important issue. The optimal therapy of patients with mantle cell lymphoma is unclear at present. Given the poor outcomes with conventional therapy, novel approaches should be considered and implemented, preferably in the context of clinical trials. Such patients should optimally be managed in specialised centres.			229 231
Chapter 14 — High-grade lymphoma **Guideline: Specialist pathologist, bone marrow and cerebrospinal fluid (CSF) assessment** Biopsies of tissues suspected to be Burkitt or other high-grade lymphoma should be referred for review by a pathologist skilled in lymphoma diagnosis. Patients with newly diagnosed high-grade lymphoma should have mandatory assessment of bone marrow and cerebrospinal fluid.	IV IV	3 8	248 248
Guideline: Multidisciplinary care Patients with newly diagnosed high-grade lymphoma should ideally be managed in specialist units experienced in treating these disorders.	IV	9, 10	248
Guideline: Intensive treatment of Burkitt lymphoma Adults with Burkitt lymphoma should be treated, where possible, with intensive combination chemotherapy of relatively limited duration, according to one of the recently published treatment regimens.	III	8, 11–15	249
Guideline: Lymphoblastic lymphoma — intensive treatment Adults with lymphoblastic lymphoma should be treated with a regimen designed for therapy of acute lymphoblastic leukaemia. This must include CNS prophylaxis.	III III	19, 21 36	250 250

Guidelines and key points	Level of evidence	Refs	Page
Guideline: **Lymphoblastic lymphoma — specialist care** Patients with lymphoblastic lymphoma should be managed in units with experience in dealing with the early complications of the disease and its treatment.	IV	19, 21	252
Prophylaxis with fluids and allopurinol should be given before starting therapy.	IV	36	252
Guideline: Radiation therapy and bulky disease Adjuvant radiotherapy is not indicated in treatment of sites of original bulk disease in high-grade lymphoma.	II	39	253
Guideline: High-dose chemotherapy and autologous stem cell support High-dose chemotherapy with autologous stem cell support is effective therapy for patients with lymphoblastic lymphoma in first remission, but it has not been proven to produce superior disease-free survival. Ideally, it should be used only in the context of a clinical trial.	III	40, 41	254
Chapter 15 — Childhood lymphoma **Guideline: Combination chemotherapy for Burkitt lymphoma** Paediatric patients with Burkitt lymphoma require intensive combination chemotherapy of relatively short duration.	III	3	261
Guideline: CNS chemoprophylaxis — advanced lymphoma Central nervous system (CNS) chemoprophylaxis is mandatory for all patients with advanced-stage disease, and for those with localised head and neck disease.	III	13, 14	261
Guidelines: Management of lymphoblastic lymphoma Children with lymphoblastic lymphoma should be treated with a chemotherapy regimen designed for the therapy of acute lymphoblastic leukaemia (ALL).	III	3	262
The duration of treatment may be able to be adjusted, based on risk factors.	III	7, 3, 15	262
Treatment must include central nervous system (CNS) prophylaxis.	III	21, 22	262
Patients with central nervous system (CNS) disease at diagnosis require cranio-spinal radiotherapy.	IV	7, 15	262
Guidelines: Management, localised large-cell lymphoma and advanced state disease Children with localised large-cell lymphoma require intensive short-term therapy.	III	1, 5, 6, 15, 31	263
Children with advanced-stage disease require intensive Burkitt-style therapy.	III	5, 6, 15, 32, 33	263
Guideline: Treating anaplastic large-cell lymphoma Therapy for anaplastic large-cell lymphoma should be based on SNCL (Burkitt's) protocol until optimum therapy is defined.	III	34–36	264
Guideline: Open biopsy to ensure less diagnostic error Open biopsy to ensure sufficient tissue for analysis is the procedure of choice to minimise diagnostic errors (see Chapter 10 — Surgical biopsy).	III	47	266

Guidelines and key points	Level of evidence	Refs	Page
Guideline: Low or intermediate risk disease — combined-modality therapy Children with localised low-risk or intermediate-risk disease (that is, they have adverse prognostic factors, for example, mediastinal mass, bulky disease, B symptoms) are best treated with combined-modality therapy.	II	55, 56	267
Guideline: Multidisciplinary treatment for advanced lymphoma For patients with advanced disease, intensive risk-adapted chemotherapy represents standard therapy. Patients who achieve prompt complete remission may not require radiotherapy. For patients who have a partial response, involved-field radiotherapy to areas of bulk disease is of benefit.	II	55, 56	268
Chapter 16 — Immunodeficiency associated lymphoma **Guideline: Immune deficiency — treatment** Patients with primary immune deficiency (PID) should be under close clinical surveillance for the development of lymphoproliferative disease. Maintain a high index of suspicion with prolonged symptoms of unidentified infection; symptoms referrable to common sites of extranodal lymphoma; and precursor lesions such as lymphoid hyperplasia and monoclonal gammopathy.	V	2, 3	276
Standard curative intent therapy appropriate for the specific lymphoma should be administered, with special attention to supportive care for expected treatment-related toxicity.	IV	16	276
Primary immune deficiency (PID) patients with lymphoma should be assessed for potential allogeneic bone marrow transplant.	opinion	10, 11	276
Guidelines: Management for lymphomas associated with HIV Full-dose CHOP should be considered the current standard of care for HIV-related lymphoma, although new data are awaited.	IV	19, 23	280
Highly active anti-retroviral therapy (HAART) should be commenced or maximised in patients with HIV-related lymphoma.	III	22, 26	280
Hodgkin lymphoma should be managed as for non-HIV patients with the addition of HAART.	III	30	280
Key point Primary CNS lymphoma should be managed as for non-HIV patients with the addition of highly active anti-retroviral therapy (HAART).			280
Key point Patients with post-transplant lymphoproliferative disorder (PTLD) should undergo standard diagnostic and staging procedures with special attention to extranodal sites including the allografted organ and/or gut, lung, central nervous system, kidney.			281
Guidelines: Post-transplant lymphoproliferative disorder (PTLD) — risk factors Two of the major known risk factors for the development of PTLD are Epstein-Barr virus (EBV) sero-mismatch and cytomegalovirus (CMV) sero-mismatch (R-, D+).	III-2	36, 37	285
Use of OKT3 is the third powerful known risk factor for PTLD.	III-2	39	285

Guidelines and key points	Level of evidence	Refs	Page
Key points			
Before transplant, the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) status of recipient and donor should be determined to identify patients at high risk of developing post-transplant lymphoproliferative disorder (PTLD).			285
Post transplant use of OKT3 should be minimised and recipients should be identified as patients at high risk for the development of PTLD.			285
Guidelines: Surveillance for PTLD patients			
Monitor Epstein-Barr virus (EBV) viral load serially by quantitative real-time PCR in plasma (preferably in the context of ongoing research).	IV	94–96	286
Monitor for the development of monoclonal gammopathy.	IV	98	286
Guidelines: Management of PTLD patients			
All patients with PTLD should have baseline immunosuppression substantially reduced or ceased as the initial therapeutic strategy.	IV	67, 68, 99	291
Consider early additional therapy in patients with risk factors for non-response to reduced immunosuppression (elevated LDH, end organ dysfunction, multi-organ involvement, late onset PTLD, rapidly progressive disease).	IV	46, 78, 99	291
Additional therapies that should be considered but the roles of which have not been clearly defined include systemic antivirals (ganciclovir, acyclovir)[102–105] and alpha interferon.[110–113]	IV	102–105, 110–113	291
Standard combination chemotherapy for aggressive lymphoma should not be delayed in patients who are not responding to initial strategies (see Chapter 13 — Aggressive lymphoma).	IV	115, 116	291
Key point:			
Standard chemotherapy should be considered as initial therapy in patients with extensive systemic or rapidly progressive disease, particularly with IPI >1.			291
Guidelines: Management of PTLD patients			
Rituximab is an active agent and should be considered as an additional therapeutic modality.	IV	122–125	291
Radiation may contribute to the management of PTLD and should be considered in the same settings as non-PTLD lymphomas.	IV	109, 115	291
Adoptive immunotherapy with allogeneic EBV-specific CTL should be considered in post-BMT PTLD.	IV	127	291
Adoptive immunotherapy with autologous EBV-specific CTL should be considered for solid organ PTLD patients in the context of continuing clinical research.	IV	128, 129	291
Guidelines: Methotrexate and lymphoproliferative disorders			
Patients being treated with methotrexate should be monitored for the development of a lymphoproliferative disorder.	IV	130–135	292
Methotrexate should be ceased in patients who develop lymphoma and observed for regression before administration of the appropriate lymphoma therapy, if clinically feasible. Methotrexate should not be reintroduced in such patients	IV	140–142	292

Guidelines and key points		Level of evidence	Refs	Page
Chapter 17 — Gastric lymphoma				
Guidelines: Gastric mucosal-associated lymphoid tissue (MALT) lymphoma staging and evaluation				
Patients should be staged as for lymphomas in general.		III	5	305
Endoscopic ultrasound should be included in the staging process if experienced operators are available.		III	6–9	305
Markers for the t(11;18) (q21; q21) translocation should be obtained on tumour biopsy samples.		III	1, 4	305
Guidelines: Treatment of gastric MALT lymphoma				
Standard triple therapy should be used in all patients (*H-pylori* positive and negative).		III	1–5, 18	308
Patients require endoscopic follow up with biopsy initially at two months after eradication, and then yearly.		III	18	308
Patients failing to respond to eradication therapy may require radiation therapy.		III	19–21	308
Guideline: Lack of role for surgery				
In general, patients with gastric MALT lymphoma do not require surgery, because results of radiotherapy and/or chemotherapy are superior.		III	22, 23	309
Guideline: Treatment of gastric and diffuse large-cell lymphoma (DLCL)				
Patients are managed as for DLCL as described elsewhere with CHOP chemotherapy.		I–III	23–27	310
Chapter 18 — Primary cutaneous lymphomas				
Guidelines: Indications for specific treatment modalities in early-stage (IA–IIA) mycosis fungoides				
Topical steroids	Limited patch-stage	III	16, 20, 48	320
PUVA/UVB	Extensive patch-stage	III	16, 21–23, 57–59	320
Topical chemotherapy	Limited patch/plaque stage	III	16, 24, 25	320
Retinoids	Extensive patch-stage (2nd-line)	III	33–39	320
Bexarotene	3rd line (not commercially available in Australia)	III	41, 42, 44	320
Alpha interferon +/- phototherapy	2nd or 3rd line	III	26–28, 60	320
Radiotherapy	Plaque- or tumour-stage	III	16, 45–47, 49–56, 61	320
Oral methotrexate	2nd or 3rd line	III	62–64	320
Systemic chemotherapy	3rd line	III	63–70	320
Denileukin diftitox	3rd line	III	71	320
Guidelines: Indications for specific treatment modalities in advanced-stage (IIB–IV) mycosis fungoides				
Topical steroids	Symptomatic control	III	16, 20, 48	321

Guidelines and key points		Level of evidence	Refs	Page
Radiotherapy	Symptomatic control	III	45–47, 49-56, 61	321
Oral methotrexate	2nd or 3rd line	III	62–64	321
Systemic chemotherapy	2nd or 3rd line	III	63-70	321
Alpha interferon +/- phototherapy	2nd or 3rd line	III	26, 27, 60	321
Alemtuzumab	2nd or 3rd line	III	76, 77	321
Bexarotene	3rd line (not commercially available in Australia)	III	43	321
Extracorporeal photopheresis	1st, 2nd or 3rd line (patients with circulating clonal cells only (i.e. Sézary syndrome)	III	72, 79–88	321
Denileukin diftitox	3rd line (not commercially available in Australia)	III	71	321
Guidelines: Indications for specific treatment modalities in C-ALCL				
Surgery and radiotherapy	If limited disease	III	95–97	323
Oral methotrexate	More extensive disease	IV	95–97	323
Systemic chemotherapy	Very rarely needed	IV	95–97	323
Guidelines: Indications for specific treatment modalities in LyP				
Observation	If limited	III	95, 98–100	323
Topical steroids	If localised	IV	95, 98–100	323
Phototherapy	If extensive	III	95, 98–100	323
Oral methotrexate	2nd or 3rd line	III	95, 98–100	323
Alpha interferon +/- phototherapy	2nd or 3rd line	III	95, 98–100	323
Systemic chemotherapy	Rarely needed	III	95, 98–100	323
Guidelines: Indications for specific treatment modalities in CD30 negative large cell (EORTC), Peripheral T-cell lymphoma unspecified (WHO)				
Systemic chemotherapy	Routine	IV	101–104	324
Radiotherapy	Additional to chemotherapy if localised	IV	101–104	324
Guidelines: Indications for specific treatment modalities in subcutaneous panniculitis like lymphoma				
Systemic chemotherapy	Routine	IV	10, 105	325
Radiotherapy	Additional to chemotherapy if localised	IV	10, 105	325
Guidelines: Indications for specific treatment modalities in cutaneous follicle centre lymphoma				
Surgery and radiotherapy	If limited	III	4, 108, 111–114	325

Guidelines and key points		Level of evidence	Refs	Page
Systemic chemotherapy	Rarely needed	IV	4, 108, 111–114	325
Rituximab	If extensive and relapsed or poor tolerance to chemotherapy	III	109, 110	325
Guidelines: **Indications for specific treatment modalities in cutaneous diffuse large B-cell lymphoma (with poor prognostic features**				
Systemic chemotherapy +/- rituximab	Routine	III	107, 109, 113, 119–121	326
Radiotherapy	Additional to chemotherapy if localised	III	107, 109, 113, 119–121	326
Guideline: Indications for specific treatment modalities in cutaneous marginal zone lymphoma				
Surgery and radiotherapy	If limited	III	113, 120, 121, 125	326
Systemic chemotherapy	Rarely needed	III	113, 120, 121, 125	326
Chapter 19 — Primary cerebral lymphoma **Guideline: Biopsy** Patients with suspected primary cerebral lymphoma (PCL) require biopsy only rather than resection.		III	3	336
Guideline: Chemotherapy Patients with PCL may be treated with chemotherapy alone or chemotherapy in combination with radiotherapy.		III	1, 5–10	337
Chapter 20 — Palliative care **Guideline: Palliative treatments in lymphoma** Principles of palliation established in solid tumour malignancies apply in the management of patients with lymphoma. Active treatments such as single-agent chemotherapy, corticosteroids and radiotherapy may be of significant value in terminally ill patients with lymphoma.		III, IV III, IV	1, 2, 4, 5 3, 6	340 340
Chapter 21 — Complications of treatment **Key point** The implications of chemotherapy on fertility should be discussed with all patients for whom this is relevant.				343
Guideline: Chemotherapy For patients receiving conventional chemotherapy for lymphoma (ABVD for Hodgkin disease, CHOP q21 for lymphoma), sperm cryopreservation in men or oocyte retrieval (in women) is not recommended routinely.		IV	3, 4, 10	343

Guidelines and key points	Level of evidence	Refs	Page
Key points In patients receiving high-dose chemotherapy prior to transplantation, the following are recommended: *(a) Pre-transplant*: referral to a fertility specialist. In women, the possibility of chemotherapy-induced premature menopause, and the acute and long-term effects of this, should be explained. Use of a continuous contraceptive pill during therapy is not unreasonable in pre-menopausal women, but is not proven. If available, enrolment in a trial evaluating GnRH agonists or antagonists should be considered. *(b) Post-transplant*: *Women* (i) if ovarian failure occurs, HRT should be considered, if appropriate (ii) regular surveillance of gonadal function off HRT to detect spontaneous recovery of fertility may be indicated in selected patients (iii) regular gynaecological review (by a gynaecologist with particular interest and expertise in post-transplant issues such as oestrogen deficiency, infection, and, in allograft recipients, vaginal graft versus host disease, is strongly recommended), cervical cytology, and, in those receiving HRT, mammography (iv) bone mineral density scans in women not on HRT, particularly if there are other risk factors for osteoporosis (v) testosterone levels should be checked in patients with symptoms suggestive of androgen deficiency *Men* (i) regular surveillance of gonadal function post transplant (ii) enquire about libido and erectile dysfunction. Consider (a) testosterone replacement if low testosterone levels and symptomatic, and (b) sildenafil if erectile dysfunction and no contra-indication.			346–47
Guidelines: Advice to patients			
During cytotoxic therapy, sexual intercourse can continue, but reliable contraception should be used. Condoms should be used within 48 hours of chemotherapy if the male is treated, to avoid seminal transmission of cytotoxics, particularly if the female partner is pregnant.	IV	41	347
Sperm banking should be offered to males who are receiving potentially sterilising chemotherapy and who may wish to have children in the future.	IV	24, 25	347
Women receiving chemotherapy in which fertility and/or premature menopause are relevant should discuss the potential impact of their treatment on these issues with their oncologist and, in some cases, with a fertility expert.	IV	11, 31–33	347
Conception of a child by men (and possibly for women) should be delayed for at least three months until after the completion of cytotoxic therapy affecting the gonads.	IV	41	347
Patients should be informed about the risks of second malignancy at the time of treatment as well as at completion of therapy.	IV	42–46	350
Patients should be informed about the effects of smoking, diet, sun exposure and lifestyle habits that may increase their risk of developing second malignancy at specific sites such as lung, skin, breast, digestive tract and cervix.	IV	55	350

Guidelines and key points	Level of evidence	Refs	Page
Lifelong surveillance for secondary cancers is appropriate. A management plan should be organised for surveillance relevant to each individual patient, with the patient, their family and the general practitioner.	IV	42–46	350
Key points:			
• More intensive chemotherapy and radiotherapy may both be associated with a greater risk of second malignancy.			351
• All patients should have at least annual full blood examination for the first decade after treatment.			351
• In women younger than thirty treated with mantle radiation, routine annual mammography from seven to eight years after treatment is recommended in addition to regular self-examination and six-monthly physician examination. Abnormalities should be further investigated with ultrasound and biopsy.		49, 53, 68–70	351
• The safety of hormone replacement therapy in postmenopausal women who have received mantle radiation is uncertain. There is some evidence that oestrogen deficiency may reduce risk of secondary breast cancer.		53, 68, 70	351
• The role of screening tests for second thyroid cancer for patients treated with radiation therapy to the head, neck and chest, is uncertain. Ultra-sound and physical examination can be used at appropriate intervals, for example, one year post-completion of therapy, then three-yearly to ten years, followed by annual thyroid ultrasound from ten years after treatment. Given the greater incidence of this complication following radiotherapy in childhood, it may be more important to screen this population.			351
Guidelines: Physician alerts after treatment for lymphoma			
Multidisciplinary care enhances psychosocial and sexual functioning, with fertility counselling and management of hypogonadism.	IV	76, 85, 86	354
Clinicians should be alert to symptoms of depression even in the longer term, particularly in the paediatric population.	III-2 IV	71, 82 76, 82	354
Memory and cognitive disturbance may occur after systemic chemotherapy. It may be worsened by anxiety, particularly at the time of clinic attendance. Patient interviews may need to be enhanced with written material and diagrams.	IV	72, 80	354
At the patient's request, clinicians may need to communicate with the education facility and/or workplace (with regard to patient privacy) to counter discrimination in employment or study.	IV	71, 77, 78, 84	354
Chronic fatigue and prolonged restriction of strenuous physical activity may follow treatment for lymphoma.	IV	71, 72, 73	354
Key points:			
Patients should understand that they should not donate blood or organs.			354
Keep the patient's treatment team and other doctors informed.			
Chapter 22 — Communication with the patient			
Guidelines: Patient information			
Patients and their carers often seek information about their cancer at the time of diagnosis, but studies have shown that only part of the initial consultation is remembered. Therefore, the provision of information should not end with the initial consultation.	II	1	364

Guidelines and key points	Level of evidence	Refs	Page
Information for patients with lymphoma should include: • the meaning of lymphoma, suspected risk factors and the extent of disease • proposed approach to investigation and treatment, including information on expected benefits, the process involved, common side effects, whether the intervention is standard or experimental and who will undertake the intervention • the likely consequence of choosing a particular treatment, or no treatment • the time involved • the costs involved • the effect of cancer and its therapy on interpersonal, physical and sexual relationships • typical emotional reactions • entitlements to benefits and services, such as subsidies for travel or prostheses • access to cancer information services.	IV	3, 4	363
Guidelines: Preparing patients for treatment Providing patients with lymphoma with information about the procedure they are about to undergo significantly reduces their emotional distress and anticipatory side effects, and improves their psychological and physical recovery.	I II	11–14	364
Various formats for providing information about procedures have been shown to decrease anxiety and psychological distress. They include discussions with a clinician or allied health professional, booklets, and videotape information.	II	15–17	365
Sensory information significantly reduces anxiety in patients undergoing medical procedures. The best results appear to be achieved by providing both sensory and procedural information.	I	11, 12	365
Guidelines: Patient support Support needs for individuals with lymphoma and their families may include:			
• counselling	I	12	365
• exploring feelings with a member of the treatment team	III	19	365
• access to a cancer support service and/or support group education	III	20, 21	365
• assistance with practical needs (e.g. child-minding, transport).	III	19	365
Key point: There is a need to develop culturally competent methods to assess the needs of patients with lymphoma. In the design of questionnaires and surveys, objective comparison of psychosocial adjustment to cancer in different cultures requires instruments that are valid and reliable in each culture.[10] There is a place for qualitative methods, which allow the collection of greater depth information, identification of processes and relations among behaviours, and framing of variables and hypotheses for quantitative research.			366

Guidelines and key points	Level of evidence	Refs	Page
Chapter 23 — Nutrition, exercise and psychotherapies **Guidelines: Nutrition and dietary recommendations**			
Studies have stressed the importance of incorporating nutritional evaluation, counselling, intervention (as needed) and follow up in the routine care of the oncology patient.	IV	4	372
Dietary guidelines for lymphoma patients are essentially the same as those for the general population, that is, a healthy balanced diet. Recommendations have been developed by the Department of Health and Family Services from recent research in nutrition.	IV	5	372
A dietician can offer guidance in determining the appropriate macronutrient and micronutrient needs for individuals.	IV	4	372
Guideline: Energy and fat intake Adults should be advised to keep within healthy weight range and their fat intake to less than 25% of their energy intake.	IV	5	372
Guidelines: Fibre requirements Eat five or more serves per day of a variety of vegetables and fruits, all year round.	III	6, 11, 14	373
It is recommended that adults consume a minimum of 30g of fibre daily in keeping with the general healthy diet guidelines.	IV	7, 8	373
Key points: The Australian dietary guidelines recommend two standard drinks for women and four standard drinks for men per day, with two alcohol-free days per week. Drink no more than 2–4 cups of coffee/tea per day.			373
Guideline: Nitrate and lymphoma risk No cohort or case-control study to date has found any association with nitrate levels in drinking water and lymphoma risk.	III	21, 22	373
Guideline: Antioxidant vitamin supplementation Antioxidant vitamin supplementation is not advised at present to protect against lymphoma.	III	12, 13 23, 24	374
Guidelines: Effects of chemoradiotherapy Chemotherapy toxicity adversely affects nutritional intake, digestion, or absorption through one or several mechanisms, including the gut and central nervous systems.	III	2, 30	376
The patient's metabolic needs may increase 25% with a temperature of 39°C.	III	2, 30	376
Protein deprivation has also been shown to increase risk of infection and enhance myelotoxicity caused by chemotherapy.	III	31, 32	376
In patients with a weakened immune system, ensure good food hygiene and proper food handling.	IV	33	376
Guidelines: Bone marrow transplantation Poor transplant outcome has been associated with both underweight and overweight patients who are having stem cell transplants.	III	34, 35	377

Guidelines and key points			Level of evidence	Refs	Page
Allogeneic bone marrow transplant (BMT) patients experience more profound and severe clinical conditions in the post-BMT period, including graft versus host disease (GVHD) and opportunistic infections. This may result in decreased oral intake, malabsorption of nutrients, and loss of nutrients — especially amino acids — from the gut.			III	36	377
Protein requirements are generally satisfied by the provision of 1.4–1.5 g/kg body weight per day.			IV	36	377
Zinc deficiency was shown to correlate with mortality after BMT.			III	36	377
Appropriate nutritional management of these problems includes a hyperalimentation during the severe stage of the disease; followed by low-fibre or low-residue, low -lactose, low-fat and bland diet.			IV	36	377
Guideline: Nutritional support in bone marrow transplantation A study showed positive results by using enteral nutrition as a transition step from total parenteral nutrition (TPN) to oral diet			III	42	378
Guideline: Exercise to prevent co-morbidity Recent data suggest an increased level of fitness in less active subjects can improve their survival.			II	50	379
Guideline: Exercise on psychological and physical health Regular aerobic and resistance exercises are recommended to patients.			II–III	49, 50 56, 57	379
Guideline: Psychotherapy Some form of psychotherapy should be offered to patients with certain cancers because it has a positive affect on quality of life, and possibly in the overall treatment of lymphoma.			II	61-72	379
Chapter 24 — Alternative and complementary therapies **Guideline: Herbal and related products in common use**					
Common name	*Indication*	*Evidence for effectiveness*			
Aloe vera	Various	Poor	IV	23	387
Cannabis	Nausea/vomiting	Good	II*	24	387
Ginger	Nausea/vomiting	Encouraging	III	23	387
Ginseng	Various	Poor	IV	23, 24	387
Kava	Anxiety	Good	II	23, 24	387
Mistletoe	Cancer	Poor	IV	23	387
Shark Cartilage	Cancer	Poor	III	23	387
St John's Wort	Mild/moderate depression	Good	II	23, 24	387
Valerian	Insomnia	Encouraging	III	23	387
*Efficacy has only been compared to moderately effective anti-emetics.					

Guidelines and key points	Level of evidence	Refs	Page
Key points: There is no evidence that CAM practices can cure lymphoma. Natural does not always equate to harmless. Alternative medications should be questioned when suspected drug reactions occur and included in notification reports.			389
Guidelines: Evaluation of complementary or alternative medicine (CAM) practices and armamentarium Some herbal products sensitise the skin to radiotherapy. Some interact with anaesthetics and blood pressure fluctuations. Herbs such as garlic, feverfew, ginger and ginkgo have anti-coagulant action. The risk of interaction between drugs and herbal compounds is highest for patients with renal and hepatic dysfunctions. There is good evidence for the use of acupuncture to treat nausea and vomiting (both chemotherapy induced and post-operative).	IV II	23 26	389 389
Chapter 25 — Cost effectiveness			394
Chapter 26 — Late breaking developments — impact of anti-CD20 monoclonal antibodies on lymphoma therapy **Guideline: Low-grade lymphoma — aggressive combination chemotherapy** Where it is considered appropriate to treat patients with combination chemotherapy, the addition of rituximab increases both complete response rate and duration of response.	II	1–8	419
Guideline: Diffuse large-cell lymphoma The outcome of patients, both over and under the age of 60, who are treated with CHOP chemotherapy, is improved by the addition of rituximab.	II	9, 10	419

CHAPTER 1 FOREWORD AND INTRODUCTION

It seemed logical that guidelines be developed for the management of malignant lymphomas. Based on 2001 incidence and mortality data, malignant lymphoma (including non-Hodgkin lymphoma and Hodgkin lymphoma) represents the sixth most common cancer in both incidence and mortality in Australia. Incidence figures were of the order of 4300 new cases in Australia in 2001, with some 1680 deaths.

Data from the Cancer Council of Victoria's publication *Trends in cancer mortality, Australia 1910–1999* note that mortality from non-Hodgkin lymphoma has more than doubled since 1950 in both sexes, with annual increases of around 4% consistent with international trends. In contrast, the Hodgkin lymphoma mortality has fallen by about 2% annually and faster since the 1970s, due to improved chemotherapy. This increase in mortality from non-Hodgkin lymphoma is matched in other western countries. For example, over the last 50 years, mortality in the United States has increased from 3.2 per 100,000 person years to a rate of seven. Similarly, the Hodgkin lymphoma mortality rates decreased from 1.7 to 0.4 deaths per 100,000 person years.

There have not been any systematic surveys of lymphoma management in Australia. However, it is hard to imagine a more complex category of diseases than malignant lymphoma. The classification system is evolving rapidly. Management aims vary from curative for certain subtypes to simple palliative approaches (albeit with long survival) for other subtypes. Lymphomas represent some of the most curable of malignancies and have been a prototype for the development of multi-modality approaches to the management of cancer. The complexity of integrating surgery, radiotherapy and medical treatments is well recognised.

A major impetus for the development of appropriate guidelines is the economic burden created by the lymphomas, not only in terms of the morbidity of the disease process and its economic implication, but the costs of many of the modern treatments that employ the latest fruits of biotechnology.

A working party to develop guidelines for the management of the malignant lymphoma was assembled with assistance from Emeritus Professor Tom Reeve and Mrs Christine Vuletich of the Australian Cancer Network. It met for the first time in Melbourne in 2001. Members of the working parties (diagnostic and clinical) were selected because of their areas of expertise and to ensure a wide geographic representation reflecting the national nature of the project.[1] Separate working parties developed parts of the diagnostic process and clinical sections. In the clinical section, for simplicity and clarity, it was elected to group the various lymphomas into a clinical concept of low-, intermediate- and high-grade while using the World Health Organization (WHO) pathological classification system. The working parties decided that the management of multiple myeloma and chronic lymphocytic leukaemia would not be part of its brief.

The evidence would be researched and assigned to a level according to the following scale:

I Evidence obtained from a systematic review of all relevant randomised controlled trials.

II Evidence obtained from at least one properly designed randomised control trial.

III.1 Evidence obtained from well-designed pseudo randomised controlled trials (alternate allocation or some other method)

III.2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group.

III.3 Evidence obtained from comparative studies with historical control, two or more single arm studies or interrupted time series without a parallel control group.

IV Evidence from case series, either post-test or pre-test and post-test.

In general level III evidence has not been subclassified, however, in some instances where it was possible, some subclassifications of level III evidence have been defined.

Apart from specific guidelines, key points are used in various chapters. These are items felt to be of considerable importance or recommendations, but not as strong as guidelines with specific levels of evidence.

For some clinical scenarios, high-level evidence supporting one intervention over another may not be available. Where this is the case, the guidelines say so, and make recommendations about the further research that is required. The biological and clinical complexity of lymphoma is reflected in its classification into some 30 subtypes. This has led to a massive literature (there are over 30,000 papers published in this field since 1966). It is not feasible to conduct detailed Cochrane-style analyses of the evidence available with current resources.

The recently evolving molecular, pathological and clinical subtypes, as well as new therapeutic modalities emerging from biotechnology, have resulted in some 7500 publications since 2000.

The rapid appearance of new information makes it difficult to maintain appropriately up-to-date guidance. We have included a chapter on late-breaking news, in particular, the implications of new therapeutic breakthroughs, especially with the wider use of the monoclonal antibody, rituximab.

In certain areas, the therapeutic recommendations in these guidelines may be ahead of the Australian Department of Health's funding and marketing recommendations. Clearly, with rapidly emerging new knowledge, the guidelines will need to be revised in the next few years.

It is important to note that it is implicit in the preparation of these guidelines that where possible, practitioners participate in clinical trials of the management of patients with lymphoma.

Another problem identified in the guidelines is that for many of the diagnostic studies, particularly immunological and molecular studies, and new imaging studies such as PET scanning, there are no specific sources of funding through the traditional and current route, that is, the Australian Department of Health. Here again, the guidelines are ahead of the Commonwealth funding process.

The guidelines frequently stress the need for multidisciplinary clinics in the management of patients with lymphoma. We recommend that readers refer to the National Breast Cancer Centre's document on multidisciplinary care models.

In considering the evidence, the working party has taken into account the effectiveness of an intervention rather than its cost.

The guidelines were presented to a public meeting in March 2004 and the working parties have considered the resulting recommendations. The draft manuscript was made available for public comment before its final editing and publication. They will need to be evaluated to assess their effect on the management of patients with lymphoma, in terms of both clinical and economic outcome, and then revised to ensure they reflect contemporary knowledge. It is planned to have a general review in two to three year's time. As well, if critical new information arises, specific topics will be revised in the electronic version. Meanwhile, a late-breaking chapter to address recent developments has been inserted as Chapter 25.

The Working Party hopes that health practitioners and consumers will find the *Guidelines for the diagnosis and management of lymphoma* a useful resource in the management of this difficult group of diseases. Feedback is welcomed on any aspect of the publication.

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CHAPTER 2 EPIDEMIOLOGY AND AETIOLOGY

2.1 Introduction

2.1.1 Lymphoma in Australia

Lymphoma is an increasingly common cancer with serious health consequences. It includes more than 20 lymphoproliferative malignant diseases that originate from T and B cells in the lymphatic system. The majority (70–80%) arise from lymph nodes; the remainder are extranodal. Lymphoma is primarily a disease of adults, with the highest number of new diagnoses in the seventh decade of life. It affects around 3500 people per year nationally and constitutes 4% of all newly diagnosed cancers. In men, lymphoma is the sixth most common cancer, after prostate, colorectal, lung, melanoma and bladder.[1] In women, it is the fifth most common cancer, after breast, colorectal, melanoma and lung.[1] Among children aged 0–14 years, lymphoma is the third most common cancer, after lymphoid leukaemia and brain and CNS.[1]

Lymphoma is more common in men than women (sex ratio 1.4:1 in 2001), with a lifetime risk of 1 in 64 men and 1 in 88 women in 2001.[1] In 2001, the annual incidence was 16.1 per 100,000 men and 11.3 per 100,000 women, with relatively high mortality rates of 6.3 per 100,000 for men and 4.4 per 100,000 for women.[1] Over the past several decades the incidence of lymphoma has increased dramatically in both men and women in Australia, and in a number of other countries. Reasons for this trend are incompletely understood.

Hodgkin lymphoma (HL), previously known as Hodgkin's disease, is a form of lymphoma distinguished histopathologically by the presence of Hodgkin or Reed Sternberg cells. There are four subtypes, in order of decreasing frequency: nodular sclerosis, lymphocyte predominance, mixed cellularity, and lymphocyte depletion.[2] HL is uncommon, making up only 0.5% of all newly diagnosed cancers. It predominantly manifests during young adulthood, but also peaks in advanced age. HL is more common in males than females (sex ratio 1.2:1 in 2001), especially before puberty. In 2001, the lifetime risk was 1 in 559 for men and 1 in 766 for women.[1] There were 401 cases diagnosed nationally in 2001, at an annual rate of 2.2 per 100,000 men and 1.8 per 100,000 women.[1] Unlike lymphoma, modern treatments are generally curative, resulting in an annual mortality rate of 0.2 per 100,000 for men and women.[1] The incidence of HL has remained relatively stable over time.

2.1.2 Impact of diagnostic classification on epidemiological research

Advances in diagnostic procedures and changes in disease classification over time greatly complicate interpretation of the epidemiology of lymphoma. The increasing availability of molecular tests has aided the diagnosis of lymphoma, in particular the differential diagnosis of HL and other haematologic malignancies. Changes in classification systems have resulted in an increasing number of distinct disease entities. The revised European–American classification of lymphoid neoplasms (REAL classification)[3] was proposed in 1993 and updated to the WHO classification[4] in 2001, allowing categorisation by postulated cell of origin (B cell, T/NK cell). Earlier classifications included the Working Formulation[5] and the Kiel classification.[6] Lymphoma classification is complex; the WHO classification incorporates information on morphology, immunophenotype, genetic features, clinical features, race, geographic distribution and microbiologic features. Some subtypes are inherently difficult to diagnose and the WHO classification recognises the increasing importance of immunophenotyping. Despite the changes in classification over time, diagnostic error does not explain the continuing upward trend in incidence, especially in the younger population.

The classification of HL has remained relatively stable over time. As a consequence, a recent investigation of the reliability of diagnosis and classification of HL in women diagnosed in the United States from 1988 to 1994 found very good agreement between cancer registry and expert review diagnoses.[7]

2.2 Descriptive epidemiology

Lymphoma is a heterogeneous disease covering a diverse range of subtypes and anatomical sites, making interpretation of data for all lymphoma types combined somewhat difficult.

2.2.1 Trends in incidence and mortality

Age and sex

Incidence and mortality rates in men and women increase steadily with increasing age, peaking after the seventh decade. [8] In Australia and elsewhere, males predominate.

In Australia and other developed countries, the age-specific incidence of HL is bimodal, with peaks in young adulthood (15–34 years) and then again after the seventh decade.[8] Around 5% of all cases are diagnosed in children less than 15 years of age. In the younger years, the nodular sclerosis subtype is most common, while the mixed cellularity subtype predominates from age 50.[2] Males predominate in both age peaks. Mortality rates are highest in the older age groups. In developing countries, HL is more common in children than young adults.[9]

Trends over time

Since the 1970s, the incidence of non-Hodgkin's lymphoma (NHL) has increased worldwide and progressively across all age groups in both sexes. Rates increased by 20% to 50% every five years during the 1970s and 1980s[10], but rates of increase have slowed in recent years. In Australia, rates increased by an average of 0.7% per year in men and 1.2% in women between 1991 and 2001.[1] These increases are largely independent of AIDS-associated diagnoses and changes in diagnostic practices and disease classification.[11,12] There is some evidence of a recent flattening of incidence rates. Population-based registry data in England and Wales from 1986 to 1993 show significant increases over time in the incidence of all extranodal lymphoma as well as lymphoma of the gastrointestinal tract, skin, central nervous system and male genital organs.[13] The greatest proportional increases were observed for middle-aged men and women and for cutaneous lymphomas. In the United States, the incidence of high-grade lymphoma has increased more than low-grade lymphoma.[11]

In Australia, the mortality rate for lymphoma decreased an average of 0.4% a year in males between 1991 and 2001.[1] Over the same period, the mortality rate in females increased on average 0.2% per annum.[1]

Since the 1980s, the incidence of all HL has declined slightly in many countries. Time trend analyses by age at diagnosis show a decrease in incidence for older adults, and an increase in incidence for young adults in some industrial countries.[2] In parallel, rates of the nodular sclerosis subtype have increased and the mixed cellularity subtype have decreased.[9] HL mortality rates have steadily decreased over time due to the increasing effectiveness of treatments.[10]

Ethnic variation

The incidence of lymphoma is lowest in Asian and African countries, at intermediate levels in European countries and highest in North America and Australia (see Table 2.1). A similar picture is seen for HL, with low rates in Asia and Africa, intermediate rates in Australia, and high rates in Europe and North America (see Table 2.1).[14] The incidence of HL among Asians across varying levels of economic development is consistently low, suggesting a low genetic predisposition or protective lifestyle factors. In the United States, incidence rates for lymphoma and HL are higher in white than black populations, but socioeconomic status is believed to be more important than ethnicity alone.[2,15]

Table 2.1 Average annual age-standardised (world) incidence rates per 100,000 population for lymphoma and Hodgkin lymphoma in select countries and regions, 1993–1997

	Lymphoma		Hodgkin lymphoma	
Country or region	**Men**	**Women**	**Men**	**Women**
Oceania				
Australia, ACT	12.8	10.6	2.1	2.4
Australia, NSW	14.2	10.0	2.0	1.5
Australia, NT	9.2	6.7	0.8	0.6
Australia, QLD	12.8	8.9	1.9	1.5
Australia, SA	14.2	11.3	2.3	1.7
Australia, TAS	12.7	10.6	2.3	2.0
Australia, VIC	14.9	10.3	2.5	1.8
Australia, WA	11.4	8.7	1.4	1.5
New Zealand	11.8	8.7	1.8	1.1
North America				
Canada	13.8	10.1	2.8	2.2
USA, SEER: White	16.7	10.6	3.0	2.6
USA, SEER: Black	15.3	7.4	2.6	2.0
Europe				
Denmark	10.3	7.3	2.5	1.6
Sweden	10.1	6.9	2.1	1.7
The Netherlands	10.9	7.1	2.2	1.7
UK, England, Oxford Region	10.8	8.1	2.8	2.0
Spain, Granada	7.6	6.0	1.7	1.5
Africa				
Uganda, Kyadondo County	5.7	4.3	1.1	0.7
Zimbabwe, Harare: African	6.5	5.3	0.5	0.5
Asia				
China, Taiwan	5.9	4.5	0.4	0.2
India, Mumbai	4.5	3.2	0.8	0.4
Japan, Nagasaki Prefecture	8.2	4.4	0.3	0.2
Thailand, Bangkok	5.0	3.7	0.2	0.1
Viet Nam, Hanoi	7.2	3.0	1.7	0.7

Source: Parkin et al. [14]

Geographic variation

A latitude gradient, or positive correlation between lymphoma incidence and ambient solar ultraviolet radiation (UVR), has been demonstrated in several Caucasian populations[16] and in England and

Wales[17], but not in the United States for lymphoma mortality[18], lymphoma incidence[16], or cutaneous lymphoma incidence.[19]

2.2.2 Correlations with other neoplasms

Patients with lymphoma are at increased risk of skin cancer and patients with skin cancer are at increased risk of lymphoma. The evidence is consistently strong for both cutaneous melanoma and non-melanocytic skin cancer, and suggests solar UVR may be a risk factor.[20] Excesses of acute non-lymphocytic leukaemia, HL, lung, kidney and bladder cancer also occur in lymphoma patients.[21] An increased risk of lip and tongue cancer after lymphoma has also been reported in NSW.[22] These associations may be due to shared aetiological factors or therapy- or disease-induced immunosuppression.

Correlations in lymphoma incidence and incidence rate trends with those for cutaneous melanoma and non-melanocytic skin cancer are also indirect evidence of a positive association with solar UVR.[16,23]

As for lymphoma, the risk of skin cancer is significantly elevated after HL diagnosis.[24] Excesses of breast cancer, thyroid cancer, leukaemia and lymphoma also occur.[25]

2.3 Analytical epidemiology

Numerous epidemiological studies have been conducted to examine the role of putative risk factors. It is difficult to summarise their findings due to the generally poor exposure classification, poorly defined study populations, small sample sizes, and lack of adjustment for confounding by known risk factors. Furthermore, very few studies have examined interactions between risk factors. Moreover, lymphoma, and to some extent HL, consists of a diverse group of neoplasms and few studies have examined risk factors by lymphoma subtype.

2.3.1 Immunodeficiency

Immunodeficiency risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Post-transplant immunosuppression is a strong risk factor for lymphoma and a weak risk factor for Hodgkin lymphoma.	III-2	26	III-2	27
Immunodeficiency in HIV/AIDs infection is a strong risk factor.	III-2	28	III-2	29
Congenital immune deficiency is a strong risk factor.	IV	30	IV	2
Acquired autoimmune disease is a moderate risk factor.	III-2	31	III-2	31

Post-transplant immunosuppression

There is strong evidence that lymphoma risk is increased in patients undergoing immunosuppression therapy to prevent rejection after transplantation with donor organs or tissues. Data from United States and Australian population-based transplant registries indicate a relative risk (RR) of at least 20 following kidney transplantation and 120 following heart transplantation.[26] Risk increases with increasing degree of post-transplant immunosuppression. The risk of lymphoma following bone marrow transplantation is low, but significant.[32] Lymphoma in transplant recipients is typically diagnosed within a few years of transplant, and is usually high grade, often extranodal, and positive for Epstein-Barr virus (EBV) infection.[33]

An excess of HL is not found in organ transplant recipients[34], but when it does occur it is usually in association with EBV infection. There is evidence of an excess (RR 5) of HL in bone marrow recipients.[27]

HIV/AIDS

HIV infection is characterised by a specific deficiency of CD4 positive T cells and the chronic stimulation of B-cells. There is clear evidence from cohort and linkage studies that HIV infection markedly increases the risk of lymphoma, with estimates ranging from 14 (low-grade lymphoma) to 350 (high-grade lymphoma) times that of the general population in developed countries.[28,35] Lymphoma risk in people with HIV infection is independently predicted by degree of immunodeficiency, duration of immunodeficiency, and chronic B-cell stimulation.[36] Risk of lymphoma is highest when CD4 count is less than 50 in late-stage HIV infection. More than 90% of HIV-associated lymphoma is derived from B-cells, and the majority are high-grade and extranodal. Around half are EBV positive.[15] The pathological spectrum includes Burkitt lymphoma, diffuse large B-cell lymphoma, immunoblastic lymphoma, primary CNS lymphoma, and primary effusion lymphoma.

Cohort and linkage studies in developed countries also consistently show increased risk of HL (RR 4–22) in association with HIV/AIDs infection, with risk generally increasing with increasing degree of immunodeficiency.[28,29,35,37] The median CD4 count at diagnosis is approximately 200. Nearly all cases are EBV positive, and the mixed cellularity and lymphocytic depletion subtypes predominate. Risk of HL is highest within six months of AIDS diagnosis.[28]

Congenital/primary immunodeficiency

Case series data show a predominance of lymphoma in patients with congenital immune deficiencies. An excess of lymphoma occurs in children with congenital X-linked immunodeficiency, severe combined system immunodeficiency and young people with ataxia telangiectasia or Wiskott-Aldrich syndrome.[30] Children with ataxia telangiectasia or Wiskott-Aldrich syndrome, and adults with common variable immunodeficiency, are also at increased risk of HL.[2] Cofactors include defective host immunoregulation, EBV infection (50%), and genetic defects.[30]

Autoimmune diseases

Autoimmune diseases characterised by persistent antigenic stimulation confer an increased risk of lymphoma. The excess risk associated with these conditions may also be due to treatment with immunosuppressive agents, although evidence from recent cohort study suggests an effect independent of treatment for rheumatoid arthritis.[38] Risk of lymphoma and HL is increased two to three-fold in rheumatoid arthritis patients.[31] Risk of lymphoma, especially T-cell lymphoma and primary gut lymphoma, is increased in celiac disease, although the magnitude of the association is unclear (RR 3–100).[39] Lymphoma risk is also increased in systemic lupus erythematosus (RR 3–7)[40] and Sjogren's (sicca) syndrome (RR 5–8).[41]

2.3.2 Infectious organisms

Infectious organism risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Epstein-Barr virus (EBV) infection is a weak risk factor for lymphoma in the general population, a strong risk factor for lymphoma in the immune deficient, and a strong risk factor for Hodgkin lymphoma.	III-2	33	III-2	42
Helicobacter pylori (H *pylori*) infection is a moderate risk factor for gastric lymphoma.	III-2	43	-	
Human T-lymphotrophic virus types I (HTLV-I) infection is a moderate risk factor for adult T-cell leukaemia/lymphoma (ATL).	IV	33	-	
Human herpesvirus-8 (HHV8) infection is a moderate risk factor for primary effusion lymphoma (PEL).	IV	44	-	
Proxy measures of delayed exposure to childhood infection are a moderate risk factor for Hodgkin lymphoma.	-		III-2	2

Epstein-Barr virus (EBV)

EBV, a herpes virus with B-cell-transforming activity, is ubiquitous worldwide. The primary EBV infection usually occurs in childhood and latent infection persists throughout life. As noted in preceding sections, there is strong evidence that EBV infection in conjunction with immune dysfunction, such as post-transplant or HIV/AIDS, is associated with increased risk of lymphoma.[33] EBV infection is more frequent in T-cell than B-cell lymphoma, and the most consistent association is with sinonasal angiocentric T-cell lymphoma.[42] EBV infection is consistently associated with Burkitt's lymphoma, a lymphoma subtype, in African children[42], and primary CNS lymphoma in people with immune deficiency.

The association between EBV infection and HL is regarded as causal.[42] Cohort and case-control studies indicate a three-fold excess of HL in people with serologically confirmed or self-reported history of infectious mononucleosis, a condition caused by delayed exposure to EBV.[2] Serologic studies suggest that endogenous EBV activation, coupled with an unusual host response, precedes diagnosis of HL.[2] Furthermore, molecular studies have detected EBV DNA in 30–50% of HL cases in developed countries.[2] EBV positivity increases with increasing histopathological grade, and a greater proportion are of the mixed cellularity subtype.[2] Males (OR 2.5), and cases in Asian and Latin American countries, rather than the United States and Europe, are also more likely to be EBV-positive. EBV positivity is more common in HL diagnosed in early childhood and older adulthood than it is in young adulthood.[45] Recent evidence suggests that delayed exposure to EBV and/or another as yet unidentified common infectious agent is a risk factor for the development of HL in young adulthood.[45]

Helicobacter pylori (H pylori)

In Australia, the prevalence of infection with the bacteria *H pylori* is around 30%. Infection is almost always acquired in childhood and persists unless specifically treated. *H pylori* infection is associated with a six-fold increase in risk of gastric B-cell lymphoma, known as mucosa-associated lymphoid tissue (MALT) lymphoma.[43] The relationship is regarded as causal; eradication of *H pylori* results in the complete regression of the majority of low-grade MALT lymphomas.[46]

Human T-lymphotrophic virus types I and II (HTLV-I, HTLV-II)

Infection with the human retrovirus HTLV-I or II is rare in Australia. In regions where HTLV-I is endemic, such as southern Japan and the Caribbean, infection, especially in early childhood and in males, is associated with increased risk of adult T-cell leukaemia/lymphoma (ATL), a form of lymphoma.[33,47] The cumulative risk of ATL in those infected with HTLV-I is 1–5% over a 70-year life span. Relative risk estimates are not available. HTLV-II has not been consistently associated with lymphoma. HTLV is not associated with HL.

Hepatitis C virus (HCV)

In Australia, at least 80% of HCV infection occurs in injecting drug users. HCV infection is the main cause of mixed cryoglobulinemia, a benign lymphoproliferation that can evolve into B-cell lymphoma.[48] There is mixed evidence for an association between HCV infection and lymphoma. Two cohort studies found no significant association[49]; one studied young Californian adults with HCV infection over 30 years, while the other followed Japanese HCV-positive patients for an average of six years. In contrast, the majority of case-control studies from areas of high HCV prevalence show a positive association with B-cell lymphoma (RR 2–4). However, these findings have not been replicated in some case-control studies from nonendemic areas elsewhere in Europe or from North America.[48] HCV infection is not associated with T-cell lymphoma or HL.

Human herpesvirus-8 (HHV8)/Kaposi's sarcoma herpesvirus

HHV8 is a human herpesvirus that is widespread in homosexual men in Australia.[50] In addition to Kaposi's sarcoma, it is associated with a rare form of B-cell lymphoma — primary effusion lymphoma (PEL) — in adults with immunosuppression related to HIV infection or organ transplantation.[44] Relative risk estimates are not available. Primary effusion lymphomas typically contain both HHV8 and EBV DNA and are located predominantly in serous body cavities. HHV8 is not associated with HL.

Simian virus 40 (SV40)

Australian children were inadvertently exposed to SV40, a macaque polyomavirus, via contaminated polio vaccines in the 1950s and 1960s. No prevalence estimates are available. SV40 causes B-cell lymphomas in rodents, but there are very limited data to suggest a role in human oncogenesis. Age-specific trends in lymphoma incidence are not consistent with a cohort effect, and laboratory data are inconsistent. SV40 DNA sequences have been detected in around 40% (n=222) of lymphoma samples from the United States[51,52], but none of 152 samples from the United Kingdom[53], despite evidence of similar levels of exposure in both nations.

There has been very limited investigation into the role of SV40 infection in HL. A United States study isolated SV40 DNA in 9% (n=30) of HL samples.[52]

Other viruses

There is inconsistent evidence of a positive association between HL and infection with other members of the herpesvirus family, including cytomegalovirus (CMV) and human herpesvirus type 6 (HHV-6).[2]

Proxies for exposure to infection

There is limited evidence of an association between lymphoma risk and factors indicating potential for infection and immunological stimulation, such as socioeconomic status and childhood crowding. Socioeconomic status was not identified as an independent risk factor in two cohorts[38,54], while the association was not reported for other cohorts.[55] A case-control study found that having five or more siblings was a risk factor (OR 3.6) for lymphoma in homosexual men[56], while others have reported both increased and decreased risk of lymphoma in association with higher educational level.[57,58] A

recent population-based case-control study found an increased risk of lymphoma in those with later age onset of common infectious diseases, which was limited to those from small-size families.[59]

Risk of HL in young adulthood is consistently associated with indicators of higher childhood social class, such as single-family housing, small family size, early birth order, and high maternal education.[2] These associations generated the hypothesis that HL in young adults is caused by delayed exposure to common childhood infections. Infections experienced during adulthood are usually more clinically severe than those normally encountered during childhood, and may alter the immunological control of a latent oncogenic infection, resulting in chronic antigenic stimulation.[2] In support of this hypothesis, risk of HL in young adults is decreased in those reporting fewer childhood infections[60], and risk of HL at all ages is non-significantly and modestly increased in those reporting older age at first infection.[57] A similar mechanism is likely for HL in middle age, with increased risk for those of higher education, while risk of childhood and older adult HL is increased in those of lower social class.[2] It is important to note there is no evidence that patients with lymphoma as such, can transmit lymphoma to other individuals.

2.3.3 Occupational and environmental toxins

Most studies of occupational exposures have been based on job title, making interpretation with respect to specific exposures problematic.

Occupational risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Exposure to pesticides or herbicides is a weak risk factor for lymphoma.	III-2	61	-	
Farming as an occupation is a weak risk factor.	III-2	62	III-2	63
Work in a wood-related industry is a moderate risk factor for Hodgkin lymphoma.	-		III-2	64

Pesticides, herbicides and agricultural exposures

Chemical exposure to both the use and production of pesticides and herbicides has been examined in relation to risk of lymphoma and HL. The balance of evidence suggests an increased risk of lymphoma,[15,61] but an inconclusive relationship with HL.[64] A nested case-control study utilising serum collected prior to lymphoma diagnosis found a positive association between lymphoma risk and total PCBs (polychlorinated biphenyls), but not DDT (dichlorodiphenyltrichloroethane) and related compounds, or organochlorines.[65,66] The authors noted, however, that the possibility of a weak association with organochlorines in highly exposed populations could not be excluded.

Farmers are at increased risk of lymphoma and may be at slightly increased risk of HL. A meta-analysis of lymphoma among farmers found a relative risk of 1.10 (95% CI 1.03–1.19) for all studies and 1.26 (95% CI 1.15–1.37) for studies conducted on farmers in the United States.[62] A meta-analysis of HL among farmers found a relative risk of 1.25 (95% CI 1.11–1.42) for all studies and 1.08 (95% CI 0.97–1.20) for cohort studies.[63] It is unclear which agent or agents are aetiologically important. Farmers may be exposed to pesticides, herbicides, fungicides, infectious microorganisms, solvents, paints, fuels, oils, and dusts; each of these agents has been inconsistently positively associated with risk of lymphoma and HL. Farmers' diet and level of physical activity may also differ from that of the general population.

Other occupations that involve work with animals, such as meat (abattoir) workers, meat inspectors, and veterinarians, have been inconsistently associated with increased risk of both lymphoma and HL. Exposure to animal-born viruses has been implicated.

Other chemicals

The relationship between occupational exposure to solvents and lymphoma[15] or HL[64] is not clear. However, a meta-analysis of cohort study data from five countries found no excess lymphoma mortality in workers exposed to benzene or benzene-containing petroleum products (standardised mortality ratio: 0.90, 95% CI 0.82–0.98).[67]

Occupational exposure to hair dyes, or the personal use of hair dyes, is inconsistently associated with increased risk of both lymphoma and HL.[68,69] Examination of the risk associated with occupational exposure to chemical compounds in hair dyes is probably confounded by the potential for increased exposure to infectious agents through personal contact with clients.

Sun exposure

Limited analytical evidence on the relationship between ambient solar UVR, a measure of potential sun exposure, and risk of lymphoma is contradictory. Cohort data suggest increased risk[54]; and mortality case-control study data, decreased risk[70], with residence in areas of higher ambient UVR.

None of the analytical studies performed to-date obtained recalled estimates of personal occupational sun exposure; all were crudely based on job title. The only cohort study to examine sun exposure found no association between occupational sun exposure and lymphoma.[54] Results from three case-control studies were equivocal[70–72] with the exception of increased risk for farmers. Several other case-control studies that examine a range of occupations have not consistently identified outdoor occupations, other than farmers, as being at increased risk of lymphoma. The relative contribution of sunlight exposure and exposure to herbicides and pesticides in farmers is not known.

The association between sun exposure and risk of HL has not been examined.

Other occupational exposures

Although mixed, the balance of evidence favours a moderate positive association between occupation in a wood-related industry and HL.[2,64] The evidence with respect to such an association for lymphoma is weak and inconsistent.

Epidemiological studies have inconsistently identified increased risk of lymphoma in industries with exposure to asbestos particles and welding, as well as metal workers, rubber workers, those in electrical occupations, and to those in occupations of higher socio-economic class.

2.3.4 Medical procedures and medical history

Medical and comorbidity risk	Level of evidence			
	NHL	Ref.	HL	Ref.
Childhood appendectomy is a moderate risk factor for lymphoma.	III-2	73	-	
Skin cancer is a strong risk factor for lymphoma.	III-2	20	-	
Diabetes is a weak risk factor for lymphoma.	III-2	74	-	
Tuberculosis is a moderate risk factor for lymphoma.	III-2	75	-	
Infectious mononucleosis is a moderate risk factor for Hodgkin lymphoma.	-		III-2	2

Ionising radiation

There is little convincing evidence of a relationship between ionising radiation and lymphoma.[15]

Blood transfusion

Blood transfusions may expose recipients to oncogenic viruses and other immune-modulating antigenic substances. Three cohort studies are consistent in showing a two-fold increase in risk of lymphoma with prior receipt of a blood transfusion; with the most recent indicating strongest associations for low-grade lymphoma.[76] However, seven of eight case-control studies found no increased risk, and there is evidence that the inclusion of transfusions in the 12-month period before diagnosis artificially inflates the risk.[77] It is unclear whether the association is related to the condition(s) leading to the blood transfusion, or the transfusion itself.

The association between blood transfusion and HL has not been examined.

Vaccinations and medications

There are no cohort data on the association between vaccination history and risk of lymphoma. One case-control study found a significant protective effect (OR 0.7) on lymphoma risk from the receipt of six or more vaccinations;[78] subsequent analyses have shown this effect is confined to the diffuse large-cell type.[79] Two case-control studies found increased risk of lymphoma (OR 2–3) in association with immunisation against tuberculosis.[31,79] The only HL case-control study found a protective effect from immunisation against tetanus (OR 0.5) and diphtheria (OR 0.6), and no association with immunisation against smallpox or poliomyelitis.[31]

The association between nonsteroidal anti-inflammatory drugs (NSAIDs) and lymphoma risk is inconclusive and may be confounded by indication for use.[38] Some studies have reported a significant increase in risk, while others have found a significant decrease in risk.

Tonsillectomy and appendectomy

Tonsillectomy is not a risk factor for lymphoma. Although mixed, the epidemiological evidence suggests that risk of HL in young and middle-aged adulthood is unrelated to tonsillectomy, but the association with disease onset among older persons is unknown.[2]

A recently published cohort study from Sweden and Denmark reported a 20–50% excess of lymphoma after childhood appendectomy, but no increase in HL.[73]

Medical conditions

Risk of lymphoma is increased following melanoma and non-melanocytic skin cancers, and vice versa. This provides further indirect evidence of a positive association with sun exposure.[20]

Data from cohort, but not all case-control studies, show an increased risk of lymphoma in those with adult-onset diabetes, although the magnitude of the increase in risk is unclear (RR 1.2–2.2).[74,80]

Cohort and case-control study data are mostly in agreement in showing a doubling of risk of lymphoma in individuals with a history of tuberculosis.[75] Cohort results indicate a significant association only for those with severe infection, diagnosed many years before.[75] The increased risk may be due to the infection itself, an underlying susceptibility, or an associated exposure.

Despite the requirement for immunosuppressive therapy, inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, appears unrelated to risk of lymphoma, but may increase the risk of HL as much as four-fold.[81]

The evidence linking lymphoma with allergic diseases such as eczema, asthma, hay fever, general allergies and allergies to plants, dust, food, animals, medications, and insect bites/stings is weak and inconsistent.[82] Significant increases in risk, as well as significant decreases in risk, have been reported, but most studies have found no association.

The relationship between history of infectious mononucleosis (IM) and risk of lymphoma is uncertain; with two case-control studies reporting a significant positive association[59,83] and another a significant protective effect for diffuse large-cell lymphoma.[79] As noted above (2.3.2 Infectious organisms), IM increases the risk of HL by two to three-fold[2], and the association is unlikely to be explained by confounding by social class.

2.3.5 Lifestyle

Lifestyle risk	Level of evidence			
	NHL	Ref	HL	Ref
Cigarette smoking doubles risk of follicular lymphoma and Hodgkin lymphoma.	III-2	84	III-2	82
Use of vitamin supplements does not affect risk of lymphoma.	III-2	55	-	

Smoking

The relationship between cigarette smoking and risk of lymphoma is unclear.[85] However, findings from recent, well-designed studies are consistent in showing a doubling of risk for the follicular lymphoma subtype.[84]

On balance, the results from cohort and case-control studies support a positive association (OR 1.5–2.0) between cigarette smoking and HL. A recent population-based case-control study of men found the strongest association for the mixed cellularity subtype.[86]

Alcohol

A number of studies have found a protective effect of alcohol consumption, in particular wine, on risk of lymphoma[87]; however, the precise relationship remains equivocal, particularly with respect to the amount and type of alcohol and the subtype of lymphoma.

There have been no cohort studies of alcohol consumption and risk of HL, while a hospital-based case-control study of alcohol and other dietary factors identified no significant associations.[88]

Physical activity

Physical activity and obesity are likely to influence immune function. Physical activity appears unrelated to risk of lymphoma[89], while cohort and case-control study data with respect to excess weight are equivocal.[89] A single cohort study examining all cancers found a significant association between obesity and HL in men (SIR 3.3),[90] but there have been no studies of physical activity and risk of HL.

Nutrition

Diets high in fat or meat products appear to double the risk of lymphoma[91,92], however, the data are inconsistent and may be confounded by an association with herbicides and pesticides. A single case-control study examined fish consumption and found no association with lymphoma.[93]

Results from two cohort and four case-control studies show no clear association between fruit and vegetable intake and risk of lymphoma, but there is a tendency towards a protective effect.[94] In addition, the balance of evidence from three cohort studies and one case-control study suggest there is no protective or harmful effect with respect to lymphoma from vitamin supplement use.[55,95]

Cohort and case-control studies are largely consistent in showing no association between risk of lymphoma and tea[96] and coffee[88] consumption. The association with milk consumption is unclear.[91] Nitrate, a contaminant in drinking water, can break down into carcinogenic compounds. None of the cohort studies and case-control studies conducted to date have found any association with nitrate levels in drinking water and lymphoma risk.[97]

There is no pattern of risk for diet and HL; two cohort studies and four hospital-based case-control studies typically examined a single food or vitamin type.[88,93]

2.3.6 Reproductive and hormonal factors

Sex hormones have immuno-modulatory effects. Evidence from cohort studies indicates a weakly protective or zero effect of pregnancy on risk of lymphoma.[98] The only study to examine it found a significantly protective effect (RR 0.5) for breast-feeding more than two children versus none.[89] In contrast, data from the same cohort of women show a weak positive association with use of hormone replacement therapy (HRT), and a strong positive association for the follicular subtype.[99]

While results from an early cohort study supported the hypothesis that childbearing is protective of HL[100], it has not been confirmed in more recent cohort studies.[101,102] No studies have examined use of HRT and HL.

2.3.7 Genetic susceptibility

There is no evidence that lymphoma occurs more commonly than expected in members of the same family[15], except in families with a history of lymphoma, HL or leukaemia among first-degree relatives (RR 3–4).[103] The very strong association between rare forms of genetic immune deficiency and lymphoma risk suggests that polymorphisms of genes controlling immune function may influence lymphoma risk, but genetic polymorphisms that independently predict risk of lymphoma have not yet been identified.

There is some evidence of genetic susceptibility in HL. There is a higher than expected incidence of HL among siblings but not spouses, and monozygotic but not dizygotic twins, suggesting a role for both genetic factors associated with immune competence and common childhood environmental exposures.[2] There is also a weak positive association between risk of HL and genes whose products play a role in the regulation of the immune response, the human leucocyte antigen (HLA) genes.[9] The oncogene *bcl*-2 and the p53 gene have also been implicated.[9] Of importance for both lymphoma and HL is an understanding of the interaction between genetic polymorphisms and environmental factors.

2.4 Conclusions

The only accepted strong risk factors for lymphoma are immune deficiency and specific infections, but these account for only a small proportion of all cases. The question of whether mild sub-clinical immune deficiency is an important cause has not been adequately addressed. Other less well-established risk factors include cigarette smoking, farming, herbicides/pesticides, specific medical conditions and animal fat or meat consumption. Solar UVR is a putative risk factor for lymphoma, however, the evidence is only indirect and awaits verification from studies where lifetime personal sun exposure has been comprehensively quantified.

The established risk factors for HL are immune deficiency and EBV infection. Other risk factors include proxy measures for childhood exposure to infectious agents, infectious mononucleosis, cigarette smoking, farming, work in a wood-related industry, and genetic susceptibility.

In summary, the aetiologies of lymphoma and HL are complex and, for the most part, poorly understood. While some important causes have been well described, these account for only a minority of cases.

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CHAPTER 3 CLASSIFICATION

3.1 Introduction

Accurate diagnosis underpins lymphoma management. Historically, competing lymphoma classifications have been a source of frustration to pathologists, clinicians and epidemiologists alike. Thus the 1994 publication of the International Lymphoma Study Group's classification, the Revised European-American Lymphoma (REAL) classification[1] marked a watershed in the field of lymphoma diagnosis and management. Its successor, the 2001 WHO classification[2], is based on the principles of the REAL classification, but with further consensus achieved on some of the diagnostic categories, and with consideration of advice from a clinical advisory committee.[3] This classification was achieved with international consensus among expert haematopathologists and is the classification adopted and promoted in these guidelines. As in the REAL scheme, the WHO classification identifies specific disease entities defined not only by morphology, but also by considering the immunophenotype, genetics, and clinical features typical of each entity.

While some diseases may be recognisable with a high (but not absolute) degree of certainty on the basis of morphology alone (e.g. follicular lymphoma), most will require immunophenotyping and/or genotyping for accurate classification. Therefore, laboratories must be able to perform, or at least have access to, immunophenotyping and molecular techniques. The relative importance of each of these parameters in the diagnostic process varies according to each lymphoma.

Particularly in the case of T- and NK-cell lymphomas, the clinical setting and site (nodal versus extranodal) are often more important than morphology in establishing the diagnosis. The pathologist plays a key role not only in establishing the correct diagnosis, but also in ensuring that biopsy material is triaged appropriately. Further ancillary studies should these be selected as appropriate to the individual case.

It is emphasised that not all tests are necessarily required in every case.

3.2 Taxonomic structure

The WHO classification considers lymphoproliferative disorders under three broad groupings of *B-cell* neoplasms, *T-cell and NK-cell* neoplasms, and *Hodgkin lymphoma*.[2] The lymphoproliferative disorders (LPD) associated with primary or acquired immunodeficiencies are classified separately within the WHO scheme, and include the post-transplant LPD. The B-cell and T/NK cell neoplasms are stratified into those of precursor cell origin (lymphoblastic lymphoma/leukaemia) and those putatively corresponding to later stages of B- and T-cell ontogeny (peripheral or mature lymphomas). Wherever possible, a postulated cell of origin or stage of lymphoid differentiation is given for each entity. Specific clinicopathologic entities are identified in the scheme, and are grouped according to whether they present as mainly disseminated/leukemic disease, as primary extranodal disease, or predominantly as node-based lymphomas. As many factors contribute to the clinical behaviour of any particular lymphoma, histological grading and clinical groupings do not form part of the WHO classification. Indeed, the WHO Clinical Advisory Committee recommended against any clinical groupings.[3] *The onus is therefore on the clinician and pathologist to be familiar with the morphological and clinical spectrum within each diagnostic category to determine therapy and predict outcome.*

In the treatment of lymphoma however, the various WHO categories fall into distinct clinical groups eg. low grade, aggressive and high grade lymphomas (see Table 3.1). These provide the framework for discussion about the management of lymphoma in these guidelines.

3.3 Validation of the WHO scheme

An international clinical evaluation and validation study of the REAL classification has been carried out by the Non-Hodgkin's Lymphoma Classification Project.[4,5] By extension, the conclusions can reasonably be applied to the WHO classification. This study established clearly that the REAL classification enabled high diagnostic accuracy (>95% for cases with adequate materials) and had high interobserver reproducibility among expert haematopathologists (>85%) for most disease categories, better than for any previous classification system. Diagnostic accuracy is not as good for some categories such as lymphoplasmacytic lymphoma, nodal marginal zone lymphoma, and atypical Burkitt lymphoma, and for grading within follicular lymphoma. The importance of immunophenotyping for some entities was clearly established, and immunophenotyping is essential for diagnosis of T-cell lymphomas. The clinical relevance of immunophenotype has been confirmed in other large studies that confirm that the T-cell phenotype is an independently significant negative prognostic factor.[6,7] The classification is of clinical relevance, as different entities have significantly different clinical presentations[5] and survivals[4,5,8], and clinical factors such as the International Prognostic Index[9] were established as critical in determining treatment and outcome in any lymphoma type. Using the REAL classification, good diagnostic concordance has been shown between an academic centre and a community hospital setting[10]; discordance occurred for those cases which also accounted for higher interobserver variability between expert haematopathologists. Several studies have now been published establishing the frequency of the various lymphoma subtypes in terms of the REAL/WHO classifications.[7,11–17] These studies also highlight important geographic differences in the incidence of the various lymphoma types.

3.4 Common forms of lymphoma

While the 36 specific disease entities in the NHL classification (excluding immunodeficiency associated LPD) may at first glance appear overwhelming, it is noteworthy that two entities, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), account for >50% of all NHL. B-cell lymphomas represent greater than 85% of all NHL globally; in Western countries at least, T-NHL accounts for less than 15% of all NHL, and most of these fall into the unspecified category.[4] Thus a minority of lymphomas encountered in routine practice are likely to need extensive ancillary investigations to establish a firm diagnosis.

3.5 Difficulties in classification

While not specifically alluded to in the WHO classification, but addressed in the earlier REAL classification, a small proportion of lymphomas may be unclassifiable due to an inadequate specimen or histological preservation, inadequate immunophenotyping or genotyping, or simply because some lymphomas defy accurate classification despite adequate diagnostic workup. Such a case should be categorised to the extent that the available data allow, but it should not be forced into a diagnostic category if the minimal criteria needed for a specific diagnosis are not met. For example, such lymphomas might be reported as 'B-cell lymphoma, unclassifiable, likely to be high-grade based on a very high proliferation fraction', or 'B-cell lymphoma, unclassifiable'.

In a very small proportion of lymphomas — 'grey zone' lymphomas — it may not be possible to distinguish definitively between NHL and HL even in the hands of expert haematopathologists, owing to significant morphological and immunophenotypic overlap.[18–20] Typically, these cases involve distinction between HD (classical HD, or the diffuse form of lymphocyte predominant HD), and anaplastic large-cell lymphoma, mediastinal large B-cell lymphoma or T-cell-rich B-cell lymphoma. In particular, the relationship between T-cell-rich B-cell lymphoma (especially cases with some nodularity — 'paragranuloma-type') and nodular lymphocyte predominant Hodgkin's disease, is a debated issue given the lack of accepted and consistent criteria by which to make the distinction.[20] Some of these grey zone lymphomas may represent true biological transitions between HL and NHL, while others, despite morphological and immunophenotypic overlap, are biologically unrelated.

The WHO classification also does not specifically refer to composite lymphomas, which are defined as the synchronous occurrence of two or more morphologically distinct types of NHL and/or HD occurring in the same lymph node or extranodal tissue[21] and which may or may not be clonally related.[22–24] These may take the form of composite B-cell lymphomas (most common), composite T-cell lymphomas (rare), composite B- and T-cell lymphoma, or composite HD and NHL.[21,25,26] Histologically discordant lymphomas may also occur synchronously or sequentially at different anatomic sites, and may or may not be clonally related.[27,28] At least some of these represent progression of one lymphoma into a more aggressive type. For reporting purposes, each lymphoma type forming these composite or discordant lymphomas should be included in the diagnostic report.

3.6 Alternative classifications

Recently, the EORTC have proposed an alternative classification scheme for cutaneous lymphomas[29], the authors arguing that particular clinicopathological aspects of cutaneous lymphomas are not adequately conveyed in the WHO scheme. We recommend the use of the WHO classification for all forms of lymphoma while recognising that much of the clinical survival data available in cutaneous lymphoma (DCLWG) have been published using the classification scheme of the European Organisation for Research and Treatment of Cancer (EORTC)[29] (see Table 3.1).

Key point

The World Health Organisation (WHO) Classification of Haematological Malignancies is the internationally accepted taxonomy for lymphoproliferative disease and should be fundamental to the classification, diagnosis and management of lymphoproliferative disease.

Table 3.1 WHO lymphoma classification

B-CELL NEOPLASMS
Precursor B-cell neoplasm
Precursor B lymphoblastic leukaemia/lymphoma
Mature B-cell neoplasms
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Lymphoplasmacytic lymphoma
Splenic marginal zone lymphoma
Hairy cell leukaemia
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Burkitt lymphoma/leukaemia
B-cell proliferations of uncertain malignant potential
Lymphomatoid granulomatosis
Post-transplant lymphoproliferative disorder, polymorphic
T-CELL AND NK-CELL NEOPLASMS
Precursor T-cell neoplasms
Precursor T lymphoblastic leukaemia/lymphoma
Blastic NK cell lymphoma **
Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukaemia
T-cell large granular lymphocytic leukaemia
Aggressive NK cell leukaemia
Adult T-cell leukaemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous anaplastic large-cell lymphoma
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma
T-cell proliferation of uncertain malignant potential
Lymphomatoid papulosis
HODGKIN LYMPHOMA
Nodular lymphocyte predominant Hodgkin lymphoma

Classical Hodgkin lymphoma
Nodular sclerosis Hodgkin lymphoma
Lymphocyte-rich Hodgkin lymphoma
Mixed cellularity Hodgkin lymphoma
Lymphocyte-depleted Hodgkin lymphoma
Immunodeficiency associated lymphoproliferative disorders
Lymphoproliferative diseases associated with primary immune disorders
Human immunodeficiency virus-related lymphomas
Post-transplant lymphoproliferative disorders
Methotrexate-associated lymphoproliferative disorders
HISTIOCYTIC AND DENDRITIC-CELL NEOPLASMS
Macrophage/histiocytic neoplasm
Histiocytic sarcoma
Dendritic cell neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma/tumour
Follicular dendritic cell sarcoma/tumour
Dendritic cell sarcoma, not otherwise specified
MASTOCYTOSIS
Cutaneous mastocytosis
Indolent systemic mastocytosis
Systemic mastocytosis with associated clonal, haematological non-mast cell lineage disease
Aggressive systemic mastocytosis
Mast cell leukaemia
Mast cell sarcoma
Extracutaneous mastocytoma

Note: Table modified to exclude myeloproliferative disorders, myeloid leukaemias and mast cell disease.
*Morphology code of the International Classification of Diseases (ICD-O), third edition. Behaviour is coded /3 for malignant tumours and /1 for lesions of low or uncertain malignant potential.
**Neoplasms of uncertain lineage and stage of differentiation.

3.7 References

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CHAPTER 4 BIOPSY TECHNIQUES AND TISSUE HANDLING

4.1 Prebiopsy

4.1.1 Biopsy planning: interaction between clinician and pathologist[1]

In an optimal situation, discussion takes place between the surgeon, the treating haematologist/oncologist, the anatomical pathologist and the laboratory haematologist before biopsy. Knowledge of the clinical history and differential diagnosis allows planning of the most appropriate biopsy site and technique, special studies needed, and time and place of the biopsy. Review of the hemogram and blood film is recommended, and the issue of patient consent can be addressed if any tissue is to be kept for research or submitted to a tissue bank.

In reality, however, this ideal situation is often unobtainable, underscoring the importance of providing full clinical information to the pathologist.

4.1.2 Clinical details required on pathology request form[1–4]

The WHO classification is a clinicopathological system in which a detailed understanding of the clinical presentation is fundamental to the diagnosis (see Chapter 3). Almost universally, however, the clinician who performs the biopsy and submits the pathology request is a surgeon or interventional radiologist rather than the clinician responsible for clinical investigation and management. It is therefore essential that the managing clinician be separately identified on the request form and that the following information be made available prior to diagnosis.

Requirements include:

i Patient demographics

ii Clinician performing biopsy

iii Clinician responsible for patient investigation and management

iv Date of procedure

v Duration lymphadenopathy or other mass

vi Localised or generalised disease

vii Evidence of organomegaly

viii Other signs and symptoms, for example, constitutional symptoms

ix Relevant haematological findings

x Underlying disease or immunosuppression

- a Viral: HIV, HTLV, EBV
- b Autoimmune disease
- c Congenital immune disorder
- d Known cofactors (e.g. Helicobacter infection)

xi Provisional diagnosis

xii Site of biopsy

xiii History of previous lymphoma:

- a Dates
- b Site
- c Previous diagnosis
- d Previous treatment (e.g. transplantation).
- e Treatment status (e.g. complete remission, partial remission, relapse)

Key point

There is a minimum amount of information that should be included on request forms. It is recommended that specific histopathology request forms be developed that include the information in Section 4.1.2, and that they be used generically in oncology (see suggested format in Figure 4.1).

Figure 4.1 Clinical request form

Clinical Request Information ....

Surname .....First name ..... UR No. ..... Sex .....DOB.....
Address .....
Name of clinician performing the biopsy .....
Name of clinician managing the patient .....

Current illness:

Disease duration: .....

Presenting complaint:

Disease extent: Unknown / Solitary / Localised / Generalised

Known sites of disease: *Nodal sites: (indicate on diagram) or:*
Specify: .....
Extranodal sites: .....

Organomegaly: Unknown / Hepatomegaly / Splenomegaly
Other: .....

Constitutional symptoms Unknown / Yes / No

Relevant haematology: Unknown / Specify:.....

Provisional clinical Dx: Unknown / NHL / Hodgkin lymphoma / Reactive
Other: .....

Relevant past Hx: Unknown / Nil / Autoimmune Disease / Medication
Other: .....

Immunosuppression: Unknown / Viral / Congenital / Transplantation / Methotrexate
Other: .....

Previous lymphoid disease: Unknown / Nil / Yes

Diagnosis: Specify:.....

Date: .....

Site: .....

Stage: .....

Laboratory: .....

Laboratory Ref. No.: .....

Treatment(s):

Modality: Specify: .....

Completion: Ongoing / Completed (date.....)

Response: CR / PR / NR

4.2 Biopsy modalities

4.2.1 Fine-needle aspiration biopsy

Fine-needle aspiration (FNA) biopsy is a useful technique for the initial triage of lymphoproliferative disease and to obtain material for flow and other ancillary studies by the least invasive technique. It has a role in the diagnosis of metastatic tumours in lymph nodes[5,6] and may aid in distinguishing between reactive lymphoid hyperplasia and lymphoma when used in conjunction with flow cytometry FCM.[1,6–8]

Key point

Fine-needle aspiration (FNA) biopsy should not be used in the definitive diagnosis or subtyping of lymphomas, for which excision biopsy remains the definitive procedure.

Indications for FNA

i Triage of lymphadenopathy or a mass lesion, superficial or deep:

- a Haematolymphoid neoplasm versus other malignancy
- b Reactive lymphoid hyperplasia versus lymphoma

ii Staging

iii Monitoring for:

- a Residual disease
- b Recurrence
- c Tumour progression

iv As an adjunct to conventional biopsy

- a To obtains better cytological detail
- b To obtain fresh material for ancillary studies such as flow studies (FCM), cytogenetics, molecular studies, etc.

Guideline — Fine-needle aspiration (FNA) biopsy	Level of evidence	Refs
FNA is the biopsy investigation of choice in the initial triage of a possibly lymphomatous lesion, and should be accompanied by flow cytometry (FCM) studies.[1,6–8]	IV	9–17

Technique for FNA

To ensure high-quality preparations, a person experienced in FNA biopsy technique should perform this procedure.[18]

A 25 G or 23 G needle is manoeuvred to the capsule or edge of the target and then repeatedly and rapidly pushed into the area in question. Between six and 20 movements are usually made before the needle is removed and the contents expunged for triage. The procedure may be performed with or without aspiration.

FNA specimens must be triaged immediately. Direct smears are prepared and stained as for imprints (see Section 4.3.2) and a suspension is submitted for FCM. Other allocations are made according to the clinical circumstances (see Section 4.3.2). It is advisable for a cytopathologist or cytologist to attend the procedure to check adequacy of the biopsy, prepare the smears for optimal morphology and assist in triaging the specimen.

Key point

To optimise fine-needle aspiration (FNA) biopsy, it is preferable for a cytopathologist or cytologist to attend the procedure to check adequacy of the biopsy, prepare the smears, and assist in triaging the specimen.

Advantages and disadvantages

The **advantages** of FNA can be summarised as follows:

i Excellent triage tool

ii Good material for flow studies is readily obtained

iii Minimal invasiveness

iv Few complications:

- a Bleeding
- b Pneumothorax
- c Infection

v Rapid result

vi Inexpensive

vii Easy to perform

The **disadvantages** of FNA include the following:

It is inappropriate for **definitive** diagnosis and subtyping due to:

i Absence of architectural information seen in tissue sections

ii Absence of immuno-architectural information seen in immunostains of tissue sections[19]

iii Sampling problems

- a Partial lymphomatous infiltration
- b Composite lymphoma
- c Lymphoma with sparse neoplastic cells:

- Hodgkin lymphoma
- T-cell rich B-cell lymphoma

iv Technical limitations

a Air-drying artefact

b Blood contamination

c Smear artefact

d Necrosis

e Dry aspirates (fibrotic lesions)

v High level of diagnostic expertise is required

vi Test performance is significantly poorer than tissue biopsy

Test performance

Differentiation of lymphoma from hyperplasia

The unsatisfactory rate for FNA is reported to be 3–16%.[20]

Using cytomorphology alone, the accuracy of FNA in the diagnosis of malignant lymphomas is reportedly between 64% and 72%[9–12], with a false negative rate up to 12–14%.[10] Small lymphocytic proliferations in particular have a high false negative rate using FNA cytomorphology alone.

With the addition of FCM, the accuracy of lymphoma diagnosis has been claimed to be between 77% and 87%[11–14], and the false negative rate as low as 3.5–5%.[9–11] Many of the studies, however, did not define the 'gold standard' by which test accuracy was measured. In those series where combined FNA and FCM findings have been verified by subsequent histological biopsy, a test sensitivity of 80–83% has been claimed.[21,22] Accuracy may be significantly improved when dealing with recurrent disease.[13,23]

The test accuracy quoted above relates to studies that consist largely of B-cell tumours, since these are the most common forms of lymphoma in western society. They do not apply specifically to the diagnosis of Hodgkin lymphoma as in this disease, FCM findings are normal and the diagnosis depends entirely upon cytomorphology. The diagnostic accuracy of FNA in Hodgkin lymphoma by FNA ranges from 30% to 85–90%[15,24–26], while the accuracy of subtyping is poor[15,24], due partly to lack of architectural information in FNA samples. Similarly, the test accuracy may be lower for T-cell lymphomas as clonality cannot be directly assessed by FCM, and many T-cell lymphomas lack phenotypic aberrancy.

Lymphoma subtyping

In defining a specific lymphoma subtype or disease category, the accuracy of FNA cytomorphology alone has been reported to be between 37% and 64%[10,23], while the accuracy of FNA combined with FCM is reported to be between 77% and 84%.[7,10,12,13,23]

A more recent literature review of FNA combined with immunophenotyping[16] has documented a wide range of precise classification (from 18% to 100%), with histological confirmation of the cytological diagnosis varying from 10% to 100%.

Most series are small and many consist almost entirely of B-cell lymphomas, both primary and recurrent, often with a predominance of one disease subtype. A particular problem arises in follicular

lymphoma, where there are no established criteria for the subtyping or grading of follicular lymphomas in cytological preparations, and the method varies in the different series cited above.[10,15,27]

The test accuracy quoted above does not apply in Hodgkin lymphoma in which differentiation of the subtypes from each other and from various NHL simulants, including anaplastic large-cell lymphoma, T-cell lymphoma and T-cell rich B-cell lymphoma, may be exceedingly difficult even after examination of good histological tissue sections and an extensive panel of immunohistochemical stains. Surgical biopsy is recommended to confirm (or make) the diagnosis and to subclassify the disease.[15,17]

Guideline — Definitive tissue biopsy	Level of evidence	Refs
Tissue (as distinct from FNA) biopsy is essential for the primary diagnosis, subtyping and clinical management of lymphoma.	IV	7, 10, 13, 15, 27–29

Key point

It is acknowledged that in rare cases where the clinical circumstances preclude tissue biopsy, it may be appropriate to proceed to treatment with a lower standard of diagnostic proof.

4.2.2 Cytological specimens other than FNA

Protocols are needed in pathology services to ensure appropriate specimen delivery, handling and rapid triage of cytological specimens other than FNA, for example, effusions (see below).

4.2.3 Needle core biopsy

For many years, image-guided needle core biopsies (NCBs) have been applied to numerous organs with excellent results and few complications.[30–32] Following the widespread adoption of the WHO classification of lymphomas and ancillary studies, NCB is gaining increasing acceptance in the diagnosis and management of deeply situated lymphoma.[33–36]

Key point

In the presence of surgically accessible, superficial lymphadenopathy, needle core biopsy has little role in *primary* lymphoma diagnosis, since fine-needle aspiration is the optimal form of triage, and excision biopsy is the investigation of choice for definitive diagnosis.

In deeply situated lesions, however, CT or ultrasound-guided core biopsies have a number of advantages, and in many cases can provide definitive primary diagnosis of lymphoma. NCB nonetheless provides material inferior to surgical specimens, and a significant minority of cases will still require surgical biopsy for definitive diagnosis. Moreover, even when a specific lymphoma subtype can be diagnosed with confidence, the risk of sampling error ensures that this modality must always be inferior in quality to surgical biopsy.

Indications

i Staging

ii Monitoring

iii Residual disease[36]

iv Recurrence[33,35,36]

v Tumour progression[33,35,36]

vi Obtaining material for ancillary studies (e.g. flow cytometry, cytogenetics)[19]

vii In cases without surgically accessible peripheral disease

viii For the primary diagnosis and subtyping of lymphoma (surgical biopsy subsequently required in a minority of cases).[19,33–37]

NCB may be deemed unsuitable in the following circumstances due to the risk of significant morbidity:

i Clotting disorders, anticoagulant therapy

ii Pulmonary or hepatic hilar disease

iii Intraparenchymal lung disease

iv Para-aortic, para-caval nodes

v Aortopulmonary window disease

vi Lesions surrounded by bowel

Technique

A variety of biopsy guns are available, with both advancing and non-advancing needles. Needle sizes range from 12 G to 20 G.

Although a recent study of 211 cases failed to show a correlation of diagnostic accuracy with needle gauge[35], most cases in the study used 16 G and 18 G needles. Few 20 G samples were included in the sample. Although we could not find any literature to provide an evidence-based guideline, the consensus view of the diagnostic committee is that NCBs of 20 G or smaller diameter are prone to fragmentation and significant crush artefact.

Key point

In the absence of a higher level of evidence to the contrary, needle biopsies of 18 G or 16 G are preferable.

There are few data correlating morbidity with needle diameter.

Sufficient material should be obtained to allow for necessary ancillary studies.

In virtually all cases, FNA biopsy should be performed concurrently, as it adds little to the morbidity of NCB yet provides superior cytomorphology and is an excellent source of a cell suspension for FCM.

It is recommended that the CB specimen be triaged at the time of biopsy, either by the attending cytologist or pathologist, or by the surgeon or radiologist, and that the specimen for histology be placed in formalin as soon as possible to prevent drying.

Key point

Needle core biopsy performed for the diagnosis of suspected lymphoma should be accompanied by fine-needle aspiration and material for flow cytometry.

Advantages and disadvantages

Compared with FNA, NCB has the following **advantages**:

i Some (limited) architectural information is available[19]

ii Sampling error is reduced

iii Paraffin sectioning enables:

- a Paraffin section immunophenotyping[19,36]
- b Immuno-architectural assessment (using CD21, CD23 or CD35 for FDCs)
- c Paraffin tissue-based PCR and/or FISH[19]

NCB has the following **disadvantages**:

i Increased complications compared with FNA (up to 7.5% of cases)[34,35]

- a Haematoma[30]
- b Pneumothorax[30]
- c Local discomfort[36]
- d Vasovagal attacks[36]

ii Cytological assessment may be compromised by:

- a Crush artefact[35]
- b Loss of chromatin detail (may impart a 'blastic' appearance)[38]

Compared with surgical biopsy, NCB has the following **disadvantages**:

i Inadequate sample (up to 14%)[19,32,36]

- a Non-representative sample, for example, surrounding tissue
- b Diseases with few malignant cells, for example, T-cell rich B-cell lymphoma, Hodgkin lymphoma[19]
- c Diseases with zonal variability, for example, MALT lymphoma[19]
- d Insufficient material for ancillary studies

ii Morphological detail compromised

iii Crush artefact[35]

iv Necrosis or sclerosis may limit sampling[32]

v Nuclear smudge artefact may impart a 'blastic' appearance[38]

vi Architectural assessment limited

NCB has the following **advantages**:

i A general anaesthetic is avoided[35]

ii Hospitalisation time is short (mean one day)[35]

iii Low cost[35]

iv Well tolerated[36]

v Lower morbidity[19,35,36]

vi Less invasive[35]

Test performance

Differentiation of lymphoma from hyperplasia

Diagnostic accuracy of NCB is reportedly between 58% and 89% overall.[33,35,36] A recent series of 66 cases of cervicofacial lymphadenopathy, however, reported a sensitivity, specificity and accuracy of 98.5%, 100% and 98.7% respectively in differentiating lymphoma from lymphoid hyperplasia.[39]

Lymphoma subtyping

The same review of 66 patients reported successful primary diagnosis and subclassification in 80% of cases, obviating the need for surgical biopsy. Other studies have reported an accuracy of 75–85% with the aid of immunoperoxidase stains.[33,36] Diffuse B-cell lymphomas and follicular lymphomas predominate in many studies.

4.2.4 Endoscopic biopsy

Endoscopic biopsies provide morphological information similar to that of NCBs — including similar issues of crush artefact and sampling error. Immunophenotyping by immunohistochemistry is readily performed. There is limited quantitative information upon the efficacy of flow surface marker studies, but a number of studies have clearly demonstrated the value of flow studies in endoscopic biopsies.

4.2.5 Surgical biopsy of lymph node where lymphoma is suspected

This is discussed in Chapter 10.

4.2.6 Bone marrow aspirate and trephine

Indications

i Staging at initial diagnosis

ii Restaging following treatment

iii Assessment of minimal residual disease

iv Assessment of cytopenias in patients with an established diagnosis

v Rarely, for the primary diagnosis and subtyping of lymphoma in patients with no other accessible disease.

For **staging**, the result should be scored as positive (unequivocal cytological or architectural evidence of malignancy), negative (no aggregates or only a few well-circumscribed lymphoid aggregates), or indeterminate (increased number or size of aggregates without cytological or architectural atypia). The extent and the pattern of marrow involvement, along with the cell type, should be reported.

Assessment of **minimal residual disease** is carried out using one or more ancillary techniques. Flow cytometry (FCM) may demonstrate B-cell monoclonality or aberrant B-cell or T-cell phenotypes. In certain disease subtypes, immunostaining may detect low levels of tumour.

In cases with no morphological or immunophenotypic evidence of residual tumour, molecular studies for immunoglobulin heavy-chain gene, or T-cell receptor gamma rearrangement, may be performed. These are generally not carried out routinely, except in the setting of clinical trials where patients are being treated in subspecialised centres that have the appropriate expertise to perform the assays and interpret the results. In certain specific subtypes of lymphoma, specific oncogenes may be assayed, for example, polymerase chain reaction (PCR) for *bcl-1* in patients with mantle cell lymphoma, *bcl-2* in follicular lymphoma, or *c-myc* in Burkitt lymphoma.

In general, lymphoma patients are currently not being treated on the basis of detectable molecular disease post-cytotoxic therapy. This may change in the future, analogous to certain leukaemias such as acute promyelocytic leukaemia and chronic myeloid leukaemia.

The cause of cytopaenia**s** can be assessed. They may be due to marrow replacement with lymphoma, cytotoxic therapy, increased peripheral destruction, or development of secondary myelodysplastic syndrome/acute leukaemia in previously treated patients.

Bone marrow examination is not recommended for the **primary diagnosis** of lymphoma because of frequent histological discordance between marrow and other sites.[40–42]

Guideline — Requirements for bone marrow examination	Level of evidence	Refs
Bone marrow examination is not recommended for the primary diagnosis and specific subtyping of lymphoma, except in special circumstances.	IV	40–42

For certain types of lymphoproliferative disease that commonly present in the bone marrow, a definitive diagnosis may be made on this material alone. Examples include acute lymphoblastic lymphoma (ALL), small lymphocytic lymphoma (chronic lymphocytic leukaemia), prolymphocytic lymphoma, lymphoplasmacytic lymphoma and hairy cell leukaemia.

For most other types of lymphoma, definitive diagnosis will require excision biopsy of representative material from the primary disease site. Disease confined to the marrow is an obvious exception.

In some circumstances, bone marrow may be the only accessible site of disease. In such cases, a lower standard of diagnostic proof may be accepted by the treating clinician and the bone marrow used for primary diagnosis.

Technique

It is important that the procedure be carried out by haematologists (trained or in training), or other medical practitioners specifically trained in this technique.

Aspiration alone is not recommended. Ideally, triage occurs at the time and place of the procedure.

For bone marrow biopsies, direct aspirate smears (without anticoagulant) should be prepared at the time and place of biopsy. However, if that is not practical, the aspirate should be placed in an EDTA tube and films made within one to two hours. Two aspirate smears and one trephine imprint should be stained with one of the Romanowqsky stains. The stain recommended by the Royal College of Pathologists of Australasia is the ICSH stain (International Committee for Standards in Haematology). The smears should be stained within 24 hours. If that is not possible, they should be fixed in methanol and stained as soon as possible.

The ideal length of a core biopsy is 20 mm.[40] For staging, this should ideally be examined at 3–4 levels 0.10–0.2 mm apart. Such examination obviates the need for bilateral bone marrow biopsies.[41–43]

Ideally, triage occurs at the time and place of the procedure.

4.3 Transport, handling and triage of biopsy material

4.3.1 Transport of fresh excision biopsy tissues

Where lymphoma is suspected, all specimens should immediately be sent intact and unfixed in a closed sterile container to the laboratory (anatomical pathology) for triaging.[4] The specimen must be identified and accompanied by a detailed request form (see Section 4.1.2). Drying must be avoided. If paper or PVA pads are used, they should be moistened with physiological saline. If there will be any delay in transportation, the specimen should be floated in sterile physiological saline, Hanks solution, or RPMI 1640 culture medium. Immunofluorescence transport medium containing ammonium sulphate is not suitable.

Specimens may be transported at room temperature for up to two hours. For delays of 2–24 hours, they may be stored at 4°C or cooled on wet ice, but not allowed to freeze. Dry ice is not appropriate as it will freeze the specimen.

Specimens for conventional cytogenetics should be kept sterile and at room temperature, in RPMI 1640 (Section 4.3.4).

4.3.2 Laboratory handling and triage of fresh tissue

Tissue should be handled quickly to preserve morphology, antigens and cell viability. Specimens other than needle core biopsies should always be sliced to allow proper fixation. Drying must be avoided at all stages and each time tissue is sliced, it should be immersed in the appropriate fluid immediately. A written protocol should be available for specimen handling in each institution.[1,4,44–49]

Many centres have established tissue banks for prospective studies. It is recommended that this practice be encouraged.

Macroscopic description should include

i Patient identifiers (name, medical record number)

ii Organ or site

iii Received:

- a Fresh, in fixative or other fluid
- b Intact, sectioned, fragmented

iv Nature of biopsy (core, incisional, exisional, resection)

v Weight (for spleen and other organs)

vi Dimensions

vii Description of capsule and cut surface: (colour, consistency, necrosis, haemorrhage, nodularity)

Universal handling

As the WHO classification of lymphoma is based on a combination of morphology, immunophenotype, genetic features and clinical features, almost all specimens, including tissue, cytology specimens and bone marrow specimens, need to be divided to allow ancillary investigations. The constraints of specimen size, cost and service availability mean that the most appropriate ancillary tests need to be selected on a case-by-case basis, taking into account the information from the preoperative consultation and initial triage (intraoperative examination or FNA).

i. Slicing

Using a sterile technique, slice the lymph node or tissue cleanly with a sharp scalpel or razor blade, in 2 mm thick slices, perpendicular to the long axis so the poles are then available for ancillary studies that require fresh tissue.[4]

NCB specimens are rarely divided, except when required for triage.

Spleens should be sliced at 3–5 mm thickness, especially if removed for staging. Initial fixing of 10 mm thick slices in formalin may facilitate thin slicing.[4] Splenic lymph nodes should be dissected from the hilum and treated in the same way as lymph nodes.

Extranodal tissue and large resection specimens such as stomach, salivary gland, bowel, lung or other organs will require dissection and detailed description in addition to the above.[2] They should be submitted fresh and triaged for ancillary studies in the same manner as nodal disease.

ii. Make imprints

Surgical specimens: Make imprints or touch preparations of the freshly cut surfaces, taking care not to drag, squash or traumatise the tissue. Touch the prelabelled glass slide lightly to a freshly cut surface that is held face up to avoid blood draining down onto the slide. Some may be air-dried and Giemsa stained, formalin fixed and H&E stained, or alcohol-fixed and PAP stained. Imprints may be used for intraoperative diagnosis, and to supplement later histology. Others may be fixed later and stored frozen for possible cytochemistry and immunocytochemistry for cell surface and other antigens or interphase FISH.[50]

Needle core biopsy specimens: Touch imprint preparations are not generally used, but may be of use in the rare cases an FNA has not been performed. The tissue used for imprint can then be used for FCM studies. A separate core of undamaged tissue should be submitted for formalin fixation and paraffin embedding.

Bone marrow specimens: Trephine touch imprints are desirable for morphology, cytochemistry, and immunohistochemistry, especially if an adequate aspirate could not be obtained.[51]

Use of imprints for immunostaining: Fixation in 0.1% formol saline for 2–14 hours eliminates the troublesome background protein and red blood cells, and provides excellent preservation of lymphocyte membrane antigens other than immunoglobulin.[52]

iii. Fix sufficient tissue for good histology

Well-prepared, formalin-fixed, paraffin-embedded sections remain the gold standard for lymph node diagnosis and are the highest priority of triage.

Guideline — Lymph node diagnosis — 'gold standard'	Level of evidence	Refs
Well-prepared, formalin-fixed, paraffin-embedded sections remain the gold standard for lymph node diagnosis and are the highest priority of triage.	IV	53

Cut a number of 2 mm slices of lymphoid tissue and place immediately in 5–10 times their volume of fixative for morphologic diagnosis. Immunohistochemistry, molecular studies (by PCR or FISH) can also be performed on this tissue.

iv. Submit a cell suspension for flow cytometric analysis

For FCM analysis, all specimens must be in a single cell suspension. Unless the specimen can be delivered to the flow laboratory immediately, the specimen is usually suspended in RPMI 1640 medium stored at 4°C, Hanks solution, or physiological saline. This specimen should reach the laboratory within 24 hours, but useful results can sometimes be obtained with an even longer delay. Suspected cases of Burkitt's lymphoma/leukaemia and cerebrospinal fluid require more rapid transport and processing. It is recommended that if the specimens are received for immunophenotyping 24 hours or more after collection, a viability test, for example, trypan blue exclusion test, is performed.

FNA: The aspirate is simply expelled into the appropriate fluid and transported at 4°C or room temperature.

Cytological specimens other than FNA: Specimens may be submitted directly to the flow laboratory if a delay of less than two hours can be ensured. For longer delays, the specimens should be placed in RPMI 1640 or Hanks solution and transported at 4°C or room temperature. There is no need for anti-coagulation of cytological specimens such as pleural, ascitic or cerebrospinal fluid.

Surgical or NCB: A thin slice of lymphoma tissue should be placed in RPMI 1640 at 4°C. It is important that it be transported at this temperature to slow autolysis. For lymph nodes, a very effective alternative technique is to scrape a scalpel blade over the cut surface of freshly sliced tissue — usually taken from one end of the node to preserve the central slices for histological section.[54] The scrapings are then placed in RPMI 1640 as above.

Blood or bone marrow: The blood or bone marrow aspirate should be collected and placed in an anticoagulant, either EDTA or heparin, and transported as above.

Immunophenotyping of every case is not universally recommended. Generally it is carried out in patients in whom the morphology is inconclusive or the lymphoma needs to be subtyped.

Additional allocations depending on the indications and the amount of tissue available

i Sterile specimen for microbiology. Transport at 4°C

ii Specimen frozen for intraoperative assessment (see Section 4.3.3)

iii Other ancillary techniques.

The majority of lymphomas can be diagnosed and classified by morphology plus immunophenotyping for lineage and clonality, using a combination of immunohistochemistry and flow cytometry. Only a minority of cases require molecular genetic testing or cytogenetics.[55–58] Increasingly, these tests can be done on formalin-fixed, paraffin embedded tissues. The method used depends on the differential diagnosis.[55–61] RNA detection methods still require fresh or frozen material[57], and many institutions cryopreserve fresh tissue for possible future studies using emerging technology such as microarrays. However, for small specimens, a good fixed sample for morphology always takes precedence.[45]

a Frozen tissue (refer also to Section 4.3.3):

i Immunostains for cell surface and other antigens that do not survive paraffin processing (infrequently required)

ii Molecular studies by Southern blot, PCR, and techniques where RNA is needed

iii Cryostorage for:

a Emerging techniques such as cDNA microarrays

b Tissue banking for clinical trials and laboratory research (subject to ethics approval and patient consent)

b Sterile specimen in RPMI or physiological saline (5x2x2 mm) for:

i Molecular studies. (Unless there is an immediate indication for these techniques, freezing tissue is more economical) (refer to Section 4.3.3).>>>

ii Metaphase cytogenetics and FISH techniques in RPMI tissue culture medium or preferably, immediate delivery at room temperature, or at 4°C if more than two hours delay (see Chapter 6).

c Electron microscopy. Small blocks of tissue <1 mm thick in 2.5% glutaraldehyde kept at 4°C for electron microscopy, especially if intraoperative microscopy shows large anaplastic malignant cells. (Note that well-fixed tissue can also be retrieved from neutral buffered formalin for electron microscopy).

4.3.3 Freezing tissue

Tissue to be frozen for intraoperative diagnosis and later ancillary tests should be placed in optical cutting temperature (OCT) embedding compound on a cryostat chuck, and snap frozen in a super-cooled mixture such as isopentane and dry ice mixture (–79°C). Freezing of slices less than 1–2 mm thick on a rapid-freeze chuck accessory in a cryotome can be satisfactory, though not ideal. Freezing in liquid nitrogen (<–195°C), or in an EM embedding capsule in liquid nitrogen and isopentane (–150°C) are preferable if intraoperative frozen section is not required.[1,45–47,57,62] Frozen sections can also be transported.

For storage, frozen tissue should be wrapped in aluminium foil or plastic to avoid desiccation. Storage is ideally at –70 or –80°C, especially for nucleic acids, but –20°C is sufficient for many antigens. Any thawing must be avoided and tissue should not be stored in cryostats or freezers with automatic defrost cycles. Frozen tissue should be transported in a Styrofoam container with sufficient dry ice to prevent thawing in transit. Long-term cryopreservation should be at <170°C.

4.3.4 Fixation of tissue

Ten per cent neutral buffered formalin is the recommended general fixative for lymphoma diagnosis. It is universally available, inexpensive, stable and relatively safe. Fixation time is not critical and it

can be disposed of without environmental problems. It can be used in tissue processors and autostainers with other routine tissue. Preservation of antigens (using antigen retrieval) is good if adequately fixed. Fixation should not exceed 24 hours.[63,64] Fixation in 10% neutral buffered formalin also ensures that DNA is well preserved for PCR studies.[45,47,51,57,65,66]

For bone marrow biopsies, addition of acetic acid (formol acetic acid) has been reported to improve cytology.[63]

Laboratories with a special interest in haematopathology may use other fixatives. Metal-based fixatives such as B5 and Zenker's, and acid fixatives such as Bouin's, give good morphology and immunohistochemistry, but require special preparation and processing. Mercury is a toxic environmental pollutant that is difficult to dispose of safely, and picric acid is toxic and explosive. B5 is commonly used.[1,44] Mercuric fixatives and Bouin's are not recommended for PCR[65,67], though satisfactory results have been reported with B5.[68] Routine use of these fixatives has diminished due to environmental concerns.

4.3.5 Decalcification of tissue

Bone marrow trephines are routinely decalcified before processing. Other specimens involving bone may also require decalcification.

Decalcification with 10% neutral EDTA is superior to stronger acid decalcifiers such as RDO for immunohistochemstry.[63] Formic acid decalcification is also satisfactory for immunohistochemistry[64], but has been reported as inferior to EDTA for PCR.[69] Decalcifying agents containing hydrochloric acid, such as RDO, are best avoided because they produce the carcinogenic by-product bis-chloromethyl ether when mixed with formaldehyde.[70–72] Hydrochloric and picric acids damage antigenicity and should be avoided.

4.4 Referral of lymphoma material

4.4.1 General note

Centres performing biopsies for diagnosis of lymphoma need to develop referral arrangements for ancillary studies not available locally. Access to immunohistochemistry and microbiology services is necessary, and routine availability of flow cytometry is strongly recommended.[1] Molecular genetics techniques should be available in selected cases.

4.4.2 Referral of fresh, frozen or fixed tissue or cells for ancillary studies

See transportation requirements described in previous section

4.4.3 Referral of processed lymphoma material for histologic second opinion or review prior to therapy

Second opinion may be requested by an anatomical pathologist because of diagnostic difficulty, or by a treating clinician prior to therapy. To minimise delays and waste of tissue, it is often convenient to refer the material to the pathologist who functions as a member of the multidisciplinary team where the patient will be treated.

The consulting pathologist must have access to haematoxylin and eosin stained slides, immunohistochemistry, the original pathologist's report, clinical details, and results of any ancillary studies such as flow cytometry and molecular genetics. Ideally, the original slides including H&E and immunohistochemistry stains should be sent (to be returned to the original pathologist after review).

Either a representative paraffin block (to be returned) or at least 12 unstained sections on sialanised or charged slides (to be retained by the consultant).

At present, there is no Medicare funding to cover referral for second opinion. Strategies for funding referrals must be addressed so that cost does not act as a disincentive.[73]

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CHAPTER 5 IMMUNOPHENOTYPING AND PROGNOSTIC MARKERS

5.1 Immunohistochemistry

5.1.1 Introduction

Immunophenotyping of frozen section material, once the mainstay of lymphoma immunohistochemistry, has been superseded by improvements in antigen retrieval techniques[1,2] and the development of antibodies that recognise fixation resistant epitopes. The detection of antigens in paraffin sections obviates the requirement for fresh material for immunohistochemistry, provides a much better morphological context for the interpretation of immunostains, and has enabled immunophenotyping of paraffin-embedded archival material.[3,4]

5.1.2 Choice of antibody panels

Diagnostic antibodies that are immunoreactive in paraffin sections are as follows (many of these are enhanced by some form of heat-induced antigen retrieval procedure)[4,5]:

- *Markers to exclude simulators of lymphoma*: CD45, cytokeratin, S100, HMB45, Melan-A (CD30, CD20 and CD43 as a second line)
- *Markers of B-lymphocytes*: CD20 (L26), Cd75 (LN1), CD79a
- *Markers of T-lymphocytes*: UCHL1 (CD45RO), MT1 (CD43), polyclonal CD3, OPD4, βF1 (TCRβ chain), CD4, CD8, CD5
- *Markers of Reed-Sternberg cells*: CD15, CD30, CD75 (LN2), peanut agglutinin, Fascin, LMP1, (negative for CD45, Oct2, Bob1)
- *Markers of immature lymphocytes*: TdT (paraffin sections and imprints), CD79a, CD43, CD10, cytoplasmic CD3, CD34
- *Immunoglobulin restriction*: Kappa and Lambda light chains (Microwave retrieval with 4 M urea solution combined with protease digestion (imprints and paraffin sections)
- *Markers of myeloid cells and monocytes*: anti-myeloperoxidase, anti-neutrophil elastase, anti-lysozyme, CD34, CD68, Mac387, Ham56, CD43 (expressed but not specific)
- *Markers of plasma cells:* CD38, CD79a, CD138, monoclonal cIg, EMA, CD45 (weak), CD30.
- *Markers of dendritic reticulum cells, Langerhans cells and interdigitating reticulum cells:* CD21, CD23, CD35, S100, CD1a
- *Others*: *bcl-6*, ALK protein, CD30, EBV-LMP1, EBER (*in situ* hybridisation), cyclin D1 (antigen retrieval in EDTA pH8.0, preferably at 120°C), CD10 (CALLA), CD23, MIB1, CD56, CD10, PAX5 (BSAP), Oct2, Bob1, MUM1.

Panels for specific lymphoid neoplasms

- *Follicular lymphoma versus follicular hyperplasia: bcl-2*, CD45RA (MT2), immunoglobulin light chain restriction, CD21 or CD35 (DRC pattern)
- *For small cell lymphoma:* CD3, CD5, CD10, CD43, CD23, *bcl-2*, cyclin D1, CD10 (CALLA), CD21 or CD35 (DRC pattern).

- *For blastic lymphomas:* TdT, CD1, CD3, CD4/CD8, CD5, CD10, CD20, CD34, CD43, CD79a, cyclinD1. MIB1 may be useful to identify high proliferation index, Myeloperoxidase.
- *For large-cell lymphoma:* CD45, CD20, CD3, CD43, (MIB1, *bcl-2*, MUM1, CD10, *bcl-6* as prognostic indicators).
- *For classical or LP Hodgkin lymphoma:* CD15, CD20, CD30, CD43, CD45, ALK, CD57, EMA, (Negative CD45, Oct2, Bob1).
- *For anaplastic large-cell lymphoma:* CD45, EMA, ALK1, CD3, CD45RO, CD4, CD8, CD20, CD30, CD15, cytotoxic antigens (TIA1, perforin, or lysozyme).

5.1.3 Interpretation

Interpretation of immunostained sections must be done in conjunction with adequate positive and negative control sections. It requires an understanding of the specific staining patterns unique to each antibody. Although immunophenotyping may be relatively simple in the case of diffuse, monomorphous lymphomas, the interpretation of polymorphous infiltrates with complex immunoarchitecture may be problematic. More detailed discussion of immunophenotypic interpretation[6] is beyond the scope of these guidelines.

5.2 Flow cytometry

5.2.1 Introduction

Flow cytometry is the technique whereby suspensions of intact cells are stained with a range of fluorescent antibodies and exposed in single file to a laser light source at a specific wavelength. By measuring individual cell fluorescence and light scatter, the expression of surface antigens can be correlated with cell size and structure. Computer analysis and gating of the individual cell data enables the detection and characterisation of abnormal immunophenotypes.[7]

The technique may be performed on a surgical biopsy of lymph node or extranodal tumour tissue, blood, bone marrow aspirate, fine-needle aspirate or other fluid sample.

Flow cytometry is particularly useful in the assessment of fine-needle aspiration (FNA) samples to establish cell type, lineage and B-cell clonality. It is also useful in following a specific cell phenotype in monitoring residual disease.

5.2.2 Technical aspects

Intact tissue slices undergo dissociation into cell suspensions in the flow laboratory. This step is omitted if a cell suspension has been prepared at the time of triage (refer to Chapter 4).

Flow cytometry can be applied to FNA biopsies and blood and bone marrow samples without the need to isolate mononuclear cells in suspension, thus simplifying laboratory procedures and making immunophenotyping of high-risk samples, such as HIV samples, safer. For these and many other specimens (e.g. fine-needle aspirate specimens) red cell lysis is required to remove contaminating red cells. An appropriate lysis reagent (e.g. ammonium chloride) is used to lyse the red cells without denaturing or destroying cellular antigens. Density gradient centrifugation (e.g. Ficoll hypaque) can also be used to remove red cells and dead cells from specimens. This method also concentrates the cells of interest.

For peripheral blood and bone marrow aspirate specimens, a stained smear should be available for morphologic assessment. For tissue, fine-needle aspirates and fluid samples, a cytocentrifuge preparation of the cell suspension should be made. These can be assessed morphologically before analysing by flow cytometry, which ensures adequacy of the specimen and guides antibody selection

for cell analysis. Cellular viability should also be checked on the cell suspension. This can be done using fluorescent dyes such as propidium iodide, 7-AAD, or Trypan blue exclusion.

Isotype controls should be included for all analyses. These are negative controls that ensure that there is no non-specific binding of the primary antibody to the cell population of interest. Most samples analysed will contain some negative cells (i.e. normal cells that do not express the antigen of interest) that also act as internal negative controls.

Gating on the lymphoid cells of interest can be done using one of two methods:

1. Cell size (forward scatter) and cell complexity (side scatter), or

2. CD45 expression and cell complexity (side scatter).

Increased forward scatter and side scatter are seen in large-cell lymphomas. Most lymphoma samples have the same CD45 expression as normal lymphoid cells.[8]

5.2.3 Choice of antibody panels

Antibodies used in the flow cytometric assessment of lymphomas recognise T-cell antigens (e.g. CD3, CD4, CD5, CD7, CD8, CD1a, T-cell receptor), B cells (e.g. CD10, CD19, CD20, CD23, CD79b, FMC7, IgM, kappa and lambda light chains) and differentiation related antigens (e.g. TdT). B-cell lymphomas are identified by the expression of B-cell associated antigens and light chain (kappa or lambda) restriction, indicating clonality. Many lymphomas exhibit characteristic phenotypes that assist in disease classification.

Assessment of flow cytometry requires interpretation of the cell phenotype, together with the gating and cell morphology. To interpret flow cytometry, it is important to understand cellular antigen expression in normal differentiation. Neoplastic cells may display the same phenotype as their normal counterpart.[9] However, some malignancies acquire an antigen not normally expressed (e.g. CD2 expression in acute myeloid leukaemia), or have aberrant loss of an expected antigen (e.g. loss of CD7 in T-cell malignancies).

The number and type of antibodies included in the panel would depend upon:

- The clinical question, for example, initial diagnosis of lymphoma, follow-up studies in someone with established diagnosis, subtyping, detection of minimal residual disease or others, such as the number of T helper cells post-chemotherapy in a patient with known lymphoma.
- The type of flow instrument, for example, three or more colours
- Cost considerations

Table 5.1 shows the panel recommended by the British Committee for Standards in Haematology[10] for the diagnosis of chronic/mature lymphoproliferative disorders.

Table 5.1 Diagnosis of chronic/mature lymphoproliferative disorders

First line:	B-cell	T-cell	B-cell and T-cell	
	CD19 CD23. FMC7 SmIg* (kappa/lambda) CD22*, CD79b*	CD2	CD5	
Second line:	**I**	**II**	**III**	**IV**
	CD11c, CD25 CD103, HC2	Cyt Ig (kappa/lambda) CD79a, CD138	CD3, CD7 CD4, CD8 CD25	Cyclin D1

Source: modified from British Committee for Standards in Haematology (BCSH)[10]
*Intensity of membrane expression. I = disorders with villous cells; II = disorders with suspected lymphoplasmacytic or plasma cell differentiation; III = T-cell disorders; IV = suspected mantle cell and unclassifiable B-cell lymphomas. Optional markers: natural killer associated (CD16, CD56, CD11b, CD57); thymic markers (TdT); markers associated with activated T-cells (CD25); cytotoxic T-cell or NK marker (TIA-1).

The panel of antibodies recommended for a routine clinical laboratory includes most of the following: CD5, CD19, CD20, CD10, CD23, CD22, CD16, CD56, CD3, CD4, CD8, FMC7, CD103, CD25, CD11c, CD7 and CD79b antibodies.

5.2.4 Findings in specific diseases

B-cell neoplasms

One of the important applications of flow cytometry in haematology is to establish whether the B cells in a sample are monoclonal. This is performed by demonstrating light chain restriction (i.e. B-cell population expressing only kappa or lambda light chain) of the B cells present in the sample. A kappa: lambda ratio of >3:1 or <1:2 is strongly suggestive of the presence of a monoclonal B-cell population. This can be applied to peripheral blood, bone marrow, fine-needle aspirate, tissue or fluid samples. B-cell clonality can be backed up by demonstration of a characteristic phenotype of specific B-cell lymphomas/leukaemias.

Table 5.2 Low-grade B-cell lymphomas: immunophenotypic features[11]

Lymphoma type	SIG	CIG	CD5	CD10	CD23	CD43+
B-CLL/SLL	+	-/+	+	-	+	+
Lymphoplasmacytoid	+	-	-	-	-	-/+
Mantle cell	+	-	+	-/+	-	+
Follicle center	+	-	-	+/-	-/+	-
Marginal zone	+	40%+	-	-	-/+	-/+

+ = 90% positive; +/- = >50-% positive; -/+ = <50% positive; - = <10% positive

It should be noted that clonal B-cell populations phenotypically resembling CLL/SLL may rarely be detected in clinically healthy individuals with normal blood parameters.[12]

T-cell neoplasms

The flow cytometric assessment of T-cell lymphoproliferative disorders is more difficult than for the B-cell malignancies as few have a characteristic phenotype. However, many T-cell malignancies show atypical T-cell phenotypes with aberrant antigen acquisition or loss. Examples include aberrant loss of an expected T-cell antigen (typically CD5 or CD7), and loss of or co-expression of CD4 and CD8. Where the malignancy makes up the majority of cells present in the sample, flow cytometry can

usually establish the phenotype of the abnormal cell. If, however, the malignant T-cell population makes up only a small proportion of cells in the sample, it is usually not feasible to detect these against the background of normal T cells.

For T-cell processes there is no comparable phenotypic marker for monoclonality. Monoclonal antibodies to Vβ repertoire antigens can be used by flow cytometry. Restricted Vβ repertoire expression can be used as a screening test for T-cell monoclonality. The definitive demonstration of T-cell clonality is dependent on molecular biological techniques (Southern blotting or PCR).[13]

Hodgkin lymphoma

In Hodgkin lymphoma (HL), the neoplastic cell population often represents as little as 1% of the total number of cells in suspension. For this reason, and the fact that neoplastic Hodgkin cells are CD45 negative and usually express a 'null' cell phenotype, flow cytometry findings are non-contributory in this disease. Flow is therefore not generally helpful in Hodgkin lymphoma except by excluding a monoclonal or any other immunophenotypically aberrant lymphoid cell population.

5.3 Prognostic markers

5.3.1 Introduction

Although the WHO classification divides lymphomas into apparently distinct entities, many are heterogenous. For example, the t(14;18), which is characteristic of follicular lymphoma, is found in a substantial minority of diffuse large B-cell lymphomas (DLBCLs) suggesting that this group of lymphomas encompasses more than one entity. This heterogeneity is also reflected in the clinical behaviour of DLBCL, as 50–60% are cured with anthracycline-containing regimens, while the remaining 40–50% are not cured. The search for markers of prognostic significance has concentrated mainly on DLBCL, but more recently, the molecular events in small lymphocytic lymphoma/CLL have been shown to have highly significant prognostic importance.

5.3.2 Diffuse large B-cell lymphoma

A number of markers have been examined as possible prognostic indicators in DLBCLs, but no single candidate has achieved universal acceptance. For each of the following markers, the cut-off percentages used for defining positivity are critical, and the use of different thresholds may account for some of the apparently contradictory findings in some series.[14]

Proliferative index as measured by Ki-67 fraction

The Ki-67 antigen that identifies cells in the G_1, S, G_2 and M phases of the cell cycle has been used to identify the proliferative index in a large variety of lymphomas, in particular DLBCLs. Studies performed on frozen sections have produced inconsistent results, but most suggest that a proliferation index of >80% is a poor prognostic indicator, independent of the international prognostic index (IPI) group. [15] More recent series using paraffin sections have produced similar findings.[16]

In contrast, a study of relapsed lymphomas not restricted to DLBCL[17] found that patients with tumour proliferation rates of <80% were significantly more likely to have no response to therapy, fail to achieve a complete response, and tend to have shorter progression-free survival and overall survival, than patients with a higher proliferation index.

p53 alterations

p53 alterations in DLBCL are more difficult to assess because of the different methods of analysis, including immunostaining, loss of heterozygosity analysis, single strand conformational polymorphism analysis, and direct sequencing. Immunostaining represents the simplest means of studying p53. Multivariate analysis in one study revealed shorter overall survival for those patients with p53 mutations in the low and low–intermediate IPI group.[18] Others suggest that p53 protein

expression is not an independent risk factor for CR and survival[19,20.] Studies correlating drug resistance with p53 expression have yielded conflicting results[17,18], The development of p53 expression in some lymphomas, however, may be associated with tumour progression.[21]

bcl-2

There is no evidence that *bcl-2* translocation per se has prognostic significance in DLBCL. Expression of *bcl-2* protein, however, has been shown to be a significant adverse prognostic indicator in DLBCL[22,23] and has been used to further stratify cases defined as intermediate risk by IPI.[24] Speculation that the anti-apoptotic effect of *bcl-2* expression may mediate drug resistance[25] is supported by animal models.[26] A more recent study of elderly patients has indicated that the adverse prognostic effect of *bcl-2* protein expression in DLBCL is annulled by the addition of rituximab to standard combination chemotherapy treatment protocols.[27]

In a study of relapsed lymphomas not restricted to DLBCL, however, *bcl-2* protein expression was found to be a surrogate marker for low proliferation index and to have no independent effect upon drug resistance, progression-free survival or overall survival.[17]

bcl-6

Studies attempting to correlate *bcl-6* translocation with prognosis in DLBCL have produced conflicting results.[28,29] *Bcl-6* gene expression, however, has been associated with significantly improved survival in DLBCL in two recent series[30,31]. In the former study, the patients with high *bcl-6* gene expression showed longer overall survival in multivariate analysis with and without elements of the IPI compared to the group with low *bcl-6* expression, both by real-time reverse transcriptase PCR and immunostaining.

A recent and larger study of 128 cases using a different threshold for positivity (10% versus 25%), however, failed to show prognostic significance for *bcl-6* expression in DLBCL.[23]

CD10

CD10 expression in DLBCL has been examined in several recent studies using both immunohistochemistry and flow cytometry, with contradictory results.[14] The largest study performed to date, however, has shown a significantly better survival for CD10+ versus CD10- DLBCL when selected for low-risk IPI. CD10 expression did not predict for survival in the high-risk IPI patients, however.[32] CD10 expression appears to correlate with presence of the t(14;18)(q32;q21) in DLBCL, and, in combination with *bcl-6*, it has been shown to be a surrogate for the 'germinal centre' or 'GC phenotype' identified in cDNA microarray studies.[33,34] Combining *bcl-2* negativity with this GC phenotype appears to further enhance survival in the intermediate-risk IPI group[24]. Contradictory findings in some studies[23] may be partly explained by the recent observation that late relapse in DLBCL is more often observed in cases with a GC phenotype.[35]

MUM1

The MUM1/IRF protein is normally expressed in plasma cells and late GC B-cells. In microarray studies, MUM1 clusters within the 'activated B-like DLBCL' rather than GC-like group[29], and the combined staining for *bcl-6*, CD10 and MUM1 in tissue sections has been shown be predictive for these prognostic groups.[30] The same study, using tissue microarrays, found that the expression of MUM1 correlates with a poor clinical outcome in DLBCL.[30]

cDNA microarray studies

Gene expression profiling has stratified cases of DLBCL into highly significant prognostic groups independent of IPI, principally those of 'germinal centre' versus 'activated B-cell' profiles (see Section 6.2.6).

The same approach applied to mediastinal large B-cell lymphoma (MLBCL) has demonstrated a distinctive gene expression signature quite unlike other forms of DLBCL, and more in keeping with that of classical Hodgkin lymphoma.[36,37]

At present, cDNA microarray studies currently have practical application in only a few specialised centres. It is expected that more widely applicable surrogate markers using immunoperoxdase techniques will follow from this technology.

5.3.3 Other lymphomas

Small lymphocytic lymphoma (SLL)/chronic lymphocytic leukaemia (CLL)

CLL can be divided into two highly-significant prognostic groups according to the presence or absence of somatic mutations in the expressed immunoglobulin heavy chain variable (IgVH) regions.[38] The expression of ZAP-70 (zeta-associated protein 70), a tyrosine kinase protein normally expressed in T and NK cells, has been shown to correlate inversely with IgVH mutation status.[39,40] The expression of ZAP-70 measured by flow cytometry and immunohistochemistry has been shown to correlate closely with ZAP-70 mRNA expression and unmutated IgVH gene status.[41]

Mantle cell lymphoma

The proliferation index in mantle cell lymphoma (MCL), determined by immunohistochemical staining for the Ki-67 antigen, has been shown in multivariate analysis to have prognostic significance.[42] Over-expression of survivin, an inhibitor of apoptosis, can be detected by mRNA or immunohistochemistry. It has also been shown in multivariate analysis to have a significantly adverse effect on survival, but less than that of proliferative index.[43]

Studies of IgVH mutation status analogous to CLL have produced controversial results.[44,45] Moreover, no surrogate marker of mutational status analogous to ZAP-70 in CLL has yet been found in MCL.

Recently, cDNA microarray studies have characterised the gene signatures of MCL and created a survival predictor based on gene-expression for this disease.[46,47] At this stage, however, there is no surrogate marker identified for widespread use in routine diagnostic laboratories.

CD30+ anaplastic large-cell lymphoma (ALCL)

Although not generally considered a prognostic marker, ALK1, is detectable immunohistochemically in paraffin sections. ALK1 expression in ALCL has been shown to be strongly associated with better prognosis.[48,49] Expression of CD56 in a subset of CD30+ ALCL has been shown in multivariate analysis to correlate with poor survival independently of ALK expression or IPI.[50] MUC-1 expression has also been shown to correlate with poor survival in ALK negative, but not ALK positive cases.[51]

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CHAPTER 6 MOLECULAR AND CYTOGENETIC STUDIES — TECHNIQUES

6.1 Introduction

In most lymphoid proliferations, morphological assessment and immunophenotyping are sufficient to establish a diagnosis. In a minority of difficult cases (5–10%)[1,2], molecular investigation may be required for definitive diagnosis. Approximately 75% of these cases will be resolved by molecular studies.[3,4] Up to 5% of lymphomas defy lineage assessment despite all investigation.[5]

Tissue acquisition and transport (see Section 6.4) are critical in determining the outcome of molecular investigations. To maximise the chances of a meaningful result, communication between the referring laboratory or clinician and the molecular laboratory prior to biopsy or collection of cellular material is important. It is essential to know the limitations, sensitivity and specificity of each test.

Key points

Molecular tests should be performed by laboratories that have the required expertise and participate in relevant quality assurance programs. The results should always be correlated with clinical, morphological, immunophenotypic and other laboratory data, and should never be considered in isolation.

At present, there is no Medicare funding to cover molecular studies. Strategies to overcome this issue should be addressed so that cost does not act as a disincentive.

6.1.1 Indications for molecular testing

- Where not previously determined by morphology and immunophenotyping:
  - demonstration of monoclonality (and presumptive malignancy)
  - determination of lineage
  - determination of the specific lymphoma subtype
- Minimal residual disease (MRD) detection and monitoring (MRDDM)
- Detection of viruses in lymphomas
- Provision of molecular data of possible prognostic relevance

6.1.2 Techniques

i Southern blot (SB) analysis

ii Polymerase chain reaction (PCR), and real-time quantitative PCR (RQ-PCR)

iii Conventional cytogenetics

iv Fluorescence *in situ* hybridisation (FISH)

Other technically demanding and expensive investigative modalities include multi-colour FISH (M-FISH) and spectral karyotyping (SKY), comparative genomic hybridisation (CGH), and gene expression profiling by cDNA microarray technology. These are not presently in general diagnostic use.

6.1.3 Molecular targets

i Antigen receptor (AgR) gene rearrangements:

- Immunoglobulin heavy chain (IgH)
- T-cell receptors (TCRγ and TCRβ)

ii Chromosomal translocations

iii Specific viral sequences

6.2 Techniques

6.2.1 Southern blot (SB) analysis

While PCR-based techniques have replaced SB as the primary molecular diagnostic modality, it still remains the gold standard in clonality testing, and its utility in establishing clonality in diagnostically difficult cases is proven.[6]

Indications for SB

SB is indicated:

- where PCR assays are not possible or are too insensitive
- to detect monoclonal AgR gene rearrangements that are missed in PCR assays.

Advantage of SB analysis

The main advantage of SB analysis is the low false-positive and false-negative rate.[1,7,8]

Disadvantages of SB analysis

- Requires fresh tissue yielding large amounts of high-quality DNA, therefore largely precluding the use of fixed material.
- Time consuming of the order of several days.
- Relatively expensive and labour-intensive procedure.
- Radioactive materials are often used.
- Low analytical sensitivity (see Section 6.2.4 below), thus limiting its utility in entities containing low proportions of monoclonal cells (e.g. T-cell rich B-cell lymphoma; Hodgkin lymphoma) and in MRDDM.

Targets and probes for SB analysis

In routine lymphoma diagnosis, IgH and TCRß gene re-arrangements are analysed. A variety of restriction enzymes, probes and detection systems are available and have been optimised for detecting IgH and TCRß gene rearrangements.[9–12] At least three informative restriction enzymes should be used for each assay to avoid false positives in single digests arising from restriction site polymorphisms or somatic mutations in antigen receptor genes. Apparent clonality in only one of three enzyme digests should be confirmed by using a fourth restriction endonuclease. For IgH and TCRß rearrangements, joining region probes are more informative than constant region probes.[11]

Guideline — Assay — quality assurance	Level of evidence	Refs
Southern blot (SB) protocols should be optimised in each laboratory. At least three informative restriction enzymes should be used for each assay.	IV	9–12

Test performance

SB will detect >90% of B-NHL and T-NHL.[1,11–13] Its analytical sensitivity is 1–5% in a polyclonal background, that is, at least 1–5% clonal cells are needed to be detected as a novel rearrangement.[11,12]

Interpretation of results and pitfalls

Interpretation of SB data and assignment of clonality should be according to accepted guidelines.[11,12,14] False positives may arise from cross-hybridising bands, incomplete DNA digests, restriction fragment-length polymorphisms, transient clonality in abnormal immune states, pseudoclonality in TCRγ assays (this gene has a limited recombinational repertoire), and lineage infidelity (cross-lineage rearrangements), especially in lymphoblastic lymphomas.[6]

Guideline — Assigning clonality	Level of evidence	Refs
Interpretation of Southern blot (SB) data and assignment of clonality should be according to widely accepted guidelines.	IV	11, 12, 14

6.2.2 Polymerase chain reaction (PCR) techniques

Preferred approach to molecular diagnosis

PCR-based assays are now the preferred first-line approach to the molecular diagnosis of lymphomas.[3,15–19] PCR has the following distinct advantages over SB analysis:

- rapid turn-around time
- minimal tissue requirements
- DNA or RNA may be used as templates
- DNA quality is less critical, thus fixed and archival materials may be used
- superior sensitivity enables MRDDM
- radioactive materials are not required
- assays may be automated and multiplexed.

Guideline — Preferred approach to molecular diagnosis	Level of evidence	Refs
Polymerase chain reaction (PCR)-based assays are the preferred first-line approach to the molecular diagnosis of lymphomas.	IV	3, 15–19

Indications for PCR analysis

- To detect clonal rearrangements of the AgR genes.

- To detect recurring chromosomal translocations, which characterise some lymphomas.
- MRDDM.

Specimens suitable for PCR analysis

Because of the less stringent requirements for large amounts of high-quality DNA, a range of specimens are suitable for PCR studies, including:

- small tissue biopsies, for example, from brain, gut
- fine-needle aspiration biopsies
- decalcified bone marrow biopsies
- bone marrow aspirates
- cells scraped from histological or cytological slides
- cells microdissected from tissue specimens.

Archival paraffin-embedded tissue is suitable for many PCR assays and the sensitivity of clonal detection may approach that achieved in fresh specimens.[6] There is significant variation between laboratories in the sensitivity of clonal detection when evaluating paraffin-embedded material, and there is a need for assays to be standardised.[8]

RT-PCR requires good-quality mRNA obtained from fresh specimens of blood, bone marrow or tissue (fresh or immediately snap-frozen). Paraffin wax material is usually unsatisfactory because of RNA degradation.

PCR methodology

PCR assays are either qualitative (most diagnostic assays) or quantitative. Qualitative assays simply detect the presence or absence of a specific genetic event (e.g. AgR gene rearrangement; chromosomal translocation), whereas quantitative assays quantify the PCR product in the setting of MRDDM. There is a wide range of PCR assays available, of varying complexity, cost and sensitivity, and whose designs vary according to the nature of molecular target and whether the assay is for primary diagnosis or for MRDDM.

Many factors affect each assay's sensitivity. They include primer design (whether consensus, gene family-specific or patient-specific), assay design (single primer pair or hemi-nested/nested assays) and PCR product detection systems. There are many gel electrophoretic systems of varying complexity that allow discrimination of PCR products based on their size, or nucleotide sequence and conformation, or DNA melting characteristics, which affects DNA mobility and hence resolution in various types of gels.[6] In routine diagnostic laboratories, non-denaturing polyacrylamide gel electrophoresis (PAGE) is the method most frequently used, combined with either ethidium bromide staining and UV illumination, or hybridisation with labelled probes to visualise the products. Capillary electrophoresis with automated fluorescent DNA fragment analysis (GeneScan) (CEGS) is rapidly becoming a detection system of choice, particularly in academic and research centres, because of its sensitivity and high throughput (see Spagnolo et al.[6] for details). CEGS offers distinct advantages over PAGE and more complex gel systems, but it has some limitations, including significantly higher costs. Its high sensitivity to the level of one base pair increases the potential for misinterpreting pseudoclonality as monoclonality, and strict criteria for interpreting results need to be defined.[6]

PCR assays should be optimised in individual laboratories and carried out according to accepted guidelines for the performance and interpretation of PCR tests.[14] Further, the sensitivity and

limitations of each assay being performed should be known[20,21], bearing in mind that these will need to be reappraised in the setting of new high-resolution automated assays.[22–26]

Guidelines — Assays — quality assurance	Level of evidence	Refs
PCR assays should be optimised in each laboratory, using accepted guidelines for performance and interpretation of results, and with knowledge of the sensitivity and limitations of each assay.	IV	14, 20, 21
In particular, new high-resolution automated assays, including multiplexed assays using comprehensive primer sets, will require a reappraisal of test sensitivities and specificities.	IV	22–26

Test sensitivity of PCR

Two related but different measures of test performance need to be considered when interpreting clonality tests. *Qualitative sensitivity* in the diagnostic setting refers to the percentage of positive (i.e. monoclonal) cases that are detected in a cohort of cases, with reference to a 'gold-standard' benchmark of clonality (e.g. SB). *Analytical sensitivity* is a quantitative measure of the lowest number of clonal cells that need to be present in a sample to be detected by the assay employed. This is affected by a number of biological and methodological factors, including the type of sample, the nature of the cellular background in which the clonal cells are present, and the sensitivity of the detection system, which is critical (e.g. simple gel electrophoresis versus capillary electrophoresis), particularly in MRD testing. As a general guide, for AgR gene rearrangements, using consensus primers and routine gel electrophoresis may achieve, at best, analytical sensitivities of ~1% (one clonal cell in 100 cells), but with a range of ~1–10%, depending on the number of polyclonal cells in the sample. This approach is not sufficiently sensitive for MRD testing. For chromosomal translocations, using either DNA-PCR or RT-PCR may achieve sensitivities of 1 in 10^4–10^6 cells, depending on the nature of the sample, the assay design and the sensitivity of the detection system.

Test specificity of PCR

Cross-lineage rearrangements may occur in lymphomas, particularly in lymphoblastic lymphoma. With some exceptions[3,5], the lack of sufficient detail in published data and the lack of test standardisation make it difficult to draw meaningful conclusions about test specificities and positive predictive values. With the increasing impetus to standardise assays that involve more numerous primer combinations, and with the use of automated high-resolution analysis of PCR products, the frequency of detecting inappropriate AgR gene rearrangements, even in reactive conditions, is likely to increase.[25,26]

6.2.3 Pitfalls in SB and PCR

In both SB and PCR assays, there is the potential for false positive and false negative results secondary to any number of technical and biological factors, as well as from errors in interpretation of results.

False positive results

These may arise from any of the following factors[6]:

- DNA contamination
- nonspecific products from excess amplification cycles, primer-dimer formation or nonspecific primer binding to unrelated DNA sequences through poor primer design
- canonical TCRγ gene rearrangements

- pseudoclonal AgR gene rearrangements as a result of low quantities of target DNA[20,27,28]
- inappropriate AgR gene rearrangements resulting from lineage infidelity, incomplete rearrangements or biclonality
- detection of chromosomal translocations in normal individuals
- the occurrence of clonal lymphoid populations in a range of benign conditions or in the setting of immune dysregulation.

If there is doubt over the assignment of monoclonality versus pseudoclonality in the setting of low quantities of target DNA, PCR assays should be repeated using further DNA from the sample, to ensure that a clone is reproducible.[3,29–31]

Guideline — Assays — quality assurance	Level of evidence	Refs
PCR assays should be performed using a range of target DNA concentrations to avoid misinterpreting as monoclonal any discrete oligoclonal bands resulting from selective amplification of oligoclones in samples containing small numbers of lymphocytes.	IV	20, 27, 28
Where there is doubt over assignment of monoclonality, PCR assays should be repeated to ensure that a clone is reproducible.	IV	3, 29–31

False negative results

These may arise because of:

- sampling errors
- DNA/RNA degradation
- design of the PCR assay, for example, consensus primers will not detect all possible rearrangements of the AgR genes; incomplete AgR rearrangements can be missed if the primer design is not appropriate to detect these
- biological factors, for example, primer mismatch in CDR3 assays as a result of ongoing somatic mutations in the IgH variable region genes, seen particularly in follicular and marginal zone lymphomas.

6.2.4 Cytogenetics

Introduction

Over the past two decades, a large number of chromosomal and genetic abnormalities have been detected in lymphomas. The most prominent are translocations affecting the immunoglobulin heavy chain (IgH) locus on chromosome 14q32. Early investigations were based on conventional karyotype analysis, but in more recent years, developments in molecular cytogenetics ranging from metaphase and interphase fluorescence *in situ* hybridisation (FISH) to multi-colour SKY and comparative genomic hybridisation (CGH) have vastly increased the scope of detection of cytogenetic abnormalities.

It should be noted that whereas interphase FISH can be performed on fixed paraffin-embedded material, other techniques (conventional cytogenetics, metaphase FISH, and SKY) require rapid transport of fresh, viable cells to the laboratory for short-term culture and metaphase production.

Conventional cytogenetics

Since the first cytogenetic abnormality was detected in chronic myeloid leukemia in 1960, chromosome studies have been used to understand the genetic basis of tumorigenesis. Most cytogenetic studies of lymphoma are based on analyses of lymph node specimens. For optimal results, a piece of lymph node should be transported in sterile tissue culture media (RPMI 1640) to the cytogenetics laboratory as soon as possible after excision. A single cell suspension may be obtained by mechanical disaggregation using a scalpel and needle. Short-term culture in RMPI 160 supplemented with 10–20% foetal calf serum has been found by a number of groups to be optimal. Cultures are usually successful only if set up on the same day as the specimen was taken.[32,33]

Chronic B- and T- lymphoid leukaemias are particularly problematic, as they tend to have a low spontaneous mitotic index and a poor response to most common mitogens. The mitogens that have been shown to be most effective in stimulating malignant B cells to divide are TPA and EBV, with TPA the most commonly used. FISH has allowed detection of numerical and structural abnormalities in the majority of cases, overcoming the difficulties inherent in conventional cytogenetic analysis in this group of disorders.

6.2.5 Fluorescence *in situ* hybridisation (FISH)

Introduction

Fluorescence *in situ* hybridisation (FISH) is a valuable technique that allows detection of both structural and numerical chromosomal abnormalities, down to the single cell and single gene level.[34,35]

It has enabled the detection of genetic changes in cases for which conventional cytogenetics has proved uninformative. Virtually any genomic DNA can be used as a probe for interphase and metaphase cells. The most common probes used are those specific for the repetitive sequences at individual chromosome centromeres, whole chromosome paints and locus specific probes.[35] FISH is based on the ability of single-stranded DNA to hybridise to complementary DNA. The target DNA is chromosomal, either in metaphase or interphase cells, and fixed onto a glass slide. The probe is either directly labelled with a fluorescent tag or with a reporter molecule bound to either biotin or digoxigenin. Both the labelled probe and the target DNA are denatured and hybridised together to allow annealing of the complementary sequences. After excess probe is washed away, the directly labelled probes are detected at the site of annealing using fluorescence microscopy. Biotin or digoxigenin labelled probes require the addition of fluorescent-labelled streptavidin or antidigoxigenin antibodies for detection.

Probe types

Centromeric probes: Probes that hybridise to specific chromosome centromeres target the satellite sequences present in the heterochromatin. Centromeric probes are commercially available and allow the number of each chromosome present in either a metaphase or interphase cell to be determined.

Chromosome paints are collections of sequence from the entire length of a specific chromosome, derived from chromosome-specific libraries, flow-sorted chromosomes or microdissected DNA. They allow the identification of complex rearrangements that cannot be determined by conventional cytogenetics and may also reveal cryptic translocations. However, whole chromosome paints are not useful for detecting rearrangements in interphase cells as the un-contracted nature of the chromosome in interphase produces an extremely diffuse signal from which little useful information can be discerned.

Locus-specific probes hybridise to specific sequences and are extremely useful in the identification of translocations. They have been used to identify what are otherwise ‘cryptic’ translocations. Locus-specific probes only provide information on the presence or absence of a particular sequence, and whether particular sequences co-localise. Two locus-specific probes are each labelled with a different coloured fluorescent tag — red and green, for example — and a third colour (yellow) is formed when

the two co-localise, indicating that a translocation has occurred to bring the two loci together. Alternatively, if the two colours co-localise on either side of a particular breakpoint on one chromosome involved in a translocation, the colours separate into their individual colours when a translocation is present.

While FISH has been used most successfully on cytogenetic preparations, a number of methods are now available for extracting cell nuclei from paraffin-embedded sections. Interphase FISH studies have successfully demonstrated translocations in lymphomas using paraffin sections.[36] Interphase FISH may be performed on paraffin-embedded sections in either of the following ways:

- by hybridising directly to thin sections of tissue that have been leeched of paraffin (the advantage of this technique is that it preserves architecture; limitations include overlapping and truncated cells making scoring of individual cells difficult)
- by making individual cell suspensions from thick sections of tissue, to which standard FISH techniques may then be applied.[36,37]

Imprints made on sialinised slides at the time of tissue triage, fixed and stored frozen, are an alternative and inexpensive method of preserving material for possible FISH studies.[38]

Indications for metaphase and interphase FISH

Metaphase and interphase FISH are of proven utility in the detection of numerical chromosomal anomalies (centromeric probes) and translocations (single, dual or triple colour probes) that characterise certain lymphomas.[39–41] Their ability to detect numeric chromosomal abnormalities is a distinct advantage over PCR. They are particularly useful in detecting translocations with widely dispersed breakpoints (e.g. in mantle cell lymphoma and Burkitt lymphoma) that are not readily amenable to PCR analysis.

Advantages and disadvantages of metaphase and interphase FISH

Metaphase FISH has the relative disadvantages of requiring viable cell suspensions. It may be limited in lymphomas with low proliferation rates and where the malignant cells are present only in low numbers. It also has a relatively low resolution of between 2 and 3 Mb, due to the highly condensed nature of DNA in metaphase.

Interphase FISH has the advantage of being applicable to air-dried smears, paraffin sections and nuclei isolated from fresh or frozen tissue, or from paraffin sections. As for metaphase FISH, a variety of probes are suitable for interphase FISH, but unless the probes are of similar stringency they usually cannot be used in combination in a single hybridisation. The resolution of interphase FISH ranges from 100 to1000 Kb (interphase DNA has complex foldings resulting in an inconstant relationship between genomic and physical distances).[41] It is the method of choice to detect translocations where no RT-PCR assays are available, and where breakpoints are widely dispersed. One drawback with interphase FISH in paraffin sections is the overlapping and sectioning of nuclei, which makes it difficult to score individual cells. If available, cytospin and touch preparations are often easier to interpret,.

Advanced techniques

While metaphase and interphase FISH are the most widely used hybridisation techniques in the diagnosis and study of lymphomas, more complex and costly techniques include DNA fibre-FISH, multicolour FISH (M-FISH) and the related SKY, and comparative genomic hybridisation (CGH). The latter techniques require sophisticated digital image capturing and manipulation systems with appropriate software, and are beyond the scope of these guidelines. More detailed discussion and bibliography may be found elsewhere.[6]

6.2.6 Gene expression profiling: cDNA microarray technology

cDNA microarray technology allows for genomic-scale gene expression profiling of lymphomas. While it is mainly a research tool at this point, pathology laboratories play a central role in the harvesting and storage of fresh lymphoma and normal control specimens for these studies, which require undegraded mRNA. For a summary of details relating to methodology and data analysis, refer to Spagnolo et al.[6] Several recent excellent reviews of gene expression profiling in lymphoma are available.[42–46]

Utility of gene expression profiling of lymphoma

Gene expression profiling promises the refinement of lymphoma sub-classification at a molecular level. It may identify genes of potential pathogenetic and predictive significance, and it may direct the development of novel targeted therapies.[46] The clinical utility of such studies has been demonstrated in several lymphoma types. For example, distinct molecular classes of DLBCL have been delineated, which have important outcome differences after anthracycline-based therapy[47,48], while molecular differences have also been shown between early and progressed DLBCL.[49] In multivariate analysis, a model independently predictive of five-year survival after chemotherapy in DLBCL has been achieved.[48] Further, molecular profiling is identifying specific pathogenetic pathways in different molecular groups of DLBCL, with the potential for targeted therapy.[50] Similarly, clinically relevant molecular data are emerging in chronic lymphocytic leukemia, follicular lymphoma and mantle cell lymphoma (see Spagnolo et al.[6] for further details).

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CHAPTER 7 MOLECULAR AND CYTOGENETIC STUDIES — DIAGNOSTIC APPLICATIONS

7.1 B-cell clonality testing by PCR for diagnostic purposes

7.1.1 Immunoglobulin gene rearrangements

Assessment of IgH gene rearrangements is the principal approach to B-cell clonality testing. Ig light chain (IgL) gene rearrangement assays are also available but are not routinely used. A number of PCR approaches and detection systems may be used for IgH clonality testing. The most commonly used are complementarity determining region 3 (CDR3) strategies, which amplify the CDR3 region where the greatest junctional diversity is generated during gene rearrangement. Typically, degenerate consensus primers annealing to framework region (FR3) of the variable (V) region genes are used in conjunction with consensus primers to the 3′ ends of the joining (J) region genes in monoplex, hemi-nested or nested assays. Additional reactions using consensus FR1 or FR2 primers, or use of gene family-specific primers (usually directed at FR1 or leader sequences), can increase the frequency of clonal detection.[1]

Qualitative sensitivity of PCR testing for IgH rearrangement

Qualitative sensitivities vary widely, from <50% to virtually 100% of B-cell lymphomas, depending on the assay design, case-mix, primer selection and detection system employed. For example, false negatives are more likely to occur with follicular, marginal zone and diffuse large B-cell lymphomas, owing to V-region somatic hypermutations, particularly in follicular lymphoma, which affects primer annealing in CDR3 assays.[2–7]

Using CDR3 assays with consensus primers (typically FR3 region V primers) and conventional gels, the frequency of clonal detection ranges from approximately 60% to 80%. This increases to >90% of cases by using additional assays employing FR2 and/or FR1 or leader region primers, by including assays for IgL gene rearrangements, by adding assays for specific chromosomal translocations, and by using more sensitive gel systems, including CEGS.[1]

Analytical (quantitative) sensitivity of PCR testing for IgH rearrangement

Using simple CDR3 strategies, consensus primers and non-denaturing gels, analytical sensitivities are in the range of 1–10% clonal cells in a polyclonal background. Greater sensitivity (0.1–1% clonal cells in a polyclonal background) may be achieved with higher resolution denaturing/sequencing gels with or without automated fluorescent DNA fragment analysis.[1]

Specificity and positive predictive value of PCR testing for IgH rearrangement

Specificities of clonal IgH gene rearrangements range from approximately 80% to 100%, and positive predictive values from 70% to 100%.[1]

Interlaboratory variability and standardisation

There is a need for interlaboratory standardisation of assays. Significant interlaboratory variations in qualitative sensitivity have been reported using the same lymphoma samples (range 20–90% frequency of clonal detection), particularly in paraffin-embedded tissue.[8] The BIOMED-2 Concerted Action collaborative study has addressed such deficiencies in PCR clonality testing, and has published standardised primers and protocols for multiplex PCR assays for clonality studies, reporting unprecedentedly high rates of clonal detection.[9]

Guideline — Interpretation of assay results	Level of evidence	Refs
PCR results for IgH clonality testing should: (i) be interpreted in the context of a detailed knowledge of the nature of the assay used, its qualitative and analytical sensitivities, and predictive value (ii) recognise that the most commonly employed CDR3 assays using consensus primers may have a significant false negative rate, particularly in follicular, marginal zone and diffuse large B-cell lymphomas.	IV	2–7

7.2 T-cell clonality testing by PCR for diagnostic purposes

7.2.1 TCRγ gene rearrangements

Because of its simple genomic structure and the requirement for few Vγ and Jγ primer combinations to detect all possible rearrangements of the gene, the TCRγ gene is the preferred gene for T-cell clonality testing in routine laboratories. As the gene has only four variable region families and five joining segment genes, construction of consensus or gene segment-specific primers is relatively simple. Assays vary in their design and complexity, and a range of different detection systems, including CEGS, may be used, all of which affect the qualitative and analytical sensitivities of the assays.[7,10–19]

Qualitative sensitivity

There is a wide range in the reported frequency of clonal detection (~60% to virtually 100%), reflecting the effects of the case-mix, nature of the PCR assay employed, primer selection and sensitivity of the detection system. By using multiple primer combinations, which will detect all possible TCRγ gene rearrangements, and routine PAGE, clonal detection rates of 80% to 90% may be achieved. This may be increased to >90% and approaching 100% by employing high-resolution complex gels or automated fluorescent DNA fragment analysis.[1] Additional testing for TCRβ gene rearrangements (see below), either in separate assays or by including TCRβ primers in multiplex TCRγ and TCRβ primer mixes, will increase the clonal detection rate by as much as 20%.[1]

Analytical sensitivity

Between 1% and 5% of clonal T cells can be detected in a background of polyclonal TCRγ gene rearrangements in non-denaturing polyacrylamide gels, although inferior sensitivities may result using paraffin-embedded tissue.[20] A ten-fold increase in sensitivity (0.1–1%) may be achieved with high-resolution complex gels, or by CEGS, which is fast, accurate, has a high analytical sensitivity at least equal to denaturing gradient electrophoresis DGGE (~0.1–1% in a polyclonal T-cell background), and is able to detect $\geq$90% of T-NHL (reviewed in Spagnolo et al.[1]).

Test specificity and positive predictive value

As for mature B-NHL, these values range widely and it is difficult to compare data. Both specificities and positive predictive values range from approximately 70% to 100%.[1] In cutaneous B-NHL, the incidence of TCRγ and/or TCRβ clonal gene rearrangements may be particularly high[21] (i.e. relatively low positive predictive value). Similarly, dual genotypes in mature T-NHL are disproportionately higher in cutaneous cases, compared with non-cutaneous cases.[21] In inflammatory skin disorders in particular, PCR assays should be repeated because of the frequent occurrence of pseudoclonal TCRγ rearrangements, which in a single PCR assay could be misinterpreted as being monoclonal.[22,23]

7.2.2 TCRβ gene rearrangements

Because of its complexity, the TCRβ gene is used less often in T-cell clonality testing. It has a large germline repertoire that includes numerous V gene families and J segments, thus restricting the design of sensitive but simple assays based on limited numbers of consensus primers. The large intron separating rearranged VDJ segments from C regions largely precludes DNA-based assays using V and C region primers, which requires RT-PCR, adding to the complexity of the assays. A variety of PCR approaches are published, varying in design complexity, qualitative and quantitative sensitivities.[1]

Guideline — Interpretation of assay results	Level of evidence	Refs
PCR analysis of TCRγ gene rearrangements is the recommended first-line approach for T-cell clonality testing. The results should be interpreted in the context of a detailed knowledge of the qualitative and analytical sensitivities, and the predictive value of the assay used.	IV	7, 10–19

7.3 Minimal residual disease detection and monitoring (MRDDM)

PCR assays, and RQ-PCR in particular, are being used increasingly for MRDDM in lymphoma. The critical interpretation and clinical significance of results requires consideration of technical, biological and clinical factors.[24] There is a need for greater standardisation of methodology and criteria for interpreting results[25], along the lines proposed by the BIOMED-2 Concerted Action[26,27] and the Europe Against Cancer Program[28,29], but there are significant cost implications in this approach.

7.3.1 Molecular targets in MRDDM

These are essentially the same as those used for primary lymphoma diagnosis, specifically AgR gene rearrangements (which may involve using patient-specific oligonucleotide primers or probes), chromosomal translocations (DNA based) or fusion gene transcripts resulting from chromosomal translocations (RT-PCR). Sensitive assays are needed to achieve the required analytical sensitivities of 10^{-4} to 10^{-6}, particularly in AgR gene rearrangement assays where clonal rearrangements need to be distinguished from any background polyclonal rearrangements.[1]

7.3.2 RQ-PCR in MRDDM

RQ-PCR assays are now the preferred approach to MRDDM[25]. The choice of strategy depends on the disease category, the nature of the molecular target, the analytical sensitivity required, and the expertise of the laboratory. Each method has potential advantages and disadvantages.[25]

7.3.3 Analytical sensitivity of RQ-PCR, controls and quantitation

Using fusion gene mRNA transcripts as PCR targets, sensitivities of 10^{-4} to 10^{-6} can be achieved, with little risk of false positivity from detection of low-level fusion transcripts present in normal cells. With AgR gene rearrangements as targets, sensitivities between 10^{-3} to 10^{-5} are achieved.[25,30] Control genes must be included in the assays to correct for DNA or RNA/cDNA quality, as this affects product quantitation.[25,31]

7.4 Testing for chromosomal translocations

Recurring chromosomal abnormalities (see Table 7.1) characterise certain non-Hodgkin lymphomas (NHLs) and are used for both diagnostic purposes and MRDDM. They may be detected by a variety of techniques, including SB, DNA-PCR, RT-PCR, classical cytogenetics and FISH. The method of

choice depends on the particular translocation being assessed. Among the most frequently assessed translocations in lymphoma diagnosis are the t(14;18)(q32;q21) in follicular lymphoma, the t(11;14)(q13;q32) of mantle cell lymphoma, and the t(2;5)(p23;q35) of systemic anaplastic large-cell lymphoma (ALCL).

7.4.1 t(14;18)(q32;q21)

This is the most common non-random chromosomal translocation occurring in NHL. It is detected by cytogenetics in 80% to 90% of follicular lymphomas and in 20% to 30% of diffuse large B-cell lymphomas. Although genomic PCR may be used for detection, other modalities are more sensitive, namely SB (but PCR is more cost effective), conventional cytogenetics, FISH and fibre-FISH (in increasing order of sensitivity).[32–39]

PCR diagnostic assays for t(14;18)(q32;q21)

Comparable qualitative sensitivities may be achieved in frozen or paraffin-embedded tissue approaching that of conventional cytogenetics, and optimised assays may achieve analytical sensitivities of 1 in 10^5 cells.[1] Employing two sets of primers specific for both the major breakpoint region and minor cluster region, the translocation will be detected in 60% to 80% of cases. The presence of small numbers of translocation-positive cells in normal individuals and in hyperplastic nodes[1] argue against the use of very sensitive, nested assays, or RQ-PCR assays designed for MRD detection. These potential false positives are avoided by using standard single-primer set diagnostic assays.

t(14;18) PCR for MRDDM

Sensitive nested t(14;18) PCR assays with sensitivities of 1 in 10^5–10^6 are used for MRDDM, and for assessing the efficacy of marrow purging prior to autologous transplantation. Where available, RQ-PCR assays are now the preferred method of testing, using TaqMan and LightCycler systems that are at least as sensitive as conventional nested assays.[1] Their high analytical sensitivity mandates caution in interpreting 'molecular relapse' in treated patients, as translocation-positive cells in normal individuals can be detected at levels as high as 1 in 10^4 cells.[40]

Interlaboratory variability

Multi-institutional studies have reported a wide interlaboratory variability in *bcl-2* testing methodology, with a large proportion of laboratories not knowing the analytical sensitivity of their system (i.e. the lower limit of detection), and having significant false-positive rates and low sensitivities.[38,41] These indicate the need for greater interlaboratory standardisation for these assays, especially in the setting of MRD detection.

Guideline	Level of evidence	Refs
FISH or PCR assays are the methods of choice for detecting the t(14;18)(q32;q21).	IV	32, 34–38

7.4.2 t(11;14)(q13;q32)

This translocation between the *CCND1/BCL-1* and *IgH* genes, which characterises mantle cell lymphoma (MCL) and is rarely found in other lymphomas, results in deregulated cyclin D1 expression. In decreasing order of qualitative sensitivity, the modalities for detecting aberrations of the *bcl-1* gene are DNA fibre-FISH (~100%), conventional FISH including interphase FISH (>95%), *in situ* mRNA hybridisation (>80%), immunohistochemical staining for cyclin D1 protein (range 70% to >90%), conventional cytogenetics (60–70%), SB (~70%), and genomic PCR (most studies <50%).[33,39,42] Almost all translocation-positive MCL will be detected by the various FISH techniques

available[36,37,43–46]. Genomic PCR, including real-time quantitative PCR assays, is of limited sensitivity (40–50%), as only translocations involving the major translocation cluster of *bcl-1* will be detected with standard assays. Immunohistochemical demonstration of nuclear cyclin D1 protein expression is the most cost-effective ancillary diagnostic test for MCL, with sensitivities ranging between 70% and >95%.[45–49]

Guideline	Level of evidence	Refs
Immunostaining for cyclin D1 protein is the recommended modality for confirming a diagnosis of mantle cell lymphoma.	IV	45–49
FISH techniques, if available, are the most sensitive means of demonstrating the t(11;14)(q13;q32).	IV	36, 37, 43–46

7.4.3 t(2;5)(p23;q35)

This translocation between the novel ALK and the NPM genes, which characterises most ALCL of T/null cell phenotype, generates a fusion gene — ALK/NPM — resulting in dysregulated ALK protein expression in nucleus and cytoplasm. At least 20% of ALCL harbour variant ALK translocations involving a translocation partner other than NPM, but still resulting in dysregulated ALK protein expression restricted to the cytoplasm and/or cell membrane.[1]

The t(2;5)(p23;q35) translocation may be detected by a variety of methods. The most sensitive and practical is ALK protein immunostaining[50,51], which correlates well with other detection methods.[52] Virtually all translocation-positive cases can be detected by RT-PCR, but variant 2p23 anomalies will not be detected, false positives from contamination will be missed owing to the constant size of the PCR product, and low-level transcripts present in normal individuals may be over interpreted. Long-range genomic DNA-PCR is the preferred PCR modality to avoid these potential pitfalls, but requires high-quality undegraded DNA.[1] FISH, including interphase FISH, can also detect the t(2;5)(p23;q35) and variant 2p23 anomalies.[1]

Guideline — Immunostaining — anaplastic large-cell lymphoma	Level of evidence	Refs
Immunostaining for ALK protein expression is the recommended test for detecting ALK and anaplastic large-cell lymphoma of T/null cell type	IV	50–52

Table 7.1 Common chromosome translocations in non-Hodgkin lymphomas

Chromosome aberration	Lymphoma	Genes involved
t(14;18)(q32;q21)	Follicular Diffuse large B-cell	*BCL-2, IgH*
t(8;14)(q24;q32)	Burkitt lymphoma	*C-MYC, IgH*
t(8;22)(q24;q11)	Burkitt lymphoma	*C-MYC, IgL*
t(2;8)(p11;q24)	Burkitt lymphoma	*C-MYC, IgK*
t(11;14)(q13;q32)	Mantle cell B-CLL, small subset	*CCND1 (cyclin D1; BCL-1), IgH*
t(11;18)(q21;q21)	Marginal zone/extranodal MALT	*API2, MALT1*
t(14;18)(q32;q21)	Marginal zone/extranodal MALT	*MALT, IgH*
t(1;14)(p22;q21)	Marginal zone/extranodal MALT	*BCL-10, IgH*
t(1;2)(p22;p12)	Marginal zone/extranodal MALT	*BCL-10, IgK*
t(2;18)(p11;q21)	CLL/SLL (5%)	*BCL-2, Igκ*
t(18;22)(q21;q11)	CLL/SLL (5%)	*BCL-2, Igλ*
t(14;19)(q32;q13)	CLL/SLL (<5%)	*BCL-3, IgH*
t(9;14)(p13;q32)	lymphoplasmacytoid lymphoma	*PAX5, IgH*
t(3;14)(q27;q32)*	*de novo* diffuse large B-cell	*BCL-6, IgH*
t(3;22)(q27;q11)	*de novo* diffuse large B-cell	*BCL-6, Igλ*
t(2;3)(p12;q27)	*de novo* diffuse large B-cell	*BCL-6, Igκ*
2p13–15 amplification	diffuse large B-cell, extranodal	*REL amplification (NFKB family member)*
t(2;5)(p23;q35)**	Anaplastic large cell, T/null	*ALK, NPM*

* many other *bcl-6* translocation partners are also described
** >20% of ALCL harbour variant 2p23 rearrangements involving genes other than *NPM* as a translocation partner (e.g. *TPM3, TFG, ATIC, MSN, CLTCL*).[1]

7.5 Virus detection by *in situ* hybridisation

A number of viruses are implicated in the development of human lymphomas. EBV is the best known. EBV genomic material may be detected in almost 50% of classical Hodgkin disease, in nearly all endemic Burkitt lymphomas, in nasal-type natural killer/T cell lymphoma, angiocentric B-cell lymphoma (lymphomatoid granulomatosis), post-transplant lymphoproliferative disorders, AIDS-associated lymphomas, and primary effusion lymphomas.[53] The presence of EBV can be demonstrated in a number of ways, including SB and PCR, but the method of choice is by EBV

EBER *in situ* hybridisation[54–57], which is easily applied in paraffin sections with high sensitivity, and is not expensive.

7.6 Standardisation of molecular tests

There is a relative lack of interlaboratory standardisation in molecular testing[58], which complicates the comparison of data. Few multicentre studies have addressed this issue. Significant interlaboratory variations in assay methodology and clonality detection rates have been found in TCR gene testing[20], IgH gene testing[8] and t(14;18) detection.[38,41]

Recent multicentre European collaborative studies have been instituted to optimise and standardise PCR assays for the purposes of clonality studies in lymphoma (BIOMED-2 Concerted Action)[9,59], leukaemia diagnosis, and MRD detection (Europe Against Cancer Program).[28,29] While this approach to standardisation and improved clonal detection is to be lauded, the complexity and costs involved are major drawbacks in a routine laboratory setting. The need for standardisation and guidelines for assignment of monoclonality becomes even more critical with the increasing use of new and sensitive detection methods, such as CEGS, in order to avoid false positive results.

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CHAPTER 8 DIAGNOSIS AND REPORTING OF LYMPHOPROLIFERATIVE DISEASE

8.1 Introduction

The WHO classification, based as it is on 'clinicopathological entities', requires for diagnosis the correlation of diverse types of information (clinical, morphological, immunophenotypic and genotypic).[1] This information is of varying complexity, often assembled from different laboratories, and often containing elements of different diagnostic confidence. Clinical information is a prerequisite for the diagnosis of certain WHO categories, especially cutaneous disease, extranodal lymphomas in general, and various forms of NK-cell and T-cell neoplasia.

The challenge in *diagnosis* is to weigh the relative importance of each piece of diagnostic information against the possible differential diagnoses.

The challenge in *reporting* lymphoproliferative disease is to record concisely the diagnostic findings and WHO diagnosis in such a way that the diagnostic decision-making trails, and areas of uncertainty (if present), are clearly documented.

8.2 Diagnostic difficulties

Two main causes may affect *diagnostic certainty*:

- inadequate or insufficient biopsy material or ancillary tests
- diseases that are intrinsically difficult to classify despite adequate biopsy material and ancillary tests.

8.2.1 Inadequate material or ancillary tests

Morphology remains the keystone of lymphoma diagnosis and the production of a well handled, high-quality H&E section remains the single most important element of accurate lymphoma diagnosis.[2–4]

What is an adequate biopsy?

An adequate biopsy is one in which there is material of sufficient quantity and quality; and sufficient ancillary investigations have been performed, to enable a confident and specific WHO diagnosis.

Factors influencing adequacy of materials and ancillary studies

i Pre-biopsy

- a Inadequate or misleading clinical information
- b Inappropriate investigational modality

ii Biopsy

- a Inappropriate biopsy site
- b Sample error
  - i Reactive tissue adjacent to tumour[5,6]
  - ii Partially involved peripheral lymph node
  - iii Composite disease[5]

iv Necrosis[7,8]

c Insufficient sample[5]

i For morphological assessment (e.g. needle core or endoscopic biopsies)

ii For ancillary studies

d Artefact

i Crush

ii Air drying

iii Diathermy

iv Nuclear artefact in endoscopic and core biopsies

iii Post-biopsy (technical, laboratory issues)

a Routine processing

i Inappropriate fixation

ii Laboratory processor errors, or staining artefact[2,5,6]

iii Loss of antigenicity

iv Loss of DNA

b Immunohistochemistry unsatisfactory

c Molecular studies unsatisfactory

8.2.2 Diseases that are difficult to classify despite adequate biopsy material and ancillary tests

There are three categories of such diseases:

i ‘Atypical lymphoid hyperplasia’

ii Unclassifiable and ‘grey zone’ lymphomas

iii Unavailability of a pathologist experienced in haematopathology

‘Atypical lymphoid hyperplasia’

‘Atypical lymphoid hyperplasia’ is a condition in which it is not possible to differentiate between a benign or malignant lymphoproliferative condition (see Figure 8.1).[9] It is not a true clinicopathological entity and is used as an interim label while further investigation is performed, or while the disease declares itself clinically.[10]

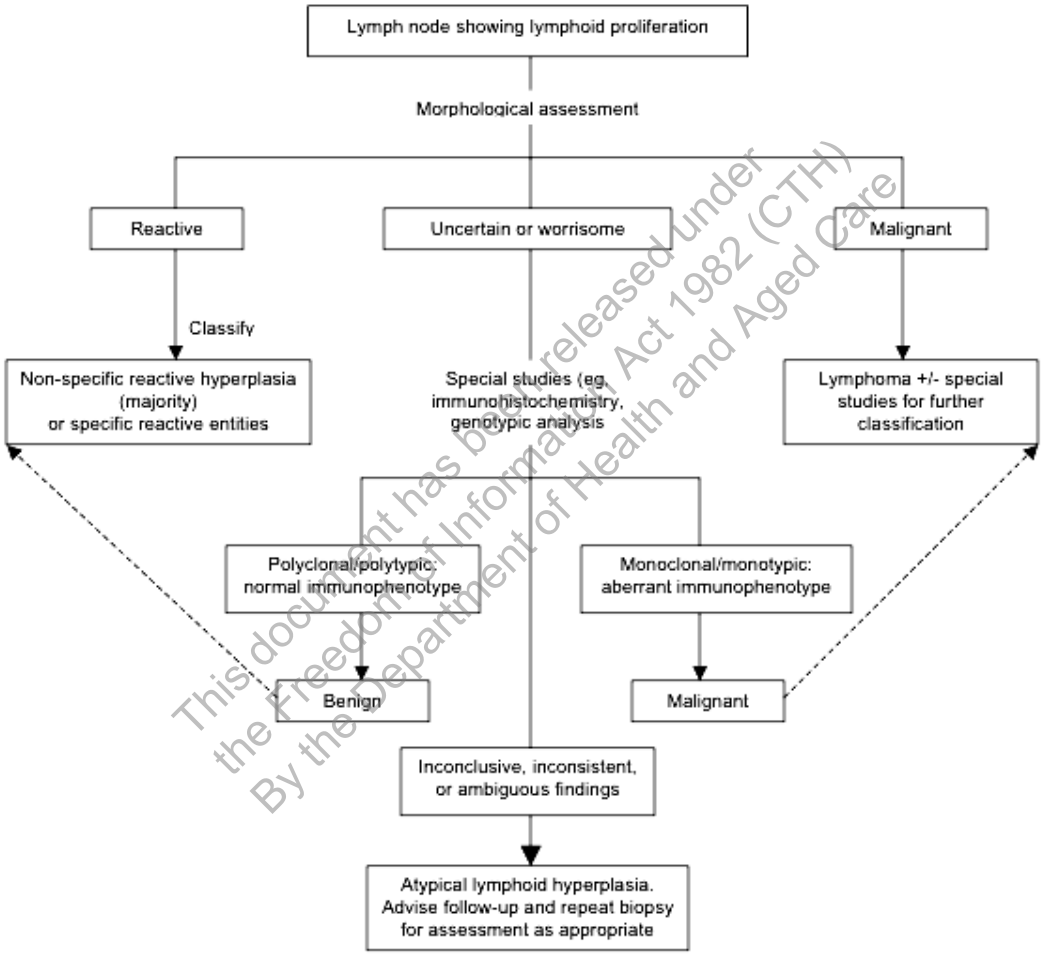
Most studies have indicated a significant risk for the subsequent diagnosis of lymphoma in this group.[10–12] Once accounting for between 3% and 40% of all lymphoid diagnoses[9], the term ‘atypical lymphoid hyperplasia’ is now used much less frequently, due to the use of ancillary studies.[12]

Unclassifiable and 'grey zone' lymphomas

This refers to cases in which the disease is clearly a lymphoma but subtyping is difficult due to conflicting or discordant clinical, morphological, immunophenotypic, molecular or genetic findings.[13,14] Some of these may be variants or new diseases that are not yet recognised within the WHO classification. It is recognised, however, that there may be significant overlap in the morphological and immunophenotypic features of some WHO entities.

The term 'grey zone lymphomas' is generally applied to cases that fall into the differential diagnosis between classical Hodgkin lymphoma (often syncytial), anaplastic large-cell lymphoma, T-cell rich B-cell lymphoma, and mediastinal large B-cell lymphoma.[15]

Figure 8.1 Atypical lymphoid hyperplasia



Source: Reprinted from Chan[9] with permission from Elsevier.

8.3 Course of action in non-diagnostic cases

8.3.1 Technical causes

In cases where the diagnosis is compromised by insufficient biopsy material, or the quality of the material is compromised by the biopsy technique, this should be clearly stated in the report. On occasion, a poorly fixed sample may be rendered diagnostic by post fixation. In general, however, the

only satisfactory recourse is re-biopsy, preferably by excision biopsy. ***In consulting, there is little value in referring inadequate or unsatisfactory material to another pathologist or institution.***

If there are technical problems with immunophenotyping technique (identified by using appropriate positive and negative control sections), correction may be attempted within the laboratory, or material may be sent to a reference laboratory for staining.

8.3.2 'Atypical lymphoid proliferations' and unclassifiable lymphomas

When good material has been extensively examined and subjected to a full range of ancillary tests with indeterminate results, and a specific lymphoma diagnosis has still not been established, the following courses of action may be considered:

i Referral of the patient to a unit experienced in haemato-oncology

ii Referral of the material to an experienced haematopathologist (preferably part of the above clinical unit)

iii Re-biopsy

iv Staging procedures

v Close clinical follow up

Key point

To minimise delays and waste of tissue in diagnostically difficult cases, it may be convenient to refer the material to the pathologist who functions as a member of the multidisciplinary team where the patient will be managed.

8.4 Reporting

8.4.1 Typical report information

A report of lymphoproliferative disease would normally record the following:

i Patient demographics

ii Anatomical site of biopsy or organ, whether nodal or extranodal

iii Type of sample (needle core, endoscopic, incisional, etc.)

iv Histological diagnosis:

v WHO classification recommended[1] (see Chapter 3)

Use of alternative classifications is not recommended but should be clearly stated if used.

vi Composite disease (where relevant)

vii Tumour progression/transformation (where relevant)

viii Statement of diagnostic certainty (see Section 8.3.3)

ix Reasons for any uncertainty (see Section 8.2)

x Grading (where relevant)

xi Focal or diffuse tissue involvement

Where essential to the diagnosis, specific findings should be discussed (see Section 8.3.3 below):

i Clinical features

ii Microscopy (architecture and cytology)

iii Immunophenotypic findings

iv Genetic findings

v Recommendations for further action or investigation (where appropriate)

8.4.2 Reporting of ancillary studies[16]

Immunophenotyping

i State whether flow or histochemistry, FS or PS

ii Specify all markers investigated, positive or negative

iii Avoid the use of terms such as 'T-cell marker'

iv Specify which cells are positive or negative

v Specify the percentage of cells and cellular staining pattern where relevant

vi Discuss diagnostic interpretation and significance

vii State where performed if reference laboratory used (attach that laboratory's report)

Molecular or cytogenetic studies

i Type of specimen used (FS versus PS)

ii Method (SB, PCR, conventional cytogenetics, FISH, etc.)

iii Specify test conditions (primers targets, etc.)

iv Discuss diagnostic interpretation and significance. (This requires an understanding of the test performance characteristics specific for the laboratory that performs the test — see Chapters 6 and 7)

v State where performed if a reference laboratory is used and attach that laboratory's report

8.4.3 Statement of diagnostic certainty

As there are many factors which may detract from the degree of diagnostic confidence; and as the treating clinicians may have to manage patients on the basis of reports from pathologists who are unknown to them, we recommend that all pathological reports of lymphoma include a clear statement of diagnostic confidence level (see Table 8.1 for a suggested synoptic report). This may be simply expressed by stating that a diagnosis is either 'definitive' or 'provisional'. A report incorporating a provisional diagnosis should clearly document the reasons for diagnostic uncertainty, with recommendations for further action to achieve a definitive diagnosis.

8.4.4 Recommendations for further action or investigation given in the report

Recommendations given within a pathology report may include any of the following:

i Rebiopsy (indicating preferred modality)

ii Specific investigations (e.g. imaging of specific areas)

iii Referral of pathology material for a second opinion

8.4.5 Synoptic reporting of lymphoma

Synoptic formats have been widely adopted for pathology reporting in oncology, yet lymphoid neoplasia has proven an exception. This reporting format provides a roadmap for diagnostic testing.

Key point

A synoptic approach to reporting is encouraged wherever possible.

To assist in this, a checklist is provided as Table 8.1. It includes recent recommendations from the Association of Directors of Anatomical Pathology in the United States[16], together with possible values for each heading.

It is noted that integration of information from the full blood examination and bone marrow biopsy (if done) will be desirable as synoptic reporting is developed. However, this will present practical problems as this data may emerge from different laboratories.

Table 8.1 Synoptic reporting of lymphoproliferative disease

Synoptic report template for lymphoproliferative disease

Surname ……..First name ……. Ref. No. …….. Sex … DOB……

BIOPSY SITE ……..
☐Nodal ☐ Extranodal ☐ Unknown

DIAGNOSIS

☐ **WHO category (specify)……..**
% Follicular (if appropriate): …….
Grade (if appropriate): …….
ICDO-3/Snomed /SNOP code:…….
☐ Lymphoma, unclassified*
☐ Atypical lymphoid hyperplasia*
☐ Haematolymphoid neoplasm NOS*
☐ Reactive lymphadenopathy (specify)…….
☐ Non-lymphoid tumour (specify)…….
Comment: ……

Diagnostic certainty:

☐ Definitive diagnosis
☐ Provisional diagnosis only*

*** For unclassified lymphomas, haematolymphoid neoplasm NOS, atypical lymphoid hyperplasia or provisional diagnosis state:**

Differential diagnosis(es):

Uncertainty due to:
- ☐ Insufficient material
- ☐ Morphological artefact
- ☐ Immunophenotype undetermined
- ☐ Immunophenotype ambiguous
- ☐ Genotype undetermined
- ☐ Genotype ambiguous
- ☐ Discordant clinicopathological pattern

Comment: ……

Further action recommended or taken:
- ☐ None
- ☐ Further immunophenotyping (specify)
- ☐ Further genotyping (specify)
- ☐ Rebiopsy: (specify type - NCB, Excisional, etc.)
- ☐ Further clinical investigations: (specify)
- ☐ Second opinion sought from: (specify)
- ☐ Other:

Comment: ……

LINEAGE & CLONALITY

Lineage: Null / B-cell / T-cell / NK/T-cell / Histiocytic / Dendritic / Myeloid / Non-haemopoietic / Not tested / Indeterminate / Other……

Clonality: Monoclonal / Oligoclonal / Polyclonal / Unknown

Clonality assessed by: Immunohenotype / Genotype / Inferred from morphology

SPECIMEN

Specimen type: ***Cytology****:*
FNA / Body Cavity Fluid / Other
Tissue biopsy:
NCB (state gauge) / Incisional / Excisional / Resection (state type) / Endoscopic / Bone marrow / Peripheral blood

Specimen dimensions: …. X … X … mm

Received: Fresh / In saline / In formalin / Other

Consultation material: Stained slides / Unstained slides / Paraffin blocks / Other

Specimen triage: Paraffin / Flow / Imprints / Microbiology / Frozen / EM / Tissue Bank / Cytogenetics

Checklist of relevant clinicopathological features

CLINICAL

Disease duration: Unknown (specify)……

Known sites of disease: *Nodal sites: (specify) ……*
Unknown / Solitary/Localised / Generalised
Extranodal sites:
Unknown / Liver / Spleen / Thymus & Ant. Mediastinum / Waldeyer's ring / Skin / Bone / Peripheral blood / Pleura, pericardium, peritoneum / Disseminated

Organomegaly: Unknown / Hepatomegaly / Splenomegaly / Other (specify)

Constitutional symptoms: Unknown / Yes / No

Relevant Haematology: Unknown / Specify:……

Relevant clinical Hx: Unknown / Autoimmune Disease / Medication (eg phenytoin)

Immunosuppression: Unknown / Viral / Congenital / Transplantation / Methotrexate / Other

Provisional clinical Dx: Unknown / NHL / Hodgkin lymphoma / Reactive / Other (Specify)…

Previous lymphoma: Unknown / No / Yes Prev. Diagnosis:……
Date: …… Site: ……Stage: …..
Treatment(s): ……..
Treatment: Ongoing / Completed (date……) Response: CR / PR

MORPHOLOGICAL

Degree of involvement: Partial / Complete

Architectural pattern: Indeterminate / Diffuse / Mantle zone / Sinusoidal / Follicular / Marginal zone / Paracortical / Pseudofollicular / Nodular / Composite / Other

Tumour cell size: Indeterminate / Small / Intermediate / Large / Mixed small/large / Other

Cellular features: Indeterminate / Monomorphous / Polymorphous / Granulomatous / Histiocyte rich / T-cell rich / Eosinophil rich / Neutrophil rich / Sarcomatoid / Other ……

Cytomorphology: Indeterminate / Pleomorphic / Hyperlobate / Cerebriform / RS-like / Prolymphocytic / Centroblastic / Paraimmunoblastic / Immunoblastic / Anaplastic / Plasmacytic / Plasmablastic / Monocytoid / Centrocyte-like / Clear cell / Giant cell / Signet ring cell / Other…….

Secondary features: None / Necrosis / Sclerosis / Angiocentricity / Erythrophagocytic / Epidermotropic / Lymphoepithelial lesions / Enteropathic / Amyloid / Other …….

Interpretation of results: ……

Correlation with diagnosis: Typical / Atypical or variant / Discordant / Non-contributory

IMMUNOPHENOTYPING

Flow studies: Positive: ……
Negative:……

Immunohistochemistry: Positive: ……
Negative:……

Interpretation of results: ……

Correlation with diagnosis: Typical / Atypical or variant / Discordant / Non-contributory

CYTOGENETICS:

Not done / Conventional / FISH / Other (specify) ……..

Results & Interpretation: ……

Correlation with diagnosis: Typical / Atypical or variant / Discordant / Non-contributory

GENOTYPING

PCR **Not done / Done**
F/S / P/S

- **IgH** +ve / -ve
- **TCR** +ve / -ve
- **t(14;18)** +ve / -ve
- **Other (specify)** ……

Southern blot: Not done / Done

Results & interpretation: ……

Correlation with diagnosis: Typical / Atypical or variant / Discordant / Non-contributory

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CHAPTER 9 APPROACH TO THE PATIENT

9.1 Introduction

Reaching a diagnosis of lymphoma in patients who may present with a varied range of clinical features is often challenging. Patients may have peripheral lymphadenopathy plus or minus splenomegaly, or a constitutional illness characterised by weight loss and fever. Less commonly extranodal lymphoma may involve a specific organ or organs. The approach to diagnosis will clearly vary, depending on the modes of presentation described above. However, once a definitive histologic diagnosis is achieved, the patient enters a common pathway typical of the management of all patients with malignant disease. This involves staging, prognostic assessment, and a treatment plan reflecting either a curative or palliative approach. This required delineation of treatment modalities, which may be surgery, radiotherapy, chemotherapy, biological, or supportive therapy. Often a combination of treatments is used in a multi-modality management approach.

Developing appropriate guidelines for lymphoma is complicated by the wide variability of clinical presentation. Patients may be referred to almost any medical speciality. Therefore, the guidelines need to be recognised across the spectrum of specialities as distinct from a single unit. The accurate workup of patients with lymphomas requires integrating a series of various investigations.

The following issues are discussed in this chapter:

- peripheral lymphadenopathy
- thoracic and intra-abdominal disease
- splenomegaly
- weight loss
- fever
- biopsy
- staging
- multidisciplinary management
- follow up

9.2 Peripheral lymphadenopathy

Apart from malignant diseases involving lymph nodes, for example, lymphoma or metastatic tumour, infectious and immunological diseases may cause lymphadenopathy. In general practice, less than 1% of patients who present with peripheral lymphadenopathy actually have malignant disease. Of the patients with benign lymphadenopathy, the majority have non-specific or reactive aetiology requiring few diagnostic tests.

Enlarged intra-abdominal or retroperitoneal nodes are usually malignant. By contrast, intra-thoracic lymphadenopathy in the young can be associated with infectious mononucleosis and sarcoid. However, tuberculosis is a common cause of lymphadenopathy at any site in certain immigrant groups.

Evaluation of patients requires the usual full medical history, physical examination and, in some circumstances, certain laboratory tests. Only a small percentage will require some form of lymph node biopsy.

Over the age of 50 years, the chance of malignant disease as a cause of lymphadenopathy increases. Nodes less than 1 cm in diameter generally reflect benign causes, while a diameter greater than 2 cm serves as a discriminate predicting malignant or granulomatous disease. Tender lymph nodes are

usually benign. Patients can usually be triaged to observation after blood tests for infectious mononucleosis and toxoplasmosis unless there are symptoms and signs of an underlying systemic illness.

Retrospective analysis of various series of patients has led to the development of algorithms to identify patients with peripheral lymphadenopathy who require biopsy. To develop a model to differentiate patients whose biopsy results do not lead to treatment (normal, hyperplastic or benign inflammatory lymph nodes) from those whose biopsy results do lead to treatment (malignant or granulomatous nodes), the medical records and histopathology slides of 123 patients aged 9–25 who underwent biopsies of enlarged peripheral lymph nodes were reviewed for pathological diagnoses. Fifty-eight per cent of patients had biopsy results that did not lead to treatment and 42% had results that did lead to treatment. A predictive model was developed that assigned 95% of the cases to the correct biopsy group, based on lymph node size, history of recent ear, nose and throat (ENT) symptoms, and chest x-ray. When tested prospectively on new patients, the model classified 97% of 33 patients correctly. It was concluded that this simple model could help select adolescents and young adults with peripheral lymphadenopathy for biopsy.

The predictive features for biopsy were lymph nodes greater than 2 cm in diameter and an abnormal chest x-ray while recent ear, nose and throat symptoms had a negative predictive value.[1]

Similarly, in another study, the charts of 249 patients with enlarged lymph nodes were audited to provide a primary care database and to clarify recommendations for evaluation of lymphadenopathy. A firm diagnosis was made in only 36 patients, despite an average of 1.7 visits and two laboratory tests per patient tested. Serious or treatable causes of lymphadenopathy were rare and were always accompanied by clinical conditions that suggested further evaluation. Lymph nodes were biopsied in only 3% of patients. No patient was found to have a prolonged disabling illness without a prompt diagnosis. The data suggest that in patients without associated signs or symptoms, a period of observation is safe and likely to save unnecessary expense in biopsy.[2]

A further study evaluated 220 lymphadenopathy patients. It identified five variables: lymph node size, location (supraclavicular or non-supraclavicular), age (greater or lesser than 40 years), texture (non-hard or hard), and tenderness. Positive predictive values indicating biopsy were found for age >40, supraclavicular location, node size >2.25 cm, hard texture, and lack of pain.[3]

Investigation can follow an algorithm based on patient's age, history and physical findings as described above. Full blood count may provide definitive diagnostic information, as can simple serological studies for EBV, CMV, HIV and other viruses, and so on. It might be obvious that lymph node biopsy is required, for example, lymph nodes over 2 cm in diameter or hard, or in older patients, or if there is doubt delayed for a few weeks. Early biopsy should occur if malignancy is suggested, for example, firm or hard, non-tender cervical lymph nodes, supraclavicular lymphadenopathy or firm lymphadenopathy.[4]

Guideline — Indicator — peripheral lymph node biopsy outcome	Level of evidence	Refs
Predicted indicators for lymph node biopsy are age greater than 40 years, supraclavicular location, node diameter over 2.25 cm, firm–hard texture, and lack of tenderness.	III	1–4

Guideline — Fine-needle aspiration biopsy	Level of evidence	Refs
Fine-needle aspiration (FNA) is generally the biopsy investigation of choice in the initial triage in peripheral lymphadenopathy. It should be accompanied by flow cytometry (FCM) studies.	IV	5–13

In patients suspected of primary head and neck cancer, ENT examination is warranted and any mucosal lesions should be biopsied first. FNA is valuable as a triage procedure in distinguishing between carcinoma and lymphoma. However, an inconclusive or negative report may not exclude lymphoma, therefore excisional lymph node biopsy may be the next step.[14] If the FNA is reported as lymphoma, excision lymph node biopsy is required for definitive diagnosis and subtyping. In some circumstances clinicians may feel that immediate excisional lymph node biopsy should be undertaken as the initial biopsy to expedite the diagnostic process.

Guideline — Definitive tissue biopsy	Level of evidence	Refs
Excisional lymph node biopsy is essential for the primary diagnosis, subtyping and clinical management of lymphoma presenting as peripheral lymphadenopathy.	IV	6, 9, 11, 15–18

In some centres, needle core biopsy has been used in the diagnosis of peripheral lymphadenopathy but this is not generally recommended except for recurrent disease or staging.

Where a lymphoma is suspected, referral to a specialised clinic may be more appropriate than referral to a general surgeon for biopsy. A full blood count prior to biopsy may exclude patients who have, for instance, B-cell chronic lymphocytic leukaemia or other haematological conditions. Cell marker studies should be carried out prior to biopsy if there is a significant lymphocytosis. Similarly, female patients with axillary lymph nodes should have careful breast examination. A chest x-ray prior to biopsy will alert clinicians to the presence or absence of more extensive disease.

In some centres, ultrasound is used to assist in the differential diagnosis of benign and malignant lymphadenopathy, however this still appears to be an investigational approach.[19] As well, some surgeons use intraoperative ultrasound to select the most appropriate node for excisional biopsy.

Guideline — Indicator — minimum investigations before surgical biopsy	Level of evidence	Refs
Full blood count and chest x-ray should be performed before biopsy.	IV	24

9.3 Thoracic and intra-abdominal presentations

9.3.1 Mediastinal mass

The differential diagnosis may include sarcoidosis, tuberculosis, metastatic carcinoma and thymoma. Mediastinoscopy with biopsy may be an appropriate approach to biopsy. In some circumstances, bone marrow biopsy prior to the procedure may be appropriate. The rare instances of lymphoma involving lung parenchyma (isolated) may require open thoracotomy and lung biopsy.

9.3.2 Abdominal and retroperitoneal lymphadenopathy

As described in the pathology section, an alternative to open biopsy is, in fact, CT-guided core biopsies or laparoscopic lymph node biopsy, depending on the location of the lesions to be biopsied.[20] These issues are discussed in Chapter 4.

9.4 Splenomegaly

The presence of an enlarged spleen is easily determined by ultrasonography and is less costly than CT. However, CT does offer the advantage of visualising intra-abdominal lymph nodes, which will be important where lymphoma is suspected. In differential diagnosis, if the patient has associated lymphadenopathy, a lymphoma (or leukaemia, etc.) is likely. Causes of splenomegaly such as the following must be distinguished:

- reticulo-endothelial hypoplasia
- immune hyperplasia
- portal hypertension
- infiltrative disease of spleen (metabolic or benign or malignant cellular infiltrate), and
- extramedullary haemopoiesis

A significantly enlarged spleen, for example, greater than 8 cm below the left costal margin, is usually due to a malignant haematological cause (excluding malaria or kala-azar in the tropics).

Investigation may be more specifically directed after a full blood count and assessment of any apparent underlying systemic illness. Bone marrow biopsy and/or biopsy of any lymphadenopathy may be indicated.

Rarely, splenectomy will be performed for diagnostic purposes where no other site of disease is detected.

9.5 Weight loss

In the elderly, common causes of weight loss are depression, malignant disease and benign gastrointestinal disease. By contrast, in younger individuals, diabetes, hypothyroidism, psychiatric disturbance, infection and/or lymphoma need to be considered. Patients with fever and night sweats may have either malignancy or chronic infection. Objective confirmation that weight loss has occurred is important, with a focus on signs or symptoms that are associated with systemic disease that may cause weight loss.

Apart from general routine physical examination, a search for lymphadenopathy and/or splenomegaly should be made. Key laboratory investigations will be a full blood count, serum LDH, ESR, chest x-ray and, where appropriate, CT examination of the abdomen and bone marrow biopsy.

9.6 Fever

Careful history taking is necessary in terms of the potential for systemic disease, such as infection, inflammatory disease or malignancy, as well as drug reactions. The physical examination should compliment the history taking as outlined in Section 9.5.

Investigations will depend on clinical manifestations, but should include a full blood count with examination of the film with appropriate biochemistry and cultures. The course of the illness is critical, and either the patient recovers spontaneously or the initial examination leads to a diagnosis. For continued fever, the patient is diagnosed with fever of unknown origin, which requires more

intensive investigation. This may include CT scan of abdomen and chest, and bone marrow biopsy. The role of PET scanning is undergoing investigation in this setting.

The eventual diagnosis of lymphoma depends on a tissue biopsy. Peripheral lymph node excision biopsy is preferable and where there is intra-thoracic/abdominal or solid organ involvement, a radiologically guided core biopsy is frequently adopted. The diagnosis depends on obtaining adequate tissue to evaluate the histology of the tumour and subtype, as well as immunohistochemical and molecular diagnostic information.

9.7 Biopsy

Arrangements for an appropriate biopsy should be made with an experienced operator. The use of FNA, core or excision biopsy will depend on the nature and location of the target lesion as discussed in Chapter 8. It is critical that the biopsy be interpreted or reviewed by a pathologist expert in haematopathology. These issues are discussed elsewhere in the guidelines.[21–23]

Guideline — Expert haematopathologist for optimal diagnosis	Level of evidence	Refs
The biopsy should be reviewed by pathologist who is a recognised expert in haematopathology.	III	14, 20, 21

9.8 Staging

A synthesis of the information developed from the multidisciplinary approach described above allows identification of sites of disease, and from this, prognosis and a treatment approach. The Ann Arbor staging description is described in Section 11.7 and is applicable both to Hodgkin lymphoma and to the other varieties of lymphoma.

9.9 Multidisciplinary management

It is critical that centres develop an appropriate multidisciplinary team, in particular to correlate the investigative techniques — including histopathological, molecular and imaging information — with the clinical data. The various sub-specialities, especially medical/haematological oncology in conjunction with radiotherapeutic and surgical specialists, need to be familiar with the management protocols and guidelines.

Once a diagnosis of lymphoma is made, the patient should be managed in a multidisciplinary collaboration between the haemato-oncologist, radiotherapists, and other members of the medical team as required. After diagnosis, the next step is to determine disease extent by suitable staging. This will allow appropriate determinations of prognosis when the lymphoma subtype, clinical stage, serum LDH, presence or absence of constitutional features, performance status, and so on, can be assessed.

At this point, a treatment plan can be made in conjunction with the patient's informed views, with the aims of treatments defined in terms of potentially curative treatment or a palliative management plan. Apart from the adoption of appropriate defined protocols for management of the specific lymphoma subtypes and stages, the haemato-oncologist should be prepared to manage complications of both the disease and its treatments, and the various psychosocial problems that may be associated with such severe disease. The need for long-term follow up and the potential for late complications of treatment need to be recognised and discussed with the patient. In patients who have advanced disease where specific anti-lymphoma therapy is inadequate, appropriate supportive and symptomatic and palliative care measures need to be organised.[24,25]

Guideline — Best practice in multidisciplinary care	Level of evidence	Refs
Patients should be managed in a multidisciplinary clinic or setting.	IV	24, 25

9.10 Follow up

The need for long-term follow up should be recognised, particularly for patients with potentially 'curable' disease. This may best be the responsibility of one particular member of the multidisciplinary team. The follow-up program should encompass appropriate detection of (a) current or relapsed disease, and (b) long-term side effects of therapy.

In addition, it is appropriate to arrange general care by a general practitioner/family doctor to cope with other medical issues that the patient, progressively ageing, will encounter. This could include appropriate screening for other diseases such as breast and bowel cancer, and diabetes. Such patients often concentrate on their original disease, not appreciating that as the years pass, they are increasingly vulnerable to other medical problems.

For patients with relapsed or progressive disease that is not responding to appropriate anti-lymphoma therapy (chemotherapy, biologic modifiers, radiation, etc.), standard symptom control and palliative care measures are appropriate. These are generally not specific to lymphoma and are described in other papers and texts.

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CHAPTER 10 SURGICAL BIOPSY IN LYMPHOMA

An adequate diagnosis of lymphoma often requires careful assessment of nodal architecture in addition to assessment of cytologic abnormality.

An incisional biopsy may provide only a glimpse of architecture, limiting interpretation. Therefore, where possible, the surgeon should biopsy the most clinically significant site, and attempt to remove an intact lymph node.[1] This should be done with as little disruption of the lymph node as possible, to allow maximum pathological assessment of nodal architecture. Where excision of an intact lymph node is not considered safe or practical, the surgeon performing an incisional biopsy must be aware of the need to provide an adequate wedge of viable tissue that includes the nodal capsule, and wherever possible, the cortex, paracortex and medulla of the lymph node. Piecemeal excision should be avoided. To minimise surgical disruption of nodal architecture, the incisional biopsy should be made with a cold scalpel rather than diathermy.[2]

Tissue samples should be sent fresh and expeditiously to a pathology laboratory with appropriate expertise (see Section 4.3.1). The laboratory should be informed beforehand. Surgery should therefore be scheduled during normal working hours wherever possible, to optimise specimen processing.[1,2]

When peripheral lymphadenopathy is absent, mediastinoscopy, thoracotomy or laparotomy may be required to access tissue for diagnosis. Endoscopic techniques may provide adequate surgical access, with much reduced morbidity. Video-assisted thoracoscopy is widely used for access to intrathoracic pathology. Despite technical challenges, the laparoscopic approach is finding increasing acceptance in assessment of abdominal lymphoma.[3–5] Irrespective of the surgical approach, the principal requirement of surgical biopsy remains the reliable provision of a diagnostic tissue sample.

CT or ultrasound-guided core biopsies can be used to obtain biopsies where peripheral lymph nodes may be clinically normal.[6–9] Such biopsies allow minimal assessment of architecture, but risk incorrect diagnoses due to inadequate sampling. This should be balanced against the morbidity of open surgical procedures.

Approximately one third of cases of non-Hodgkin's lymphoma in adults present at extranodal sites.[1] It is important for surgeons to remember to provide adequate tissue samples from such extranodal sites for lymphoma protocol studies.

Guideline — Surgical biopsy	Level of evidence	Refs
Surgical biopsy should be of the most clinically significant site. The surgeon should attempt to remove an intact lymph node.	IV	1
If an incisional biopsy is performed, trauma to the nodal architecture should be minimised.	IV	2
An appropriate laboratory should be informed before the biopsy, and specimens should be sent fresh and expeditiously.	IV	1, 2

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CHAPTER 11 HODGKIN LYMPHOMA

11.1 Introduction

Hodgkin lymphoma (HL) is one of the best-characterised malignancies of the lymphatic system and one of the forms of malignant disease most readily curable by radiotherapy, chemotherapy or a combination of the two. Modern treatment methods routinely achieve such high cure rates that a very strong emphasis is now placed on achieving cure with the least possible risk of complications from therapy. HL is often portrayed as a model for successful treatment of malignancy. The valuable lessons learned from this disease have been usefully applied to other cancers.

11.2 Incidence of Hodgkin lymphoma in Australia

In 2001, there were 401 new cases of HL in Australia. It was more common in males than females (218 and 183 respectively). The age distribution showed a bi-phasic curve, with an early peak in adolescence to young adulthood, and a later smaller peak at around 50 years of age. During 1992–1997, five-year relative survival was approximately 83%. This was significantly better than the survival recorded during 1982–86. Relative survival from HL in Australia is good compared to many other developed countries.[1]

11.3 Pathogenesis and aetiology of Hodgkin lymphoma

Despite its early recognition as a disease entity, the pathogenesis of HL is not fully understood. It is widely considered to originate from cells of the B lymphocyte series, and the neoplastic cell may be a crippled germinal centre cell.[2] The cause of HL is also unclear, but a strong association with Epstein Barr virus (EBV) has been reported[3], and the disease may occur as a complication of HIV infection.[4] Although most cases are sporadic, clusters of cases from certain geographic regions have been reported[5], as have familial cases of HL.[6] No methods for prevention of HL have been shown to be effective, although measures to prevent the spread of HIV infection should prevent some cases at least. It has been suggested that a vaccine against EBV could play a role in prevention of HL, but this has not yet been proven.

11.4 Pathology of Hodgkin lymphoma

The importance of an adequate biopsy cannot be stated too highly. Diagnosis can only be made with confidence when a representative lymph node is sampled and the pathologist has specialist knowledge and experience of lymphomas. Classically, HL is manifest by the presence of typical Hodgkin or Reed-Sternberg cells in a background of a mixed inflammatory cell infiltrate. Often the neoplastic cells are present in relatively small numbers compared to the infiltrating cells. In the WHO classification[7], the following subtypes of HL are described;

1 Lymphocyte predominance Hodgkin lymphoma (LPHL)

2 Classical Hodgkin lymphoma

- nodular sclerosis Hodgkin lymphoma (NSHL)
- mixed cellularity Hodgkin lymphoma (MCHL)
- lymphocyte depletion Hodgkin lymphoma (LDHL)
- lymphocyte-rich classical Hodgkin lymphoma (LRCHL)

11.5 Summary of clinicopathological features

11.5.1 Nodular lymphocyte predominant Hodgkin lymphoma

Clinical	30–50. Male > female. Cervical, axillary or inguinal lymph nodes. Slow onset. Often solitary — stage I or II. Rarely may be disseminated at presentation.
Morphology	Nodular or nodular and diffuse. Purely diffuse subtype questionable. A single typical area is diagnostic. L&H, 'popcorn' variant of H-RS cell within large, B-cell rich and FDC +ve nodules, often with a peripheral wreath of histiocytes. May have associated progressive transformation of germinal centres (PTGC).
Immunophenotype	L&H cells: CD20, CD79a, *bcl-6*, BSAP and CD45+ve Also EMA, CD75, J chain, Oct2 and BOB.1 +ve. CD30 usually –ve. TARC, CD15, Fascin, LMP1, EBER -ve Background cells: CD20 +ve small B-cells. T-cells are present in small numbers and CD57+ve. CD21/23/35+ve FDCs form networks in the nodules. DD: Lack of FDCs or T-cell rich environment suggests T-cell rich B-cell lymphoma.
Genetics	Follicle centre B-cell origin with somatic hypermutation and functional transcripts. Monoclonal but not often detectable, except by single cell PCR. Florid PTGC may be clonal but only within a given follicle.
Behaviour	Stage I or II >80% ten-year survival. Progression to diffuse large B-cell lymphoma in 5%. Progression to diffuse lymphocyte predominant HL. Diffuse lymphocyte predominant HL may be indistinguishable from TCRBCL.

11.5.2 Classical Hodgkin lymphoma

Clinical	Bimodal age: 15–35 years and 50+ Typically cervical, mediastinal, axillary or para-aortic lymph nodes. Contiguous involvement. Very rarely extranodal. 55% stage I or II. 40% have 'B symptoms'. Nodular sclerosing: mediastinal involvement.
Morphology	*Classical Reed Sternberg cell*: Large with abundant basophilic cytoplasm, prominent eosinophilic nucleoli. Bi-nucleate or bi-folded nuclei. *Nodular sclerosing* Nodular lymphoid aggregates divided by sclerotic bands of collagen with capsular thickening. 'Lacunar' variants. BNLI grading: NS Grade 1: >75% lymphocyte-rich NS Grade 2: >25% lymphocyte depleted *Mixed cellularity* May be interfollicular. Not nodular or sclerosing. Mixture of eosinophils, neutrophils, histiocytes and plasma cells. *Lymphocyte rich classical HL* Nodular or diffuse. Lacks polymorphs. Resembles lymphocyte predominant Hodgkin lymphoma and may have 'L&H' variants *but* defined by immunophenotype, which is that of cHD. *Lymphocyte depleted* 'Pleomorphic' variant of H-RS cell. Rare entity now. Many cases in older series were ALCL or pleomorphic T-cell or B-cell lymphomas.
Immunophenotype	*H-RS cells*: CD15, CD30 +ve and CD45-ve Also BSAP, TARC and Fascin +ve LMP1 often +ve, especially in mixed cellularity HL CD20 –ve or focally/weakly +ve but unreliable J chain, CD43, CD75, Oct2, BOB.1 –ve CD2, CD3 may be very weakly expressed *Background cells:* CD3 +ve small Th2-cells, forming rosettes. *DD*: T-cell rich B-cell lymphoma Anaplastic large-cell lymphoma Lymphocyte predominant Hodgkin lymphoma Diffuse large B-cell lymphoma Some T-cell lymphomas
Genetics	Monoclonal B-cell in >98% of cases. Somatically hypermutated follicle centre cell. Abnormal expression of Oct2 and BOB.1 transcriptional promoters => no J chain or Ig expressed. NF B abnormality prevents apoptosis.

11.6 Prognostic significance of histological subtypes

In patients treated with radiotherapy alone, histological subtype is an important prognostic factor.[8] Superior progression-free survival occurs in patients with LPHL and NSHL compared to those with MCHL and LDHL. In patients treated with chemotherapy, with or without radiotherapy, the prognostic significance of histological subtype is less important than other prognostic factors such as stage or age. In particular, the difference in prognosis previously reported for NSHL types I and II is no longer apparent in more intensively treated patients.[9] Nodular LPHL and LRCHL with localised

disease have a tendency to more indolent behaviour and have a relatively good prognosis.[10] Nodular LPHL has features of a low-grade B-cell lymphoma and will be discussed separately later.

11.7 Staging and distribution of disease

The Ann Arbor system[11] of staging (see Table 11.1) was developed to characterise the extent of disease in patients with HL, but is also applied to other lymphomas (not used in entities like CNS lymphoma or mycosis fungoids). It is more useful in HL than non-Hodgkin lymphoma (NHL) because of the common tendency of HL to spread in an orderly way to adjacent lymph node groups.[12] Common patterns of spread were recognised early and formed the basis for the initial clinical trials of extended field radiotherapy.[13] Infradiaphragmatic presentations have been found to have a worse prognosis than supradiaphragmatic[14] presentations; such patients were more likely to be male, elderly and less likely to have nodular sclerosis histology.[15] On the contrary, disease confined to the mediastinum carried a relatively low risk of disease below the diaphragm[16] and was more often seen in females. The nodular lymphocyte predominant subtype was often described with stage I disease confined to the upper neck in younger males.[10,17] The Ann Arbor system was modified at the Cotswolds meeting to include definitions of bulky disease in the CT era (>10 cm), definition of CT criteria for splenic and liver involvement (focal defects), and definition of a new category of treatment response (CR(u)) with persistent radiological abnormalities of uncertain significance.[18]

The staging procedures required in individual cases may be influenced by treatment parameters (e.g. there could be no justification for staging laparotomy if chemotherapy were to be employed in any case), and by the pattern of known disease.

Table 11.1 Ann Arbor Staging System

Stage	Distribution of Disease
I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of diaphragm alone (II) or with involvement of contiguous extralymphatic organ or tissue (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be include the spleen (IIIS) and/or limited contiguous extralymphatic organ or site (IIIE, IIIES)
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement

11.8 Initial patient assessment

When a confident diagnosis of HL is made after an adequate biopsy, a comprehensive assessment of the patient is essential, including a detailed history and examination. Careful recording of the size and distribution of all visible and/or palpable lesions is essential. ‘B’ symptoms, namely weight loss greater than 10% in the past six months, fevers over 38 degrees or drenching night-sweats, should be specifically asked about. Other disease-associated symptoms, such as alcohol-induced pain and pruritis, should be recorded. Co-morbid conditions, such as heart disease, which could influence the tolerance of treatment, should also be recorded. Full dental evaluation is recommended if radiotherapy is planned to the oral cavity or salivary glands.

11.9 Blood studies

Routine haematological and biochemical indices should include full blood counts, LDH, liver function tests, ESR, albumin and creatinine, which either document organ function or provide prognostic information. Thyroid function tests should be performed if the thyroid region is to be

irradiated. A test for HIV should be considered, although it is very rare for HIV infection to present as lymphoma.

11.10 Organ function studies

Baseline lung function tests including DLCO (or oxygen saturation) are recommended if Bleomycin[19] or thoracic radiation[20] are contemplated. If anthracycline-based chemotherapy is to be given, baseline measurement of left ventricular function is recommended.

11.11 Staging procedures

Guideline — Hodgkin lymphoma — staging procedures	Level of evidence	Refs
All patients should undergo CT scans of at least the neck, chest, abdomen and pelvis.	IV	21, 22
Bone marrow biopsy is recommended in at least those cases with stage >IIA.	IV	23
FDG-PET scanning or, if unavailable, gallium scanning, are recommended for staging in all cases. Positron emission tomography (PET) is superior to gallium.	IV	24-27

11.11.1 CT scanning and chest radiography

Chest radiography alone is inadequate to stage the thorax[21]. All patients should undergo at least CT scanning from neck to pelvis.[22] If any site is involved beyond neck to pelvis, it is recommended that baseline CT or MRI studies of the site are performed before commencing therapy, both to facilitate response assessment and to assist in planning radiotherapy if appropriate.

11.11.2 Lymphangiography

This is largely of historical interest, given the disappearance of expertise in this technique with the advent of CT scanning. Unlike CT, it has the capacity to show disease in normal-sized lymph nodes, but positron emission tomography (PET) scanning also has this capability.

11.11.3 Bone marrow examination

Bone marrow aspiration and trephine biopsy have a relatively low yield overall in HL.[28] The incidence of bone marrow involvement was 5% in the German HD4–6 study generation, which included 2307 patients in all stages.[23] The marrow positivity rate is particularly low, less than 1%, in patients without B symptoms[29] and with otherwise stage I–II disease.[30] Nevertheless, despite the extremely low yield in patients with apparently early-stage disease, the procedure is safe and if positive, has a profound impact on the management of the patients with otherwise early-stage disease. Therefore it can be considered even in these cases.

11.11.4 Functional imaging in staging

Cross-sectional structural imaging modalities, such as CT scanning and MRI, are capable of evaluating lymph node size but cannot detect HL in normal-sized lymph nodes or distinguish benign reactive hyperplasia from neoplastic involvement. Additionally, lack of contrast between tumour and normal tissue may make it impossible to visualise disease in sites such as the liver and spleen. Functional imaging can help distinguish benign from malignant nodes and may image disease in the spleen and other organs that is undetected on CT. Scanning with gallium-67[31,32] and positron emission tomography[24-26] (PET) using the radiopharmaceutical F-18 fluorodoxyglucose (FDG) have both been

used in an effort to increase the accuracy of staging in HL. Both gallium and PET scanning may also useful for response assessment, particularly if a baseline study has been performed before treatment commences. Gallium-67 appears to be less sensitive and accurate than PET[27] and also has lower resolution, making interpretation of images more difficult. PET is therefore recommended in preference to gallium scanning for staging in HL. When a functional imaging result is equivocal or may change the treatment strategy, biopsy confirmation may be required.

11.11.5 Staging laparotomy

Staging laparotomy has not been shown to improve survival in randomised trials[33] and is almost never required. It is associated with a small but significant mortality from post-operative complications and a risk of fatal, overwhelming post-splenectomy infection with encapsulated bacteria. There may, however, be rare circumstances, with equivocal imaging results, in which management will be profoundly affected by the results of staging laparotomy. For those centres with the necessary expertise, laparoscopic biopsy of equivocal intraabdominal sites may be a useful alternative to laparotomy. Splenic irradiation is as effective for controlling splenic disease as splenectomy.[34] PET scanning may provide clarification of equivocal structural imaging results and obviate the need for laparotomy in some of these rare cases.

11.12 Assessment of 'bulky' sites

The negative prognostic significance of bulky disease sites was first recognised for mediastinal masses before the advent of CT scanning. According to the classical definition, a bulky mediastinal mass has a maximum transverse diameter greater than one third of the maximum internal diameter of the thorax as measured on a PA chest radiograph. In the thorax and at other sites, a mass of 10 cm or more in maximum diameter measured on CT may also be termed 'bulky'.[18,35] It is important to measure masses in the superior–inferior directions as well as the transverse diameters. In the Stanford V protocol, splenic nodules identified on CT are considered to represent bulky disease.[36] The presence of a bulky site should be recorded.

11.13 Clinically useful prognostic indices

Many prognostic factors have been identified for HL and several prognostic indices have been developed as tools to assist in choosing therapy. For patients with limited stage disease, the EORTC index is useful and widely applied. It is described in Section 11.16.1. The Hasenclever index, developed by the German Hodgkin Disease Study Group (HDSG), is widely used to stratify patients with more advanced disease into prognostic groups.[37]

11.14 Management of Hodgkin lymphoma

11.14.1 General principles

The patient with HL requires expert multidisciplinary supervision at all stages of management. Excellent results are obtained in centres where sufficient numbers of patients are seen to for clinicians to acquire experience of managing this disease.[38,39]

Fertility

Treatment with chemotherapy or pelvic irradiation may lead to infertility and, given the long life expectancy following successful treatment and young age at which many patients present, it is crucial to address reproductive issues before treatment planning commences, except in cases where emergency treatment is required. Where relevant, that is, when treatment carries a significant risk of affecting reproductive function, referral for harvesting and storage of sperm should be made and appropriate specialist consultations arranged to discuss preservation of fertility in female patients. Ovarian transposition may be considered if pelvic radiotherapy is planned, but results of this procedure are variable.[40] Function is more likely to be preserved if the ovary is transposed laterally

rather than medially. Hormonal function is more likely to be preserved than reproductive function.[41] Laparoscopic transposition may be effective[42,43] (see also Chapter 21, including Section 21.2).

Combined-modality therapy

Combined-modality therapy is now used for the majority of patients with early-stage disease and is recommended for all patients with bulky mediastinal masses. The use of combined chemotherapy and radiotherapy offers the potential for both reduced toxicity and superior freedom from progression. Fewer cycles of chemotherapy are generally required and radiotherapy is made less toxic by the use of lower doses combined with smaller radiation fields.[44]

Such treatment protocols require considerable coordination and good working relationships between specialist teams. Early consultations with specialists in both chemotherapy and radiotherapy are recommended to ensure that the proposed combined treatment plan can be safely administered in a timely fashion, and that all relevant investigations, including the imaging studies essential for radiotherapy planning, have been completed.

Surgery

Surgery has no place in the primary treatment of HL but may play a crucial role in obtaining adequate biopsy material for diagnosis, in staging under special circumstances, and in the assessment of residual masses after therapy. PET scanning may reduce the number of cases in which biopsy of a residual mass is required, especially if the scan suggests that residual metabolically-active disease is present. Biopsy may still be required in the presence of a residual mass that is negative on PET.

Radiotherapy

HL is highly radiosensitive. Curative doses of radiation can generally be delivered that are well within normal tissue tolerances. Doses in the range of 35–44 Gy have historically been delivered to wide radiation fields, but it is likely that the dose response curve for radiotherapy alone is flat beyond 40 Gy. In fact, Brinker and Bentzen found no evidence of an increase in efficacy at doses beyond 32.5 Gy.[45] In the combined modality setting, lower radiotherapy doses are effective and 30 Gy or less may be sufficient after chemotherapy. The German HDSG showed no evidence of a relevant radiotherapy dose effect in the range between 20 Gy and 40 Gy in involved fields and extended fields after four months of modern polychemotherapy in patients with intermediate-stage HL.[46] Data from a randomised trial by the same group suggest that 30 Gy is as effective as 40 Gy for treating subclinical disease[47] when radiotherapy alone is given.

Wide-field radiotherapy has a well-established record as a curative therapy in stage I–III Hodgkin disease. When radiotherapy is used as sole therapy, coverage of all tumour sites plus at-risk clinically uninvolved nodal groups is essential because of the high relapse rate with involved-field therapy alone.[48] With analysis of patterns of failure, the classic extended radiotherapy fields evolved and were modified over the years. The most commonly used treatment fields are as follows:

Mantle field

Treatment in continuity of lymph nodes from the base of the skull, usually to the bottom of the 10th thoracic vertebral body, with customised shielding of the lungs and oral cavity. The following lymph node groups are included: cervical, supra and infraclavicular, axillary mediastinal and hilar nodes. Epitrochlear nodes and Waldeyer's ring structures are not included.

Inverted Y field

Treatment in continuity from the bottom of the 10th thoracic vertebral body to the inguinal or femoral nodes, with customised shielding of abdominal viscera and central pelvic structures. The following lymph node groups are included: retroperitoneal nodes of the para-aortic/interaortocaval/paracaval groups, common iliac, internal and external iliac and inguinal nodes with or without femoral nodes.

The spleen is also included in the field, or if the spleen has been removed, the splenic hilar nodes are covered.

Total nodal (TNI) and subtotal nodal irradiation (STNI)

Total nodal irradiation means the sequential administration of mantle and inverted Y fields. Subtotal nodal irradiation is used for stage I–IIA supradiaphragmatic disease and involves the sequential administration of mantle and para-aortic/spleen fields, without irradiation of the pelvis.

Involved-field radiotherapy

Involved-field radiotherapy is the administration of therapeutic radiation to known sites of disease with a margin of normal tissue, without an attempt to give prophylactic treatment to a large volume of clinically uninvolved sites.[49] Involved fields are commonly used in HL and stage I–II intermediate-grade lymphomas following chemotherapy. In stage III–IV HL, involved-field radiotherapy may be given to bulky or residual sites as consolidation therapy. It may also be used as sole treatment for nodular LPHD and for stage I–II low-grade lymphomas. There is no universally agreed definition for an involved field, but guidelines should be developed to reduce variability between centres. Immediately adjacent uninvolved lymph node sites may be included to facilitate design of an anatomically appropriate radiation field. Typically, an involved field will include a 5 cm margin beyond known disease along the axis of the nodal group (most often in the cranio-caudal dimension), and a 2 cm margin laterally, unless constrained by radiosensitive normal tissues such as lung or kidney.

Quality control

Because of the lifelong potential for toxicity from radiotherapy, every aspect of treatment planning and delivery must be of the highest quality.[50] The best available imaging should be used to accurately localise all sites of disease. Appropriate knowledge and training is essential for all staff involved in treatment planning. There can be significant variation between radiation oncologists in the design of mantle fields, but the use of consensus guidelines should reduce the risk of errors in shielding design.[51] A CT-based treatment planning system should be used, if available, to ensure adequate coverage of the planning target volume and to reduce radiation dose to normal tissues to a minimum.[52] Compensators should be used to minimise variations in dose across large treatment volumes.[53] The German HDSG found a high rate of errors in radiotherapy treatment planning when mandatory quality assurance was introduced. In a randomised trial of two radiotherapy doses, they found that patients without radiotherapy protocol violations had significantly better freedom from treatment failure than those with violations (82% versus 70%).[47] They have since instituted a regime of centralised prospective radiation treatment field planning to ensure that radiotherapy quality is maintained.

Chemotherapy

General principles

HL is one of the malignancies most sensitive to chemotherapy. Early studies of single-agent regimens in the 1950s and 1960s showed significant response rates. However, durable responses and apparent cures were rare until the advent of the mechlorethamine, vincristine, procarbazine and prednisolone (MOPP) combination chemotherapy regimen. The enhanced activity against the neoplastic cells exhibited by MOPP was an effect of the different mechanisms of cell killing of the different chemotherapy drugs and their non-overlapping toxicities when given in combination. The concept of ‘cross resistance’ arose. This suggested that resistance could arise to all agents of a particular class of drug, and led to the development of ‘non-cross-resistant’ regimens containing drugs of many different classes. The efficacy of such regimens is consistent with the Coldman-Goldie hypothesis. It soon became clear that dose intensity was important in obtaining the highest cure rates and that treatment should be given as rapidly as recovery from haematological toxicity would permit.

After combination chemotherapy was proven to have high efficacy for advanced disease, subsequent trials showed that it could also reduce the relapse rate and in some circumstances, improve survival

for patients with early-stage disease when combined with extended field radiotherapy. Later trials showed similar efficacy with chemotherapy and involved-field radiotherapy when modern chemotherapy was used (ABVD and similar regimens).

Choice of chemotherapy regimen

Combination chemotherapy is curative in more than 70% of patients with advanced-stage HL and can produce cure rates of more than 90% when combined with radiotherapy in patients with early-stage disease. Numerous combinations of drugs have been shown to be effective, but randomised trials have shown clearly that some regimens are superior to others. Regimens differ in their efficacy and toxicity profiles.

The most commonly used chemotherapy regimens include:

MOPP: mechlorethamine, vincristine, procarbazine and prednisolone. Chlorambucil may be substituted for mechlorethamine to produce the more tolerable ChlVPP or LOPP, which were widely used in the United Kingdom, or by cyclophosphamide to produce COPP.

MOPP was developed at the National Cancer Institute in the mid 1960s.[54] As a result of the acute (mainly neurologic and gastrointestinal[55]) and late toxicities (sterility[56] and secondary leukemia[57]), MOPP has been superseded by other regimens as first-line therapy. MOPP variants may still be used as salvage therapy.

ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine

ABVD was originally developed by the Milan group for treatment of MOPP-resistant disease. It was subsequently proved to be superior to MOPP as first-line therapy. Complete response rates were similar in ABVD and MOPP, but ABVD alternating with MOPP produced superior disease-free survival[58], as did ABVD by itself. ABVD was also less toxic than MOPP, particularly with respect to sterility and secondary leukemia.[59] This regimen has become a widely used standard for the treatment of advanced HL and as part of combined modality treatment of early-stage disease. The risk of pneumonitis caused by bleomycin[60], which may rarely be fatal, can be reduced by limiting the total cumulative dose of bleomycin and by careful attention to lung function.

MOPP/ABV hybrid: mechlorethamine, vincristine, procarbazine and prednisolone alternating with doxorubicin, bleomycin, vinblastine.

MOPP alternating with ABVD (non-cross-resistant) was proven superior to MOPP as above. ABVD therapy given for six to eight months was shown to be as effective as twelve months of MOPP alternating with ABVD. Alternating ABVD and MOPP was later shown to be equivalent to a MOPP/ABV hybrid, in which one half cycle of MOPP was alternated with one half cycle of ABVD within a one-month period.[61] A similar study in the United Kingdom, comparing alternating LOPP-EVAP and hybrid LOPP/EVA, also failed to show evidence of superiority for the hybrid regimen.[62] In a recent randomised trial, MOPP/ABV had similar efficacy to ABVD but was associated with a greater incidence of acute toxicity, myelodysplastic syndrome and leukaemia. ABVD should therefore be considered a standard chemotherapy regimen for treatment of HL.[63,64]

BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone

BEACOPP (standard or dose-escalated) was developed by the German HDSG in an attempt to further improve treatment results of treatment of advanced Hodgkin disease.[65] The dose of individual drugs was increased and given every three weeks. The escalated BEACOPP regimen is administered with granulocyte colony stimulating factor (G-CSF) support. Consolidative radiotherapy is given after completing eight cycles of chemotherapy to initial bulky disease or residual disease. The regimen has

significant acute toxicity, especially in its dose-escalated form, and may be unsuitable for older or less fit patients.

Stanford V doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone

Stanford V is an intensive regimen of short duration, given with involved-field radiotherapy to either bulky sites or all sites, depending on the extent of disease. Remarkably good results have been achieved at Stanford University, but these have not been duplicated at other centres. Early results from a European randomised trial showed that patients treated with Stanford V had worse failure-free survival compared with those treated with ABVD or MEC (P = 0.001)[66], but with no difference so far in overall survival.

11.15 Integration of chemotherapy and radiotherapy

When chemotherapy and radiotherapy are given together as components of combined-modality therapy, chemotherapy is generally administered first and to the full intended doses. Radiotherapy is commenced after enough time has elapsed to allow haematological recovery, typically two to four weeks. It is therefore important that radiotherapy is planned in a timely fashion to prevent long delays. Split-course regimens, with radiotherapy sandwiched between cycles of chemotherapy, are not used. Radiotherapy has traditionally been used as emergency therapy for patients presenting with superior vena cava obstruction. However, there is no evidence that this is a superior strategy to commencing urgent treatment with chemotherapy in those for whom chemotherapy will form part of treatment in any case.

ABVD plus mediastinal radiotherapy may result in overlapping cardiac and pulmonary toxicity. These toxicities may be minimised by limiting the volumes of heart and lung exposed to radiation and limiting the radiation dose.

11.16 Treatment recommendations by disease extent

10.16.1 Early-stage disease

Definition of early-stage disease

The definition of early stages of HL has varied between different authors, but in general, they are those with an excellent prognosis. They were originally defined as those suitable for treatment by radiation therapy alone, namely stages IA, IB and IIA without bulky disease. Patients with these stages have an excellent chance of cure, with 84% ten-year relapse-free rates and 80% ten-year overall survival.

Early stage has been divided further into favourable and unfavourable characteristics, according to the widely used EORTC criteria.[67]

Favourable characteristics are

- number of lymph node sites involved by Hodgkin lymphoma $\leq$3
- age $\leq$40 years
- erythrocyte sedimentation rate $\leq$70

Unfavourable characteristics are

- number of lymph node sites involved by Hodgkin lymphoma >3
- age >40 years

- erythrocyte sedimentation rate >70
- large mediastinal mass (mediastinal mass ratio >1:3)

Based on subgroup analysis of the results of previous trials, the EORTC attempted to identify a *very* favourable group that could be treated by mantle radiation alone. In two trials, the very favourable group had a relapse rate of 40%, which was greater than that seen in the other groups. The concept of a very favourable group has been abandoned for routine practice. The German HDSG is exploring minimal treatment for stage I lymphocyte predominant histology.

Treatment of early-stage disease

Survival after treatment for early-stage HL is generally excellent and does not depend on whether the initial strategy is extended-field radiotherapy, chemotherapy or combined chemotherapy and radiotherapy. In a meta-analysis, Shore and colleagues reported that overall survival at 12 years was the same for patients with early-stage disease managed by initial extended-field radiotherapy or combined radiotherapy and chemotherapy, but relapse-free survival was better with combined modality.[68] Survival was, however, inferior for involved-field radiotherapy alone compared to extended field. In the more recent meta-analysis by Specht, there is a suggestion of slightly better long-term survival in patients treated with combined-modality therapy (12% vs 15% dead from HL at ten years; P = .07).[69]

The aim of treatment in early-stage disease is therefore to achieve cure with the least possible toxicity from treatment while preserving an acceptable rate of freedom from progression. Concern about the risk of breast cancer in females under the age of 30 years has limited the use of mantle radiotherapy in this patient group, which can involve extensive exposure of breast tissue. For other adult patient groups treated with extended field radiotherapy, the risk of second malignancy is much lower. The rate of salvage with chemotherapy after primary radiotherapy is very high, but the reverse is not true. Patients with early relapse after primary chemotherapy are often offered high-dose chemotherapy and autologous peripheral blood stem cell transfusion if they are eligible, and are therefore exposed to risks of myelodysplasia and acute leukaemia. A pilot study in early-stage disease of six cycles of ABVD chemotherapy alone has been reported by a Spanish group[70], although radiotherapy was given to patients with bulky mediastinal disease. This study was too small to draw any reliable conclusions.

Guidelines — Hodgkin lymphoma — approach to treatment	Level of evidence	Refs
Early-stage Hodgkin lymphoma should be subdivided by favourable and unfavourable characteristics and treatment tailored accordingly.	II	66
All subgroups of early Hodgkin lymphoma should be treated with a regimen that covers the spleen, supra-diaphragmatic and para-aortic lymph nodes, such as chemotherapy and involved-field radiotherapy, or subtotal nodal irradiation.	I	34

Target volume for treatment

The lymph node regions that require treatment for early-stage supra-diaphragmatic Hodgkin are the neck, axillae, mediastinum spleen and para-aortic regions. A high incidence of relapse is seen if only the supra-diaphragmatic regions are treated (EORTC H1, and H2 studies).[34]

The options for treating this volume of lymphoid tissue are:

- radiation treatment alone

- chemotherapy alone
- a combination of radiotherapy and chemotherapy.

More than 40 years of randomised clinical trials have helped better define the concept of early HD and its management. The high cure rate with modern treatment strategies has meant that the emphasis of research has been on reducing the long-term side effects.

The management of patients with early-stage disease and favourable characteristics

Radiation alone involves the use of mantle, splenic and para-aortic fields as described above (subtotal nodal irradiation or STNI). Meta-analysis shows significantly better event-free survival with larger radiation fields.[69] Overall survival, however, was not improved. For patients with favourable characteristics, this approach has been shown to be superior to mantle radiotherapy alone (H5 trial)[71] and equivalent to or better than chemotherapy alone (NCI trial[72], Florence–Rome). STNI was accepted as the gold standard for radiotherapy by clinical trials groups (H5, H6, H7, H8, GHSG HD7 trials). The large volume of normal tissues that must be irradiated resulted in unacceptable rates of long-term complications, most notably the development of second cancers.

In an effort to reduce the long-term toxicity, recent trials have tested the use of radiation fields that only cover sites of macroscopic involvement by HL at diagnosis.[73,74] A limited number of courses of chemotherapy were used to treat those sites of subclinical involvement. EORTC H7 and H8 and GHSG HD7 trials showed that the combination of radiotherapy and chemotherapy gave significantly better event-free survival than STNI. In EORTC H8, event-free survival and overall survival were significantly better than STNI.

While there is broad agreement from the randomised clinical trials for the general approach, there are minor differences in the actual treatments delivered. The EORTC has used six cycles of EBVP (H7)[75], three cycles of MOPP/ABV (H8), and in its most recent trial (H9), has reverted to six cycles of EVBP. The GHSG has used two cycles of ABVD (HD7), and in HD10 is comparing two versus four cycles of ABVD. The long-term efficacy of only two cycles of ABVD in combination with involved-field radiotherapy has not yet been established. In the meantime, it is considered safer to rely upon four cycles of ABVD and IFRT until new information becomes available from trials in progress.

Similarly, the radiation dose to the involved field has varied from 36 Gy to 40 Gy. GHSG HD10 is testing 20 Gy, and EORTC H9 is comparing 36 Gy with 20 Gy or no IF-RT.

Guidelines — Hodgkin lymphoma (favourable) — chemo and radiation therapy	Level of evidence	Refs
Early-stage Hodgkin lymphoma with favourable characteristics should be treated by a combination of involved-field radiotherapy and systemic chemotherapy.	II	34
Chemotherapy should consist of four cycles of ABVD* .	II	74
Involved-field radiation therapy should be delivered to all the sites that were involved by Hodgkin lymphoma at diagnosis.	II	34

* This recommendation may change following completion of current studies investigating the use of two or three cycles of ABVD plus involved-field radiotherapy.

Management of patients with unfavourable characteristics

Patients with unfavourable characteristics, including more than three sites of involvement, age >40 years, ESR >70 or bulky involvement, have a high risk of relapse with radiation alone. The minimum treatment is a combination of chemotherapy and radiation therapy.[76]

In the EORTC H5 trial, six cycles of MOPP chemotherapy combined with mantle radiotherapy, when compared with STNI, showed an event-free and overall survival advantage (EFS 83% versus 66%, and overall survival 88% versus 75%, respectively). A comparison of MOPP plus IF-RT or ABVD plus IF-RT showed no difference in outcome (H6).

EORTC H7 showed that less intensive chemotherapy with six cycles of EBVP plus IF-RT was inferior to six cycles of MOPP/ABV plus IF-RT. Preliminary results from H8 show no difference between four and six cycles of MOPP/ABV plus IF-RT. The current study H9 compares six cycles of ABVD plus IF-RT with four cycles of BEACOPP plus IF-RT. A randomised trial from India showed that IF-RT improved event-free survival and overall survival in patients with unfavourable stage I–II disease after a complete response to six cycles of ABVD.[77]

Guidelines — Hodgkin lymphoma (unfavourable) — chemo and radiation therapy	Level of evidence	Refs
Early-stage Hodgkin lymphoma with unfavourable characteristics should be treated by a combination of involved-field radiotherapy and systemic chemotherapy.	II	75, 76
Chemotherapy should consist of six cycles of ABVD.	II	75, 76
Involved-field radiation therapy should be delivered to all the sites that were involved by Hodgkin lymphoma at diagnosis.	II	75, 76

11.16.2 Advanced-stage disease

Definition of advanced-stage Hodgkin lymphoma

The advanced stages of HL are those with a less than excellent prognosis. As with limited disease, there are significant variations between different series in the patients that comprise this group. Stages in the advanced-disease category, for the purposes of these guidelines, are stages I–II with bulky mediastinal mass, IIB, IIIA-B and IV-B. At all stages of disease, cure is possible with chemotherapy or combined-modality therapy, and long-term survival exceeds 50% for all groups.

Management of advanced-stage disease

Chemotherapy is the mainstay of therapy for patients with advanced HL. Apart from a favourable group of patients with stage IIIA disease who could be cured with total nodal irradiation, the outlook for patients with advanced disease was uniformly dismal until MOPP combination chemotherapy was developed at the National Cancer Institute in the mid 1960s.[54] This produced cure rates of over 50% of patients with stage III–IV disease[78] and revolutionised the management of HL.

Patients with advanced HL require more cycles of chemotherapy to obtain optimum freedom from progression and survival compared to early-stage patients treated with combined-modality therapy. Recent evidence suggests that patients with advanced disease and multiple adverse prognostic factors may benefit from the use of chemotherapy that is more intensive than ABVD.

Guideline — Hodgkin lymphoma — advanced disease	Level of evidence	Refs
Chemotherapy should be used for all patients with advanced Hodgkin lymphoma.	III	78, 79

In the pre-chemotherapy era, it was recognised that patients with limited stage IIIA disease, with infradiaphragmatic involvement confined to the upper abdomen (stage III1A), had a better prognosis,

when managed with extended-field radiotherapy than other stage IIIA patients (stage III2A). MOPP chemotherapy improved freedom from progression and survival for these patients when added to radiotherapy in non-randomised studies. Patients with stage III1A and stage III2A treated by radiotherapy alone had DFS survivals of 64% and 32% respectively. Survival was better when radiotherapy was combined with chemotherapy.[79] With the advent of more effective chemotherapy regimens such as ABVD, this distinction is no longer clinically relevant. Wide-field radiotherapy no longer forms part of first-line therapy for these patients.

Hasenclever prognostic index for patients with advanced Hodgkin lymphoma

Hasenclever and Diehl studied analysed data on more than 5000 Hodgkin's disease patients for prognostic features. Multivariate analysis identified seven prognostic factors. Each factor contributed about a 7% decrement in freedom-from-progression (FFP) at five years, according to an analysis in 1618 patients. The international prognostic score may permit comparisons of populations across studies and can be used in the evaluations of outcome. In a randomised trial, BEACOPP was superior to COPP/ABVD in each of three prognostic groups (international prognostic score 0–1, 2–3, 4+), but the most striking difference was among patients in the highest risk group.[80]

The Hasenclever index is as follows:

1. a serum albumin level of less than 4 g per decilitre
2. a haemoglobin level of less than 10.5 g per decilitre
3. male sex
4. an age of 45 years or older
5. stage IV disease (according to the Ann Arbor classification)
6. leukocytosis (a white-cell count of at least 15,000 per cubic millimetre)
7. lymphocytopenia (a lymphocyte count of less than 600 per cubic millimetre, a count that was less than 8% of the white-cell count, or both)

The score predicted the rate of freedom from progression of disease as follows:

0 factors (7% of patients), 84%

1 factor (22% of patients), 77%

2 factors (29% of patients), 67%

3 factors (23% of patients), 60%

4 factors (12% of patients), 51%

5 factors or higher (7% of patients), 42%

Treatment recommendations in advanced Hodgkin lymphoma

Choice of chemotherapy regimen

Over the years, sequential randomised trials in North America and Europe have gradually selected a small group of chemotherapy regimens with high efficacy and low levels of late toxicity. ABVD is the most widely used of these regimens. It exhibits low toxicity mainly because of the avoidance of an alkylating agent. As discussed above, ABVD produces disease control comparable to or superior to

alternating MOPP and ABVD or MOPP/ABV hybrid regimens, with frequent preservation of fertility and a low leukaemia rate.

The efficacy and safety of alternating MOPP and ABVD or hybrid regimens was studied in two comparative phase III trials. In the Milan study, stage IB, IIA bulky, IIB, III A and B, and IV patients received MOPP/ABVD or hybrid MOPP and ABVD, each for a minimum of six cycles followed by 30 Gy to initial sites of bulky disease.[81] At ten years, the FFP rate was 67% versus 69% (p = NS) and the overall survival rate was 74% versus 72% for the alternating and hybrid regimens, respectively (p = NS). A total of 23 second malignancies were documented among 427 patients, including 11 secondary leukaemias.

Guideline — Hodgkin lymphoma (advanced) — chemotherapy regimen	Level of evidence	Refs
ABVD chemotherapy is recommended as a standard chemotherapy regimen for advanced Hodgkin lymphoma patients with an international prognostic score <4.	II-IV	64, 65
ABVD is superior to alternating MOPP/ABVD or MOPP/ABV hybrid because of lower toxicity.	II	64, 65

Optimum number of cycles of chemotherapy in advanced disease

Guideline — Hodgkin lymphoma (advanced) — chemotherapy regimen	Level of evidence	Refs
Chemotherapy should be given for a minimum of six cycles.	IV	64, 65
A minimum of two further cycles of chemotherapy should be given after a complete response as been attained.	IV	64, 65

Management of the patient with multiple adverse risk factors

The German HDSG randomised 1201 patients with advanced-stage disease to COPP/ABVD, BEACOPP, or to increased-dose BEACOPP, with most patients receiving consolidative radiation therapy to sites of initial bulky disease (>/=5 cm). Patients included those with stages IIB and IIIA, patients with risk factors, and stage IIIB and IV patients. After eight chemotherapy cycles, initial bulky sites received 30 Gy and residual disease sites received 40 Gy. On this basis, the majority of patients received consolidative radiotherapy. At five-year overall survival was 83% for COPP/ABVD, 88% for BEACOPP, and 91% for increased-dose BEACOPP The actuarial rate of secondary acute leukaemias five years after diagnosis of HL was 0.4% for COPP/ABVD, 0.6% for BEACOPP, and 2.5% for increased-dose BEACOPP.[80]

Stanford V chemotherapy involves a similar aggressive approach with multiple chemotherapeutic agents. After twelve weeks of chemotherapy, patients receive 36 Gy consolidative radiotherapy to initial disease sites > 5 cm or macroscopic splenic disease.[36],[40] A group of 142 patients with bulky stage II, III or IV HL were treated with Stanford V and followed a median of six years.[10] Six-year FFS was 89% and OS was 96%. No secondary leukaemia or myelodysplasia occurred. Fertility was preserved in a significant proportion of both men and women as evidenced by a total of 43 conceptions post-treatment.

No group of patients with advanced HL has been identified with a prognosis so poor that high-dose therapy and autologous stem cell transplantation is recommended as part of initial therapy.[82] Due to its efficacy and acceptable toxicity, the standard-dose BEACOPP regimen is recommended as a suitable treatment for younger fit patients with multiple adverse factors.

Guideline — Hodgkin lymphoma — prognostic score — stem cell use	Level of evidence	Refs
BEACOPP (standard dose) should be considered in patients younger than 65 with advanced Hodgkin lymphoma and a prognostic score ≥4.	II	80
There is no group of patients that can be prospectively identified with a prognosis so poor that high-dose chemotherapy and haematopoietic stem cell transplantation can only be recommended for relapsed patients as primary treatment.	IV	82

Use of radiotherapy in patients with advanced disease but without bulky mediastinal mass

The use of combined-modality therapy for advanced disease remains controversial. It has not been adequately investigated in prospective randomised trials. The Southwest Oncology Group (SWOG) study of MOPP/BAP[83] with or without RT and the EORTC–GPMC trial of MOPP/ABV with or without RT routinely irradiated patients who achieved less than complete remissions.[84] The subsequent outcomes for these patients were excellent and suggested a benefit from radiotherapy. The SWOG trial showed no improvement in overall survival, but showed prolonged disease-free survival in radiotherapy-treated patients, especially those with bulky disease. A recently published analysis of the EORTC–GPMC trial reported the results for 421 patients who obtained a complete remission after 6–8 cycles of MOPP/ABV and were randomised to 16–24 Gy involved-field radiotherapy to all initially involved sites, or no further treatment. There was no benefit from radiotherapy[85] in patients who had achieved complete remission.

Guideline — Hodgkin lymphoma — optimal radiotherapy	Level of evidence	Refs
Radiotherapy is not recommended after modern chemotherapy as routine treatment to non-bulky sites in advanced Hodgkin lymphoma that have attained complete response.	II	85
In bulky sites and in sites that fail to achieve complete remission after chemotherapy, radiotherapy can improve freedom from progression in advanced Hodgkin lymphoma.	II	83, 84

Management of the patient with a bulky mediastinal mass

Guideline — Hodgkin lymphoma — bulky mediastinal mass	Level of evidence	Refs
Consolidative involved-field radiotherapy is recommended after chemotherapy for patients with bulky mediastinal masses.	IV	83
Chemotherapy should be given for a minimum of six cycles.	II	83, 84

11.17 Management of Hodgkin lymphoma with special features

11.17.1 Management of nodular lymphocyte predominant Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has a more indolent behaviour than any of the other histological types and has immunophenotypic characteristics of a low-grade B-cell lymphoma of follicle centre cell origin (see Section 11.5.1). In randomised trials, NLPHL has been grouped with other HL variants, despite its different behaviour. The great majority of patients have

stage I–II disease at presentation and there is a male predominance. Diehl and colleagues reviewed the outcome for patients from 17 centres in Europe and the United States and confirmed that, with adequate treatment, survival is superior for patients with NLPHL compared to the classical or lymphocyte-rich variants, at least partly due to their younger age and other favourable prognostic factors at presentation.[10] Relapses are common with advanced NLPHL and occur later than those of other HL variants, but do not have the same grave prognostic significance. However, there is no continuing pattern of late relapses, as seen in follicle-centre lymphoma. Most patients with early-stage disease are cured by their primary treatment.[86-88]

Excellent long-term survival and freedom from treatment failure (>80%) has been attained in stage I–IIA disease with extended field radiotherapy. Salvage therapy is usually effective. Mantle radiotherapy alone can produce excellent results in supradiaphragmatic disease.[89] Relapses within radiation fields treated to 36–40 Gy are rare. Patients with non-bulky stage IA disease have been treated with involved-field radiotherapy with excellent results.[86] No randomised trials have addressed the question of whether chemotherapy leads to improved survival when combined with radiotherapy specifically in NLPHL. There are no reliable data on the long-term outcome of stage I–II disease treated with chemotherapy alone, although relapses at sites of previous involvement are common with this modality. Response rates for patients with advanced disease treated with chemotherapy are high but relapse is common, although survival, even with multiple relapses, is usually long. The optimum chemotherapy regimen for NLPHL has not yet been established, but standard HL regimens are effective. There is currently insufficient evidence to support 'watchful waiting' as an appropriate initial management strategy, but in children with indolent NLPHL, some authors have reported that no further treatment may be necessary in selected cases after complete surgical excision.[90,91] Patients with advanced disease resistant to chemotherapy may respond to Anti CD-20 antibody therapy with rituximab.[92]

Guideline — Nodular lymphocyte predominant Hodgkin lymphoma	Level of evidence	Refs
Stage I–IIA nodular lymphocyte predominant Hodgkin lymphoma should be treated with radiotherapy	IV	86, 89
Involved-field radiotherapy should be used for non-bulky stage IA nodular lymphocyte predominant Hodgkin lymphoma.	IV	86, 89

11.17.2 Management of Hodgkin lymphoma in pregnancy

The prevalence of HL in women of childbearing age inevitably leads to diagnosis of some cases of this disease during pregnancy. The conflicting requirements to (a) institute optimum treatment of the malignancy as soon as possible, and (b) avoid harm to the foetus, can lead to difficult management dilemmas. Nevertheless, good treatment outcomes are usually achieved. Lishner et al. reported that a cohort of 40 pregnant patients with HL fared just as well as a set of matched controls.[93] There are no randomised clinical trials in pregnant patients with HL. Management is influenced by the extent and anatomic location of the disease and by the age and viability of the foetus, and therefore must be individualised in each case. Patients with a viable foetus should have an early delivery when this is safe. In other cases, treatment may be delayed for weeks or even months until the foetus can be delivered safely, if there is no critical need for immediate therapy and the disease status is closely monitored.[94] In many cases, however, therapy must be commenced during pregnancy and treatment may differ from the usual recommendations for treatment in non-pregnant patients because of the need to protect the foetus. A decision may be taken to terminate the pregnancy to facilitate timely treatment. Some authorities have recommended the termination of pregnancy when HL is diagnosed in the first trimester or if chemotherapy has been delivered inadvertently during this period[95], with its associated risks of teratogenesis and foetal growth retardation. Ultimately, the choice of treatment strategy must be decided by the patient with as much support and information from the multidisciplinary team as possible.

Staging in pregnancy

Staging workup in pregnancy is limited by the risks of radiation exposure to the foetus, especially in the first trimester. CT scanning is therefore avoided but plain radiographs of the chest cause insignificant foetal radiation exposure and are safe. MRI scanning involves no ionising radiation exposure and is the cross-sectional imaging technique of choice in pregnancy.[96] Abdominal and pelvic ultrasound may also be useful. The Society of Nuclear Medicine recommends against any radionuclide scanning during pregnancy, but recognises that this advice needs to be balanced by the maternal risks of inadequate diagnosis and the potential of inappropriate treatments being more injurious to the developing fetus.[97] If functional imaging is essential for adequate treatment planning, the short physical half-life and fairly rapid urinary excretion of FDG, allowing minimisation of foetal exposure by catheterisation or frequent voiding, combined with good hydration/diuresis, make FDG-PET scanning a better choice than Ga-67.

Treatment of pregnant patients with non-bulky stage I–II supradiaphragmatic disease with radiotherapy

Supradiaphragmatic radiotherapy has been used successfully during pregnancy[98] and avoids exposure of the foetus to chemotherapy, which can be administered after the pregnancy is completed. The foetal radiation exposure is related to the size and position of the uterus, the extent and location of the radiation field, and the use of shielding of the uterus. Radiotherapy should be avoided completely in the first eight weeks of gestation. In phantom studies simulating a patient with a first trimester pregnancy treated to 40 Gy, treatment of the neck and axilla, but not the mediastinum, led to radiation doses to the foetus of less than 0.1 Gy without shielding of the fetus.[99] For local field irradiation in the region of neck-mediastinum, and for mantle treatment, the radiation dose to a shielded embryo was 0.028–0.186 Gy and 0.042–0.245 Gy depending upon the distance from the field isocenter and the field size used, respectively. The corresponding dose for an unshielded foetus always exceeded 0.1 Gy. Therefore it is recommended that the radiation field should be as distant from the uterus as is consistent with providing adequate tumour coverage, and that shielding should be used to minimise foetal exposure. Upon delivery of the child, combined-modality therapy can be safely completed. An alternative strategy is to use initial chemotherapy as discussed below.

Treatment of pregnant patients with bulky mediastinal mass, stage III or IV disease, or infradiaphragmatic disease, using chemotherapy

Patients with disease in these categories generally require chemotherapy as first-line therapy because they have advanced disease or because they cannot receive radiotherapy during pregnancy due to the risks of radiation exposure to the foetus. Chemotherapy options in pregnancy include the use of a single agent, such as vinblastine[100], to buy time until definitive therapy can be given, or immediate treatment with multi-agent chemotherapy at full doses.[101,102] Successful deliveries of healthy babies have occurred with a range of chemotherapy regimens. No data exist to support any particular regimen as the treatment of choice in pregnancy, although it is reasonable to avoid or minimise exposure to alkylating agents.

11.17.3 Management of Hodgkin lymphoma in the elderly

Elderly patients have inferior progression-free survival and higher mortality from HL. They are also more likely to die with intercurrent illness or suffer a fatal toxicity from treatment. Disease in elderly patients appears on average to be more biologically aggressive[103], with a higher percentage of patients with B symptoms, advanced disease and unfavourable histology.[104] More aggressive disease, combined with a reduced capacity to undergo aggressive treatment, can make management of older patients technically challenging. Studies with MOPP/ABV hybrid and BEACOPP show that these regimens are much more toxic in elderly patients, and suggest that they should be given with caution, if at all, to persons over the age of 60 years. Forsyth and colleagues concluded that ‘the main reason for the poorer prognosis of patients aged 70 years and over was the increasing difficulty of

chemotherapy delivery associated with advancing age'.[105] The cumulative doses of doxorubicin and bleomycin in ABVD can pose particular problems for senior patients.

Nevertheless, it is important not to be nihilistic. HL is potentially curable in the elderly. Where possible, older patients should be treated with curative intent, particularly if they are found to have good organ function, including pulmonary and cardiac, and have disease with otherwise favourable characteristics. Similar principles apply to their management as to the management of younger persons with HL. Better results are likely to be achieved in elderly patients with early-stage disease with combined-modality therapy.[106]

11.17.4 Standard response categories for Hodgkin lymphoma

As discussed in Section 11.7, treatment response criteria for HL were revised at the Cotswolds meeting. The criteria, which are given below, are also widely used in response assessment for patients with NHL and other types of lymphoma.

Complete remission (CR) — The patient has no clinical, radiological or other evidence of HL, although changes due to treatment (e.g. radiation fibrosis) may be noted.

Complete remission unconfirmed/uncertain (CR[u]) — The patient has residual stable abnormalities of uncertain significance on structural imaging (e.g. CT) at sites of known involvement by HL after attaining an excellent partial remission. Clinically, and on ESR criteria, the patient should have no other evidence of disease, with functional imaging (PET or gallium) being negative. Criteria for assigning CR[u] to various sizes of lymph nodes have been determined by some groups.[107]

Partial remission (PR) — This is defined as a decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions. There should be resolution of B symptoms and no new lesions.

Progression of disease (PD) — This is defined as 25% or greater increase in the size of at least one measurable lesion, or the appearance of new lesions, or recurrence of these symptoms.

11.17.5 Response assessment during therapy course

No level II evidence is available to define the optimal timing of response assessment during treatment. The rate of response of lesions as assessed by structural imaging modalities such as CT is variable. Residual masses are common after treatment. Functional imaging with PET or gallium scanning may facilitate earlier response assessment than CT scans.

The recommendations for response assessment depend on the treatment modality.

- Assessment of response after definitive radiation therapy alone

  Clinical, radiological, functional imaging and biochemical, full blood count (FBC), erythrocyte sedimentation rate (ESR) assessment should be performed 4–6 weeks after completion of treatment. There is no role for response assessment during therapy.

- Assessment of response after chemotherapy alone or after chemotherapy followed by radiotherapy

  Physical assessment is recommended before each planned cycle. The timing of radiological response assessment may vary with the planned number of cycles and depend on whether radiotherapy is to be given to all involved sites after chemotherapy. As a minimum, at least one interim assessment should be made before the planned chemotherapy is completed, and a further assessment should be made upon completion of therapy if the first assessment did not show a complete response. Upon completion of all therapy, clinical, radiological, functional imaging and

biochemical, FBC and ESR assessment should be performed. Functional imaging reassessment is unnecessary after treatment if an interim response assessment showed complete response.

11.17.6 Functional imaging

The predictive value of intercycle review in determining outcome remains unclear. Response assessment using gallium in 37 patients after the fourth cycle of chemotherapy showed gallium negativity to be associated with very low risk of relapse.[108] Assessment following one cycle of chemotherapy is also reported to have prognostic influence with a negative predictive value of 92% but a positive predictive value of only 57%.[109] The prognostic influence of gallium and PET intercycle and following treatment may be stage-dependent. The negative predictive value for gallium post-treatment in patients with stage I–II disease was 94% as compared with 64% for patients with stage III and IV disease.[32] The positive predictive value for PET performed post-treatment ranges from 60% to 100%. The negative predictive value has ranged from 74% to96%.[25,110,111] Response assessment during therapy remains a clinical research question. Current studies of functional imaging do not permit recommendations on changes to treatment policies.

11.17.7 Response assessment at completion of treatment

This has been arbitrarily set at four to six weeks for clinical, radiological, biochemistry, FBC and ESR. Functional imaging can be performed two to three weeks following chemotherapy and radiotherapy, allowing for physiologic uptake due to thymic hyperplasia, bilateral hilar and diffuse lung uptake. Response assessment criteria have changed to be consistent with the Cotswolds revision of the staging system for Hodgkin disease in 1989[18] as discussed in Section 11.7. A new category of response was added, CR[u] (unconfirmed/uncertain complete remission), acknowledging that patients with HL can have a residual structural abnormality following treatment, which does not indicate persistent lymphoma.

Guideline — Hodgkin lymphoma — CT and PET scanning	Level of evidence	Refs
Functional imaging is recommended in addition to CT scanning to assess definitive response to treatment.	IV	25, 32, 108, 110
PET scanning rather than gallium scanning is recommended for response assessment after treatment for Hodgkin lymphoma.	IV	25, 110, 111

Other predictors of relapse

A change in ESR following treatment was found to be a strong predictor of relapse and survival for patients with early-stage HL treated in the H2 and H5 trials by the EORTC.[112] Relapse predictors included patients with a persistently elevated ESR (defined as >30 mls/hr), patients with a normal ESR before therapy but oscillating between normal and elevated following therapy, and those patients with an elevated ESR before therapy, but oscillating between normal and elevated after therapy.

Role of biopsy in the assessment of residual mass

When the only evidence of persistent disease is that on functional imaging and CT, and this significantly alters treatment policy (e.g. proceeding to high-dose therapy and autograft), a biopsy should be performed.

Follow-up recommendations to detect relapse

These recommendations are largely arbitrary. The small number of studies in this area would question the value of repeating multiple biochemical analyses, FBCs and ESR.[107,113] In one study of 709

patients with stage I and II disease, 69% of relapses were suspected primarily by history and physical examination.

Recommendations

Clinical review is recommended three-monthly during the first and second year, four-monthly during the third year, six-monthly in the fourth and fifth years, and annually thereafter.

The type of imaging investigations and frequency may depend on the sites of original disease. Note that these recommendations do not take into account second malignancies, which are addressed under long-term follow up.

Long-term follow up to detect complications of therapy

For early and advanced-stage patients, the risks of death due to causes other than HL exceed those due to HL at 13–15 years. The relative risk of mortality for these patients remains significantly elevated more than 20 years following treatment.[114,115]

Recommendation

Follow up of patients treated for HL should be indefinite. The optimal frequency of follow up is uncertain, but should be at least annually after five years. Patients should be informed of the increased risk of second malignancies and encouraged to seek early medical attention. Similarly, the general practitioners of patients should be aware of the increased risk of second malignancies in patients undergoing long-term follow up.

Specific investigations and clinical assessments

Thyroid function tests

For patients having radiotherapy to the neck, thyroid function tests (TSH, T4) should be performed yearly for an indefinite period following treatment.[116] Hypothyroidism can occur from the first year following treatment up to and beyond twenty years.

Clinical examination of the thyroid

There is an excess risk of thyroid cancer. An annual examination of the thyroid gland is advised. Any thyroid abnormality, in particular any nodule, should be fully investigated.

Full blood count

The risk of leukaemia and myelodysplastic syndrome (MDS) is maximal between three and 12 years following treatment.[117] Accordingly, a yearly FBC should be performed.

Chest x-ray

There is an increased risk of lung cancer following chemotherapy and radiotherapy for HL.[118,119] Smoking in this population significantly increases the risk of lung cancer. Therefore all patients should be encouraged to stop smoking.[120] The role of routine chest radiography is unclear and no specific recommendation is possible.

Mammography

There is an increased risk of breast cancer in women previously treated with mantle irradiation alone or in combination with chemotherapy. The majority of studies indicate this increased risk is restricted to women undergoing radiotherapy at the age of thirty or younger, although excess absolute risk has been seen in older patients.[121,122] The increased risk of breast cancer is apparent ten years after treatment and this risk persists more than 25 years after diagnosis of HL.

Women should receive information about the potential increased risk of breast cancer. Mammographic screening should begin ten years following treatment and to be performed yearly and

in conjunction with breast self examination.[123] The use of mammography in women younger than thirty years remains controversial. Any breast mass developing in women previously irradiated for HL should be investigated. This may include ultrasound and biopsy.

Chemoprevention

There is no established role for chemoprevention in relation to breast cancer in this patient group.[124]

11.17.8 Management of primary refractory Hodgkin lymphoma

Patients who experience progressive disease during chemotherapy-based induction therapy or who have disease progression within 60 days of completing induction therapy have 'primary refractory' HL.[125] Their prognosis is poor and survival with conventional-dose salvage chemotherapy is less than 10% at ten years. The best chance for long-term survival in primary refractory disease is with high-dose chemotherapy and autologous stem cell transplantation (ASCT)[126] although primary refractory patients have inferior survival compared to patients treated with ASCT who relapsed after attaining a complete remission. In highly selected cases, radiotherapy may achieve long-term survival, but this may best be delivered in conjunction with high-dose therapy and ASCT.

Guideline — Primary refractory Hodgkin lymphoma	Level of evidence	Refs
Patients with primary refractory Hodgkin lymphoma should be treated with high-dose chemotherapy and autologous stem cell transplantation.	IV	126

11.17.9 Management of relapsed Hodgkin lymphoma

The rate of relapse after primary treatment for HL is related to the initial management strategy, the original extent of disease, and the influence of other prognostic factors. The relapse rate for early-stage patents is lowest in those treated with combined-modality therapy, and is higher in patients treated with radiotherapy or chemotherapy as single modalities. The relapse rate in advanced-stage disease is most accurately predicted by the international prognostic index. Due to the difficulty of assessment of residual masses and the possibility of change in histology or development of a NHL, it is recommended that recurrence is confirmed by biopsy before embarking on salvage therapy. The choice of salvage therapy is dependent upon the initial treatment strategy, the extent of relapsed disease, and the time that has elapsed from completion of primary treatment.

Key point

Biopsy is recommended to confirm first recurrence in all cases.

Relapse after initial radiation therapy

Combination chemotherapy without high-dose therapy results in durable ten-year disease-free and overall survival[127,128]. It is the treatment of choice for relapse after radiotherapy. ABVD chemotherapy is recommended if there are no contraindications to its use. If there is a localised relapse outside the original radiation field, consolidation involved-field radiotherapy to the relapsed disease may improve progression-free survival.

Relapse after initial combination chemotherapy treated with conventional chemotherapy only at relapse

The prognosis for patients who relapse after initial combination chemotherapy is determined mainly by the duration of the first remission. Patients whose initial remission after chemotherapy was shorter

than one year (early relapse) do much worse than those with late relapses (relapses after more than one year)[129,130] and have the most to gain from aggressive treatment strategies.

11.17.10 Relapse within one year

Relapse after initial combination chemotherapy—role of high-dose chemotherapy and haematopoietic stem cell transplantation.

Relapse after initial combination chemotherapy should be treated with re-induction with a chemotherapy regimen, followed by high-dose chemotherapy and ASCT[131-133] Patients who are responsive to re-induction with second-line chemotherapy have a better prognosis. Complete remission rates with ASCT are higher if only one previous chemotherapy regimen has failed, compared to two or more treatment failures. ASCT has been associated with higher rates of freedom from treatment failure than conventional-dose salvage chemotherapy in randomised studies.[134,135]

Myeloablative allogenic transplantation is inferior to ASCT because of the high mortality associated with the procedure and subsequent complications associated with graft versus host disease.[136]

Relapse after initial combination chemotherapy—role of involved-field radiation post ASCT

Involved-field radiation therapy for residual masses after high-dose therapy results in improved progression-free survival.[137,138] It is uncertain whether there is a significant effect on overall survival.

If high-dose therapy is contraindicated

Salvage chemotherapy with or without consolidation radiotherapy is recommended in patients who are fit enough for a curative approach.[139]

11.17.11 Relapse after one year

Relapse after initial radiation therapy

Salvage conventional chemotherapy is recommended, as above, if primary treatment was radiotherapy.[127,128]

Relapse after initial combination chemotherapy

Salvage chemotherapy with or without radiotherapy should be used if high-dose therapy is relatively or absolutely contraindicated.[135] High-dose therapy incorporating ASCT also improves freedom from treatment failure in this subgroup[135] and in particular, may be considered in high-risk subgroups. The ideal choice of salvage chemotherapy for patients who are not treated with high-dose therapy and stem cell transplantation is not known. The original regimen or a non cross-resistant one may be used.

Radiotherapy for localised relapse

In highly selected patients with only limited nodal recurrence following initial chemotherapy, radiation therapy (with or without additional chemotherapy) may provide long-term survival of up to 50%.[140,141]

Palliation of patients who have had multiple relapses

Once curative options are exhausted, symptoms may respond to single-agent palliative chemotherapy[142] or to localised radiotherapy (level III). Recruitment into clinical trials is recommended.

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CHAPTER 12 LOW-GRADE LYMPHOMA

12.1 Introduction

Concepts have changed with the introduction of the WHO classification. While the most common form of 'low-grade' lymphoma, follicular lymphoma, remains largely unchanged by this classification system, many other disorders are clearly recognised as distinct clinicopathological entities for the first time (e.g. splenic marginal zone lymphoma).

Many of these entities have a low incidence. Studies utilising the WHO classification are infrequent. A difficulty with treatment recommendations is the 'relapsing and remitting' natural history of these malignancies. The overall survival of patients is influenced by the initial therapy used and subsequent therapies given for relapsed or recurrent disease.

The highest priority of treatment is to maximise patients' overall survival, maintain quality of life and avoid treatment-related morbidity. However, it is difficult to demonstrate any influence of these end-points in a single clinical trial. This reflects the long natural history of these disorders, the effects of sequential therapies, and competing causes of unrelated death in an often elderly population.

Few individual studies have demonstrated an impact on overall survival. There is now evidence that where novel treatment strategies have been serially employed within a single institution, there has been step-wise improvement in overall survival over the decades.[1] It is not clear which components of these therapies are responsible for this improved survival.

Conversely, where initial treatment strategies have remained consistent and utilised therapies based on alkylating agents, there has been no such improvement in survival, demonstrating that the natural history of these disorders has not altered with time, and that supportive care alone does not explain the improvements.[2] For these reasons, reliable 'surrogate end-points' are sometimes used to define treatment recommendations. These include overall response rates, complete remission rates, and 'molecular' complete remission rates. Where recommendations have been based upon these 'surrogate' end-points, the data supporting their validity are summarised.

The topics included in this chapter are:

- follicular lymphoma (grade 1 and 2)
- small lymphocytic lymphoma
- extranodal marginal zone B-cell lymphoma
- nodal marginal zone B-cell lymphoma
- lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinaemia)
- splenic marginal zone lymphoma

12.2 Epidemiology

While there are marked variations in the absolute and relative incidence of these disorders in different geographic regions[3], the relative proportion of consecutive cases of NHL comprising each of these entities in a Western society has been estimated to be[4]:

- follicular lymphoma — 22%
- small lymphocytic lymphoma — 7%

- extranodal marginal zone B-cell lymphoma — 8%
- nodal marginal zone B-cell lymphoma — 2%
- lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) — 1%
- splenic marginal zone lymphoma — <1%

Unfortunately, there is incomplete population-based incidence data from Australia using the currently recommended histologic classification system.

12.3 Staging

In addition to investigations directed by the history and clinical examination, staging requirements include:

- CT scanning of the chest/abdomen/pelvis
- full blood examination and manual differential with flow cytometry if there is a lymphocytosis or morphologically abnormal lymphocytes present, Coomb's test
- bone marrow aspirate and biopsy, with a minimum total length of 2.0 cm and at least four levels examined[5,6]
- full biochemical profile including uric acid, LDH, β_2-microglobulin, and serum protein electrophoresis.

In specific circumstances there may be requirements for other studies, such as hepatitis C serology in patients with splenic marginal zone lymphoma.[7]

In patients with follicular lymphoma, where 'molecular remission' is the therapeutic goal, it is mandatory to establish the presence of a disease-specific molecular marker in the diagnostic tissue, blood and marrow of that patient before the commencement of therapy, for example, *bcl-2* gene rearrangement (see Chapter 7).

12.4 Follicular lymphoma

Summary of representative clinicopathological findings

Clinical	Usually adults >20 years. Often widespread at diagnosis, with splenic and marrow involvement, but often asymptomatic. Rare paediatric variant often localised.
Morphology	Most cases at least partly follicular: >75% follicular — 'follicular' 25–75% follicular — 'follicular and diffuse' <25% follicular — 'partly follicular' Diffuse areas may be sclerotic. Cytology: small and large cleaved cells (centrocytes) and large non-cleaved cells (centroblasts). Grade 1: 0–5 centroblasts per hpf Grade 2: 5–15 centroblasts per hpf Grade 3: >15 centroblasts per hpf Grade 3a: centrocytes present Grade 3b: solid sheets of centroblasts *Variants*: i. Purely diffuse (grades 1 and 2 only) ii. Cutaneous iii. Marginal zone differentiation (10%). iv. Floral variant versus signet ring cell variant, vi. FL with plasmacytic differentiation vii. Paediatric cases usually grade 2 or 3 Any component of diffuse large B-cell lymphoma is reported separately
Immunophenotype	SIg + (occasionally SIg-ve), *bcl-2* +, CD10+, CD19+, CD20+, CD22+, CD79a+, *bcl-6*+, CD5-, CD43-, CD21+, CD23+, CD35+ FDC meshworks outline follicles. Rare paediatric cases usually *bcl-6*+, CD10+ but *bcl-2* negative.
Cytogenetics	t(14;18)(q32;q21) (*BCL2*) (except in paediatric cases) Variant: t(2;18)(p12;q21) Many additional abnormalities including 17p13 (*TP53* gene)

12.4.1 Follicular lymphoma, grade 1 and 2 ('low-grade')

Localised disease (stage I and II)

Accurate staging

Patients with stage I–III who are being considered for curative therapy with radiotherapy should undergo staging with either thallium or PET scanning, as up to 70% of patients will have more extensive disease revealed.[8,9] Gallium scanning is less sensitive.[9] Attention to the bone marrow biopsy is important, and at times, either repeat biopsy or examination of further levels of the initial biopsy may be necessary to exclude minimal disease infiltration.[5,6]

Guidelines — Low-grade lymphoma — staging pre-radiotherapy	Level of evidence	Refs
Before embarking on potentially curative radiation therapy for patients with clinical stage I–III 'low-grade' lymphoma, staging should include functional imaging with PET or thallium scanning.	III	8, 9
Before embarking on potentially curative radiation therapy for patients with clinical stage I–III 'low-grade' lymphoma, staging should include careful examination of multiple levels of a bone marrow biopsy specimen ≥ 2.0 cm in length.	III	5, 6

Involved-field radiotherapy

A recent overview has established that 40–50% of patients with stage I–II disease can obtain durable disease control and likely cure with involved-field radiotheraopy.[10–12] Most of these studies were performed when various types of 'low-grade' lymphoma were included without distinction. These results are summarised in Table 12.1.

The radiation doses ranged from 20 Gy to 50 Gy. There are no convincing data for a significant-dose response relationship beyond 30–36 Gy.[13] However, doses <30 Gy are associated with a higher local recurrence.[14] For patients with tumour masses ≥ 3 cm in size, there is some suggestion that doses of 30–36 Gy resulted in better in-field control compared with doses <30 Gy[15], but with a trend for greater late local toxicity with the higher range of radiation doses.[15] There is now general agreement that doses over 40 Gy are excessive. The dose recommended is 30–36 Gy, with a higher dose range for sites ≥3 cm in diameter. The radiation treatment volume remains controversial. There is some evidence that treatment of larger volumes can delay relapse, but it is not clear that this produces a survival benefit[10,15]. This is partly attributable to a higher rate of second malignancies.[16] Thus the recommended treatment volume is the 'involved-field', where known disease with a suitable margin (with or without nearby uninvolved lymph node groups) is irradiated. It is recognised that there will be variability in the definition of the 'involved field'.[17]

The very rare disorder of follicular lymphoma in childhood has distinct molecular and pathological features, typically lacking *bcl-2* gene rearrangements.[18,19] The childhood form of the disease also has a distinct natural history. It is usually localised at presentation and typically has an indolent clinical course, and a moderate rate of local recurrence or dissemination after adequate local excision.[20] For those paediatric patients with more extensive disease or local disease persisting after the diagnostic biopsy, no clear recommendations can be made. However, local irradiation and combination chemotherapy are useful modalities. The specific treatment administered must give adequate consideration to the associated potential late toxicities.

Conversely, for the uncommon group of adult patients with clinical stage I disease, which is apparently completely excised in the process of the diagnostic biopsy, recurrent disease almost inevitably occurs either locally or at distant sites if additional treatment is not administered, although this recurrence can be quite delayed, with a median time to recurrence of ~five years.[21] There is no evidence that any of these patients initially observed following complete surgical excision are cured of their disease.

Given its established curative potential, and low morbidity when doses are limited to 30–36 Gy delivered to an involved field, IF XRT should be the minimum treatment offered. The exception is patients with complete surgical excision of all evident disease, who have a life expectancy of less than five years from intercurrent disorders or extremely advanced age. In these cases, observation with no further therapy is a reasonable alternative.

Table 12.1 Published studies of patients with indolent, clinically-staged stage I–II lymphoma, treated with involved-field radiation therapy alone

Study	No patients (% stage II)	Median age in yrs (range)	Histology (number of patients)	Radiation dose (Gy)	10-yr results (%)		Comments
					DFS	OS	
BNLI (Kelsey et al. 1994)[22]	82 (57)	60 (30–80)	FSC (46), FM (19), FL (4), DSL (10)	abdomen=25 elsewhere=35	28	52	Prospective radiation arm of randomised multicentre study 1974–81, extent of abdominal staging unclear
BNLI (Vaughan Hudson et al. 1994)[23]	208 (0)	59 (31–86)	FSC (81), FM (72), FL (10), DSL (27), DSC (18)	recommend 35	47	64	Retrospective, multicentre 1974–91, stage I only
PMH, Toronto (Gospodarowicz et al. 1984)[24]	190 (45)	56 (18–87)	All follicular	median 30 range 20–35	53 at 12yrs	58 at 12yrs	Retrospective subgroup analysis from 1967–78 among total of 248 stage I/II nodular histology
Stanford University (MacManus & Hoppe 1996)[10]	177 (58)	52 (22–83)	FSC (101), FM (76)	35–50 most ≤ 44	44	64	Retrospective, 1961–94, includes 45 with staging laparotomy and 32 with total-nodal irradiation
MDACC, Houston (Wilder et al. 2001)[15]	80 (59)	54 (24–81)	FSC (50), FM (30)	median 40 range 26–50	41 at 15yrs	43 at 15yrs	Retrospective, 1960–88, includes 23 with diagnostic laparotomy, 37% received extended field radiation
Royal Marsden (Pendlebury et al. 1995)[25]	58 (31)	55 (21–82)	FSC (37), FM (12), DSL (9)	median 40 range 30–54	43	79	Retrospective, 1970–89 includes 27% with ultrasound as only abdominal staging and 23 who received extended field radiation

FSC = follicular small cleaved cell, FM = follicular mixed small and large cell, FL = follicular large cell, DSL = diffuse small lymphocytic, DSC = diffuse small cleaved cell, DFS = disease-free survival, OS = overall survival, BNLI = British National Lymphoma Investigation, PMH = Princess Margaret Hospital, MDACC = MD Anderson Cancer Center

Guidelines — Low-grade lymphoma — optimal treatment	Level of evidence	Refs
Treatment for adult patients with clinical stage I or II 'low-grade' follicular lymphoma should include involved-field radiation therapy of 30–36 Gy.	III	12
Patients with stage I 'low-grade' follicular lymphoma who are rendered apparently disease free after the diagnostic biopsy and have a life expectancy of less than five years may be observed without further therapy.	IV	21
Combined modality treatment with both IF XRT and combination chemotherapy based on alkylating agents is a reasonable option for adult patients with clinical stage I or II 'low-grade' follicular lymphoma.	III	26

Addition of chemotherapy to involved-field radiotherapy

There have been phase III studies exploring the benefit of adding chemotherapy to local IF XRT in patients with stage I–II disease. With the exception of the BNLI study of the addition of low-dose oral chlorambucil[22], these trials have been of marginal value because of limited power to detect differences in outcomes.[27–31]

Table 12.2 Results of randomised studies of radiation plus chemotherapy for localised low-grade lymphoma

Centre	Year	No of patients in each arm	Chemo	FFR/RFS	Survival	Comments
Finsen Institute Denmark (Nissen et a.1983[29])	1983	11 6 RT + CT	RT only CVP+S	-	-	Included DSL Survival and FFR similar in both arms
BNLI (Kelsey et al. 1994[22])	1994	82 RT only 66 RT + CT	 Chl	37% @ 10y 43% @ 10 y	52% @ 10y 42% @ 10y	Included DSL and FLC
EORTC* (Carde et a. 1984[27])	1984	28	CVP	67% 5y RFS 92% 5y RFS	100% @ 5y 100% @ 5y	Follicular lymphomas only
Instituto Nazionale Tumori, Milan (Monfardini et al. 1980[28])	1980	11 RT only 15 RT + CT	 CVP	54.6 5y RFS 63% 5y RFS	61.6 @ 5y 93.3 @ 5y	Follicular lymphomas only
MSKCC (Yahalom 1993 et al. [31])	1993	10 RT only 6 RT + CT	 CHOP	54% 10y RFS 83% 10y RFS	- -	Included DSL No difference in survival

* Stage I patients only. RT = radiation therapy, CT = chemotherapy, Chl = chlorambucil, CVP = cyclophosphamide, vincristine, prednisolone, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone, FFR = freedom from relapse, RFS = relapse-free survival, DSL = diffuse small lymphocytic lymphoma, FLC = follicular large cell, BNLI = British National Lymphoma Investigation, EORTC = European Organisation for Research and Treatment of Cancer, MSKCC = Memorial Sloan Kettering Cancer Centre.

There are phase-II data suggesting that the proportion of patients obtaining durable disease control may increase to 65–70% by the addition of chemotherapy based on alkylating agents (CVP or CHOP).[26] This is the basis for the continuing Australian TROG/ALLG study of IF XRT with or

without six cycles of CVP chemotherapy. Outside of clinical trials, either IF XRT alone or combined-modality therapy are reasonable treatment options, depending upon patient age, co-morbidities and preferences.

There are no data to support the use of chemotherapy alone, except with palliative intent. This approach is not recommended where local IF XRT can be safely delivered, and this will be for all but the frailest patients. There are two studies exploring observation alone in patients with stage I–II disease.[26,32] These establish that the rate of local progression is slow and some of these patients have a long survival, without intervention. However, there is no evidence that any proportion of such patients can sustain long-term freedom from disease progression. This approach is not recommended in patients fit enough to undergo IF XRT.

Relapse after initial stage I–II disease

Patients with stage I–II disease who relapse following either initial XRT or combined-modality therapy still have a reasonable prognosis, with estimated ten-year survival rates of 35%[33] and 46%.[26] If disease is limited to stage I–II at recurrence, further radiation can be given, with a median survival of ~six years.[33] More extensive disease should be managed as for advanced-stage follicular lymphoma.

Stage III

Wide-field radiotherapy

Patients with stage III and IV 'low-grade' lymphomas are often grouped together and considered to have incurable disease. Management is controversial for the subgroup of patients with definite stage III disease, even after extensive staging with careful examination of the bone marrow biopsy and functional imaging (see above). There have been several studies of wide-field radiotherapy for patients with stage III 'low-grade' lymphomas. In the original report of the Stanford series[34], 61 patients with FSC or follicular-mixed lymphomas received total lymphatic irradiation or sub-total lymphatic irradiation to a dose of approximately 40 Gy. In addition to this radiotherapy, 13 patients had CVP chemotherapy and a further five patients had total body irradiation with boosts to sites of known disease. For the group as a whole, actuarial survival rates at five, ten and fifteen years were 78%, 50% and 37% respectively. At ten years, 40% of patients were predicted to be free from disease relapse. These data have recently been updated and confirm that a significant proportion of patients achieve long-term disease control and probably derive a major survival benefit from very wide-field radiotherapy.[35] Jacobs et al[36] reported a series of 34 patients with stage III follicular lymphoma who received comprehensive central lymphatic radiation to doses of 20–30 Gy, with overall survival and disease-free survival rates at fifteen years of 28% and 40% respectively. McLaughlin et al[37] reported a seven year survival rate of 52%, and relapse-free survival rate of 52% for 74 patients treated with wide-field radiotherapy and chemotherapy. This does not appear to be substantially different to the rates attained by similar radiation therapy alone.

Longer follow up is required for these studies to determine whether wide-field radiation can achieve indefinite clinical remission (i.e. 'cure') for a significant proportion of patients, or whether there is a continuing pattern of relapse beyond 10–15 years that is determined by the intrinsic aggressiveness or indolence of the disease. Comprehensive lymphatic irradiation should be considered for younger patients who are motivated to pursue potentially curative therapy with stage III disease. The single randomised study comparing comprehensive lymphatic irradiation with intensive chemotherapy (12 cycles of alternating CHOD-Bleo/ESHAP/NOPP) in patients with stage I–III follicular NHL has not revealed any difference in progression-free or overall survival, but with a relatively short median follow up in this context of 71 months.[38]

If such wide-field irradiation is planned, consideration should be given to collection and storage of autologous haematopoietic progenitor cells prior to the delivery of pelvic irradiation, as it may not be feasible to collect adequate numbers of progenitor cells subsequent to pelvic irradiation if relapse occurs and high-dose therapy is considered.

Guideline — Low-grade lymphoma — lymphatic irradiation — haematopoietic progenitor	Level of evidence	Refs
Wide-field 'comprehensive lymphatic irradiation' should be considered for patients with clinical stage III disease after careful and complete staging.	III	35

Key point

Collection and storage of autologous haematopoietic progenitor cells should be considered before the delivery of pelvic irradiation.

If wide-field radiation is not used, patients with stage III disease should be managed as described below for stage IV disease.

Stage IV disease

A recent large multinational collaborative group has defined the clinical parameters that are independently associated with the long-term outcome of patients with follicular lymphoma. The follicular lymphoma international prognostic index (FLIPI) is based on the analysis of more than 4000 patients.[39] The following factors at the time of diagnosis were associated with an inferior overall survival:

- age ≥60 years,
- haemoglobin ≤12 g/dl
- Ann Arbor stage III or IV disease, and
- ≥5 nodal sites of disease involvement.

Using these four factors, the distribution of patients and their 5- and 10-year survival rates were:

0–1 risk factors (36% of patients): 5-year survival = 91% 10-year = 71%

2 risk factors (37% of patients): 5-year survival = 78% 10-year = 51%

≥3 risk factors (27% of patients): 5-year survival = 53% 10-year = 27%

These parameters should be measured and recorded at the time of diagnosis in all patients to allow estimation of prognosis. This prognostic model has a better predictive capacity in patients with follicular lymphoma than other prognostic models. It is the recommended prognostic system.

Guideline — Low-grade lymphoma FLIPI — measure and record	Level of evidence	Refs
At the time of diagnosis, the factors constituting the follicular lymphoma international prognostic index (FLIPI) should be measured and recorded in all patients.	IV	39

'Watch and wait' versus initial treatment

In general, the approach to patients with stage IV disease is determined by the presence or absence of lymphoma-related symptoms and the age, general condition and preferences of the individual patient. The available evidence base supports two management approaches as reasonable: (1) withholding

treatment until symptoms develop or are imminent, and then using the sequential application of low-morbidity therapies with the aim of ameliorating symptoms, or (2) the initial treatment using optimally effective anti-lymphoma therapy, even if associated with morbidity, aiming to alter the natural history, and potentially overall survival, of the patient.

Key point

All patients with symptomatic advanced-stage follicular lymphoma should be offered therapy.

The first approach of 'watch and wait' is based on a number of observations:

- advanced-stage follicular 'low-grade' lymphoma is incurable with therapies based on alkylating agents[40], with a relentless and steady pattern of disease recurrence, albeit over many years
- the overall survival of patients is not influenced by whether such therapies are applied at the time of diagnosis or after an initial period of observation[41–43]
- a modest proportion of patients may have a very indolent disease course and not develop symptoms related to their lymphoma for a number of years, and can thus be spared the morbidity of initial treatment[42–44]
- despite the development of an increasing number of therapies with useful overall response rates, the overall survival of patients did not appear to have altered over many decades[40], and
- moderate intensity combination alkylating agent regimens such as CVP or CHOP did not consistently show any survival advantage over less intensive regimens or single-agent alkylating agents (chlorambucil or cyclophosphamide) for initial therapy.[45–51]

These observations support an initial 'watch and wait' approach in selected asymptomatic patients. The criteria used to select appropriate patients for such an approach have varied between studies and institutions, but all are designed to identify a group of patients with little risk of imminent disease progression or organ impairment. Examples of the criteria used are:

BNLI (Ardeshna et al. 2003)[42]	Absence of all of the following: • pruritis of B-symptoms • rapid generalised disease progression • 'life-endangering' organ involvement • marrow compromise (Haemoglobin ≤100 g/L, WBC <3.0, or platelets <100) • bone lesions • renal infiltration, and • macroscopic liver involvement.

GELF (Brice et al. 1997)[43]	All of the following: • maximum diameter of any site of disease <7 cm • fewer than three nodal sites with a diameter >3 cm • absence of systemic symptoms • no 'substantial' splenic involvement (spleen <16 cm in length based on CT measurement) • no significant serous effusions clinically evident or on chest X-ray • absence of risk of local compressive symptoms (epidural, ureteral, etc.), and • no circulating lymphoma cells or peripheral blood cytopenias (haemoglobin >10 g/dl, neutrophils >1.5 and platelets >100). Using these criteria, 36% of consecutive patients diagnosed with follicular lymphoma were considered to have a 'low' tumour burden.[43]

Such a 'watch and wait' approach is still an active form of management that requires patient review, and careful monitoring and assessment of the status of disease or the development of any of the above parameters, which may require the commencement of therapy.

Guidelines — Low-grade lymphoma — 'watch and wait' criteria	Level of evidence	Refs
Where a 'watch and wait' approach is applied in the initial management of a patient with advanced-stage follicular lymphoma, regular monitoring and active surveillance for disease progression is mandatory.	IV	42
Patients who are initially managed by a 'watch and wait' policy and who either develop symptomatic disease, or have disease that progresses beyond the criteria for 'low tumour burden', should commence therapy.	IV	42
Asymptomatic patients who do not fulfil the criteria for 'low tumour burden' follicular lymphoma, using either of the validated criteria, should commence treatment at the time of diagnosis.	IV	42, 43

Where such an approach is used, and patients develop criteria for the initiation of therapy, local external beam irradiation can be used for single disease sites requiring intervention[41, 42], or systemic chemotherapy may be used. As discussed above, there has been no advantage demonstrated for using more intensive conventional alkylating-agent regimens as the initial therapy for patients with follicular lymphoma. The approaches supported by phase III trial data include:

- Oral chlorambucil 0.2 mg/kg bodyweight (maximum dose 10 mg) daily until three months beyond attainment of maximum response[42], or

- Oral chlorambucil 0.4 mg/kg on day one and prednisolone 75 mg orally for three days, both given every two weeks, with dose escalation of the chlorambucil until myelosuppression or 'therapeutic effect'[49], or
- Oral chlorambucil 10 mg (flat dose) daily for six weeks, then after a two-week gap, three 15-day courses of 10 mg daily, with 15-day intervals between the courses[47], or
- Cyclophosphamide 600 mg/m^2 IV on days one and eight, with prednisolone 100 mg/m^2 on days 1–5, with courses repeated every 28 days for 16 cycles[46], or
- Cyclophosphamide 100 mg/m^2 orally daily, with dose modifications for myelosuppression for a total of two years.[51]

There are no data to allow a selection among these approaches based on efficacy. Individual patient characteristics and preferences should influence the regimen selected. For example, there are no comparative data to support any benefit for IV compared with oral therapy, nor for the addition of corticosteroids. One feature of all of these established regimens is the requirement for relatively prolonged therapy and relatively slow therapeutic responses. Although there is no greater efficacy associated with the use of intravenous combination regimens (e.g. CVP or CHOP), the requirement for a shorter treatment duration (generally 6–8 cycles) may make them attractive in some circumstances.

Guideline — Low-grade lymphoma — therapy for advanced-stage follicular lymphoma	Level of evidence	Refs
Single-agent alkylating agents with or without corticosteroids (using published schedules) are a suitable treatment for patients with advanced-stage follicular lymphoma.	II	42, 46, 47, 49, 51
Combination chemotherapy regimens (e.g. CVP or CHOP) may be used where a shorter treatment duration or more rapid disease response is desired, although these regimens are not consistently associated with any long-term improvement in quality or duration of disease response, or overall survival.	II	46, 47, 49, 51

Where such therapies are used, two studies have explored the potential value of the addition of wide-field irradiation. Portlock et al[48] found no benefit in any of complete remission rate, disease-free interval, or overall survival for the addition of total lymphatic irradiation to CVP chemotherapy. A second study[52] randomising patients who attained a complete remission to chemotherapy to receive 30–40 Gy external beam XRT to sites of initial nodal 'bulk' (size criteria not provided) or not, claimed to demonstrate an improvement in overall survival (20 year actuarial rates of 89% versus 71%; P < 0.01). However, the innumerable internal inconsistencies evident in this report seriously question the validity of these claims. It would be unwise to base clinical management decisions on this data without independent validation in another trial.

Guideline — Low-grade lymphoma — advanced disease response and radiotherapy (clinical trial)	Level of evidence	Refs
Where a patient with advanced-stage follicular lymphoma has achieved a compete response to initial therapy, irradiation to nodal sites of disease (initially bulky or otherwise) is not recommended outside of the context of a clinical trial.	II	48

In support of the second approach of the initial application of optimally effective therapy, regardless of tumour-burden or symptoms, there are a number of emerging observations:

- some phase III studies have established that the choice of initial therapy can influence overall survival[53–56], challenging the dogma that therapeutic intervention cannot alter the natural history of advanced-stage follicular lymphoma
- at institutions where an aggressive approach to initial treatment has been consistently employed, there has been a consistent and step-wise improvement in overall survival for patients with stage IV follicular 'low-grade' lymphoma seen in recent years, independent of known prognostic factors. It appears to be restricted to those patients attained a complete remission with initial therapy (1977–82 median survival seven years, 1992–97 seven-year survival of 80%[1]), and
- the attainment of a 'molecular' complete remission (i.e. eradication of PCR-detectable cells containing the t(14;18) from the peripheral blood or bone marrow) is associated with an remission duration in patients treated with non-myeloablative therapies.[57,58]

These observations, particularly the potential utility of a 'molecular remission' as a surrogate measure of treatment efficacy, have guided the development and exploration of a number of novel regimens that are capable of achieving complete remission rates of 80–90%, and molecular remission rates of 70–90%.

Importantly, the second and third points are indirect, and have not been either reproducibly shown (second point) or validated in prospective studies (third point). Thus these observations, although promising and provocative, do not provide unequivocal proof of a clear survival benefit for patients treated using such approaches. However, it is important that this data be discussed openly and clearly with patients, particularly those patients who are younger, highly motivated and without other medical co-morbidities, as some may quite reasonably wish to pursue such approaches during the time that the required clinical trials are being undertaken.[59]

Guideline — Low-grade lymphoma — 'aggressive' treatment	Level of evidence	Refs
Pending the availability of further data from phase III studies, where motivated and informed patients have been made fully aware of the promising but inconclusive data regarding potential overall survival benefits of initial aggressive treatment approaches and wish to pursue such a strategy, initial therapy attempting to achieve maximal cytoreduction (potentially guided by molecular assessment of minimal residual disease) is a reasonable approach in carefully selected cases.	II	60–64

Regimens capable of achieving these levels of cytoreduction include:

- fludarabine 25 mg/m^2/day x 3, mitoxantrone 10 mg/m^2 x 1, dexamethasone 20 mg orally daily x 5, and concomitant rituximab 375 mg/m^2 for a total of six doses, with cycles given every 28 days for a total of eight cycles[60,61]
- 'alternating triple therapy' (12 cycles of alternating CHOD-Bleo, ESHAP, and NOPP — see references for dosage details)[60,61]
- CHOP and rituximab[62,63]
- fludarabine and rituximab[63]

The only one of the above regimens to have been compared to a 'standard' regimen for the initial therapy of patients with stage IV follicular lymphoma is CHOP and rituximab. The German Low-grade Lymphoma Group compared CHOP alone to CHOP plus rituximab and found that the combination was able to achieve superior time to treatment failure ($P < 0.0007$) and overall survival ($P = 0.016$). However, interpretation of the overall survival data from this study is confounded by a second randomisation to high-dose therapy and autologous transplantation or interferon-α maintenance.[64] The data with the longest follow up using the FND and ATT regimens did not incorporate rituximab[60]. However, a recent phase III study has demonstrated improved TTF with FND and concurrent rituximab, compared to sequential FND followed by rituximab. The mature data from a phase III study in the treatment of patients with relapsed indolent lymphomas (including follicular lymphoma) showing a clear overall survival advantage for the additional of rituximab to the FCM regimen (fludarabine/cyclophosphamide/mitoxantrone)[65,66], make the routine addition of rituximab to the above regimens highly justified when they are being utilised with 'curative' intent.

Importantly, the use of single-agent fludarabine in the initial treatment of patients with follicular lymphoma has been shown to result in inferior outcomes compared with a 'CHOP-like' regimen (CHVP) followed by interferon maintenance.[67]

Use of maintenance therapies

Some[53–56,68,69] but not all[70–72] randomised trials have shown a benefit for interferon maintenance following the initial therapy of patients with advanced-stage follicular lymphoma. A meta-analysis of the published trials demonstrated that this benefit was restricted to those patients treated with anthracycline-based therapies.[73] With the emergence of newer regimens used for the initial therapy of these patients and increasingly effective salvage therapies, the relative contribution of interferon maintenance is likely to diminish, but remains a reasonable option that should be considered on an individual patient basis.

Guideline — Low-grade lymphoma — criteria for therapy with interferon	Level of evidence	Refs
The use of interferon-α maintenance after anthracycline-based initial therapy (e.g. CHOP) may be considered on an individual patient basis.	II	55, 53, 73

There are retrospective subgroup data from a prospective randomised trial of rituximab maintenance (375 mg/m^2 every two months for four doses) in a small group of patients who received rituximab alone as their initial therapy, that this 'maintenance' schedule may prolong time to disease progression. However, no data on overall survival are yet available.[74] The more clinically relevant questions of the potential role of rituximab maintenance after either combination chemotherapy or combined chemotherapy and rituximab await the availability of results from current clinical trials. The routine use of rituximab maintenance is not recommended based on currently available data.

Relapsed stage IV disease

Despite the very large number of phase II trials describing the clinical activity of many chemotherapy regimens in patients with relapsed follicular lymphoma, there are very few phase III studies. A proportion of patients have disease that remains sensitive to single-agent alkylating agents, but the proportion of responses and the duration of responses serially decline with each episode of retreatment.[75]

The available phase III trials have compared single-agent fludarabine with CVP[76] and with the addition of rituximab to the FCM chemotherapy regimen. They have also compared single-agent rituximab with radioimmunotherapy (Zevalin, ibritumomab tiuxetan).

The study comparing single-agent fludarabine with CVP[76] demonstrated a higher response rate, complete remission rate, and progression-free survival, but not overall survival with the fludarabine treatment.

Guideline — Low-grade lymphoma — recurrent disease and fludarabine	Level of evidence	Refs
Where patients have initially been treated with an alkylating agent and have recurrent disease requiring systemic chemotherapy, therapy containing fludarabine should be considered.	II	76

Dreyling et al[65] from the German Low Grade Lymphoma Study Group have performed a phase III trial exploring the value of the addition of rituximab (375 mg/m^2, one dose per cycle) to the intravenous FCM chemotherapy regimen (fludarabine 25 mg/m^2/day x 3, cyclophosphamide 200 mg/m^2/day x 3 and mitoxantrone 8 mg/m^2 x 1) given for a maximum of four cycles. This is the first study to demonstrate a clear survival benefit from a specific chemotherapy regimen used in this setting.

Guideline — Low-grade lymphoma — therapy in relapsed follicular lymphoma	Level of evidence	Refs
In patients with relapsed follicular lymphoma, the addition of rituximab to fludarabine-based combination chemotherapy is associated with improved outcomes, including better overall survival.	II	65

Witzig et al[77] performed a randomised comparison of single-agent rituximab and the radio-immunotherapeutic approach using yttrium-90 labelled ibritumomab tiuxetan (Zevalin) in patients with relapsed or refractory follicular lymphoma who fulfilled the following criteria:

- no prior rituximab therapy
- bidimensionally measurable disease ≥2 cm
- WHO performance status of 0–2
- haemoglobin ≥8 g/dl, neutrophils ≥1.5, platelets ≥150
- adequate hepatic and renal function
- <25% bone marrow infiltration
- external beam radiation to ≤25% of bone marrow.

Among the specific patient cohort who met these criteria, the radioimmunotherapy was associated with a significantly higher rate of overall response, and complete response, but not time to progression or overall survival. This is consistent with the data showing high response rates using Zevalin (or other radioimmunotherapy strategies) in patients with disease unresponsive or relapsing within six months of previous rituximab therapy.[77]

Guideline — Low-grade lymphoma — radioimmunotherapy criteria	Level of evidence	Refs
For patients who fulfil specific criteria (specifically <25% bone marrow infiltration), the use of radioimmunotherapy is associated with a higher rate of disease control and should be considered in preference to single-agent rituximab.	II	77

In addition to the strategies listed above that have been established as efficacious on the basis of phase III trials, there are numerous regimens or approaches with useful clinical efficacy data in the setting of patients with relapsed follicular lymphoma, based on phase II studies. These studies provide the basis for the use of strategies such as:

- alkylating agent combination therapies (using cyclophosphamide/ifosfamide/prednimustine)
- nucleoside analogue therapy (fludarabine/2-chloro-deoxyadenosine/gemcitabine)
- nucleoside analogue combination therapies
- cytosine-arabinoside
- platinum compounds (cisplatin, carboplatin, oxaliplatin)
- rituximab
- chemo-immunotherapy combinations (alkylating agents or nucleoside analogues)
- radio-immunotherapy (Zevalin/Bexxar/^{131}I-labeled rituximab)
- external beam irradiation (local or extended fields, including low-dose TBI)
- anthracyclines and analogues
- vinca alkaloids and epipodophyllotoxins
- interferon-α
- topoisomerase-I inhibitors
- taxanes

Given the recurrent relapsing nature of follicular lymphoma, there are circumstances where such approaches will need to be considered. Each of these regimens has specific restrictions in terms of disease characteristics and organ function, as well as specific toxicity profiles. These will influence and guide the appropriate patients and circumstances where these are reasonable choices. There is no survival data to allow selection of any one of these approaches over another.

Histologic transformation

Patients with relapsed or refractory follicular lymphoma are at risk of developing histologic transformation to an aggressive lymphoma (usually diffuse large B-cell lymphoma, but rarely Burkitt's lymphoma). Where it is safe and reasonable, a biopsy of the dominant site of relapsed disease should be obtained to investigate possible histologic transformation. This is particularly so where there are:

- profound B-symptoms

- a disproportionately raised serum LDH level
- rapid or disproportionate growth of one disease site
- unusual areas of disease involvement (CNS, bone lesions, visceral infiltration), or
- the development of hypercalcemia.

Key point

Where it can be safely performed, re-biopsy of the dominant or clinically suspicious disease site should be performed in patients with relapsed or refractory follicular lymphoma to investigate possible histologic transformation to aggressive lymphoma.

Where histologic transformation has occurred, the patient should be managed as for the specific histology of the transformed disease (diffuse large B-cell lymphoma or Burkitt's lymphoma) (refer to Chapter 13).

- Follicular large cell (grade 3) — to be discussed in the chapter on diffuse large B-cell lymphoma (see Chapter 12 — Aggressive lymphoma).

12.4.2 Role of autologous HSCT in the management of follicular NHL

The role of autologous hematopoietic stem cell transplant (auto-HSCT) in the management of advanced-stage follicular lymphoma remains controversial.

As noted in Section 12.4.1, follicular lymphoma is a disease with a long natural history, with a pattern of cyclical response and relapse to non-intensive therapy. Most patients with advanced-stage disease, however, ultimately die from the disease[78], justifying investigational strategies, particularly in younger patients. This pattern of disease activity and management has made the design of prospective controlled trials difficult, and highlights the critical importance of long follow up.

Most published studies have been single institution phase II studies using historical controls. The largest study with the longest follow up was performed at the Dana-Faber Cancer Institute with patients enrolled between 1985 and 1995.[79] Patients were eligible if they were less than 65 years of age and had relapsed after at least one standard chemotherapeutic regimen or had sensitive disease but had failed to enter remission after at least one regimen. Autologous marrow was purged using a cocktail of monoclonal antibodies. The disease-free survival and overall survival are estimated at 42% and 66% respectively at eight years, with a twelve-year survival rate of 69%. The best outcomes were seen in those in whom purging was deemed to have been successful (using a PCR-based detection assay). The authors conclude that given that the median survival from first recurrence following conventional therapy is five years (a figure derived from the study of Johnson et al[78]), this strategy may prolong survival. Similar results are reported from a number of other groups[80–82], all reaching similar conclusions. There appears, however, to be a pattern of ongoing relapse in these studies.

Three prospective randomised controlled trials investigating the role of auto-HSCT as part of the therapy of follicular NHL have been reported recently. The European CUP trial[83] enrolled 140 patients with relapsed follicular lymphoma to initially receive three cycles of conventional salvage chemotherapy (DHAP). Responding patients were randomly assigned to receive three further cycles of conventional chemotherapy, or high-dose therapy followed by purged (P) or unpurged (UP) stem cell support.

Only 89 patients were randomised. With a median follow up of 69 months, there was a significant benefit in terms of progression-free and over-all survival for the high-dose therapy arms. The study was not powered to allow a definitive statement to be made regarding the benefit of purging. Two large studies addressing the role of auto-BMT as part of up-front therapy for follicular NHL have

recently been presented in abstract form. The French study of the GELF (GELF94) and GEOLAMS (GEOLAMS 064)[84,85] are reported to show conflicting results. GELF94 randomised 401 patients with untreated high tumour burden follicular lymphoma to either 18 months of a CHVP plus interferon alpha regimen, or to four cycles of CHOP followed by a cyclophosphamide/VP16/TBI conditioned autograft. Overall survival was significantly longer at seven years for the transplant arm (86% versus 74%). There was no excess mortality from second malignancies in the transplant arm. GEOLAMS 064 utilised a similar control arm. The transplant arm consisted of three courses of VCAP followed by a purged autograft in responding patients. At a median follow up of five years, overall survival was comparable in both arms, and there was an excess of second malignancies in the transplant arm. The conflicting findings in these studies are difficult to comment on in the absence of peer-reviewed publications, which are awaited. The modest benefits to auto-BMT shown in the GELF94 study may be largely negated by current best-practice conventional regimens that include monoclonal antibodies.

The recent reports of second malignancies complicating auto-HSCT are of concern. The Dana-Faber group has reported an actuarial incidence of MDS at ten years of 19.8% in a series of 552 patients with lymphoma undergoing auto-HSCT following Cy/TBI conditioning.[79]

Guideline — Low-grade lymphoma — auto HCST — indication	Level of evidence	Refs
Auto-HSCT may be indicated in patients who have failed at least one conventional chemotherapeutic regimen.	II	83
The use of auto-HSCT as part of up-front treatment remains controversial.	III,IV	84, 85

12.4.3 Role of allogeneic HSCT in the management of lymphoma

Registry data and a small number of phase II studies suggest that the procedure-related mortality of conventional sibling allo-HSCT in patients with follicular NHL is high, between 30% and 40%. However, relapse rates appear to be lower than those described following auto-HSCT, and there appears to be a plateau on the survival curve not evident following auto-HSCT.[86–88]

These results, together with recent studies showing convincing disease responses following non-myeloablative stem-cell transplant (NST), suggest that a graft versus follicular lymphoma effect exists, and that some patients may be cured following allo-HSCT.

The role of NST will become clearer as studies with longer follow up are presented. At this time, while significant response rates have been reported and treatment related mortality rates appear to be lower than conventional allo-HSCT, the curative potential of NST in follicular lymphoma is unknown.[89–92]

Guidelines — Low-grade lymphoma — auto-HCST and NST considerations	Level of evidence	Refs
Conventional sibling allogeneic HSCT should be limited to young patients with poor prognosis follicular lymphoma who have limited comorbidities.	IV	86–88
NST can be considered in patients with poor prognosis follicular lymphoma, but should optimally be performed in the context of approved clinical trials.	III, IV	89–92

12.5 Small lymphocytic lymphoma

Summary of clinicopathological findings

Clinical	Mostly asymptomatic, fatigue, autoimmune haemolytic anaemia, infections. Lymph nodes liver and spleen commonly involved. Rarely (Richter's) transformation to large B-cell lymphoma or Hodgkin lymphoma.
Morphology	Diffuse involvement with pseudofollicular pattern (proliferation centres containing small lymphocytes, prolymphocytes and para-immunoblasts). Small, round, regular nuclei but variants may have irregular nuclei. Early involvement may be interfollicular or unrecognised without immunophenotyping. White and red pulp involved in spleen. Bone marrow infiltration may be nodular, interstitial, and later, diffuse.
Immunophenotype	Weak SIgM +/- SIgD, CD5+, CD19+, CD20 weak+, CD22 weak+, CD79a+, CD79b usually-ve, CD23+in most but not all cases, CD43+, CD11c weak+, CD10-, cyclinD1-ve. FMC7usually-ve. SIg often reactive against self antigens.
Genetics	40–50% naïve B-cells with unmutated VH genes 50–60% post-germinal centre cells with somatically mutated VH genes Trisomy 12 (usually naïve, unmutated VH genes) del(13q14) del(11q22–23) del(6q21), del(17p13)

A consequence of the WHO classification system is that 'small lymphocytic lymphoma' has been merged as an entity with chronic lymphocytic leukaemia (CLL). This is a logical extension of the knowledge that small lymphocytic lymphoma is molecularly and immunophenotypically identical to CLL, and for a number of years has been considered to represent the 'tissue manifestation' of CLL. The full management of these patients is beyond the scope of this review. Those rare patients who present with truly localised disease after complete staging should be managed as described for:

- localised nodal marginal zone B-cell lymphoma, if isolated nodal involvement is present
- localised extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue if isolated mucosal involvement is present. Those with advanced-stage disease (stage IV, whether or not leukaemic involvement is present) should be managed according to guidelines for CLL.

The major issue with patients considered to have small lymphocytic lymphoma is the establishment of an accurate definitive diagnosis, as distinction from other diffuse mature B-cell lymphoproliferative disorders (lymphoplasmacytic lymphoma, marginal zone B-cell lymphoma, and mantle-cell lymphoma is critical). (See Chapter 8)

12.6 Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)

Summary of clinicopathological findings

Clinical	GIT (especially stomach), lung, ocular adnexae, skin, thyroid and breast. May have multiple extranodal sites and/or regional node involvement without dissemination.
Morphology	Small to medium-sized, centrocyte-like or monocytoid cells accumulate outside the follicle mantle, progressively expand to form sheets and migrate into the germinal centre. Lymphoepithelial lesions common in stomach. Zones of plasmacytoid differentiation common.
Immunophenotype	IgM+, +/- IgA or IgG, CD20+, CD79a+, CD21+, CD35+, CD5-, CD10-, CD23-, cyclinD1-, CD43+/-, CD11c +/-.
Genetics	Post germinal centre B-cell Trisomy 3 Disease associated with t(11;18)(q21;q21) (*AP12/MLT* fusion) is resistant to anti *Helicobacter* therapy

12.6.1 Gastric

The management of gastric marginal zone lymphoma is discussed separately (see Chapter 17).

12.6.2 Non-gastric sites

Extra-nodal marginal zone lymphoma can occur at many non-gastric sites, most commonly conjunctivae, skin, salivary gland, lung or thyroid. Other rare sites such as bladder, prostate and breast, are also reported.[93,94] In some of these sites, there are known associations with chronic antigenic stimulation (e.g. *Borrellia Burgdorferi* and skin disease[95], *Chlamydia Psittaci* and conjunctival disease[96], Sjogren's disease and salivary gland involvement[97], and Hashimoto's thyroiditis and thyroid disease.[98] Where an infectious agent is implicated, by analogy, with gastric marginal zone lymphoma and *Helicobacter pylori* infection, eradication of the organism should be considered as the treatment of first choice. It can result in regression of the associated lymphoma, although there are insufficient data on specific organs to accurately determine what proportion of patients may respond to such eradication therapy. Nevertheless, given its low toxicity, this approach is recommended where there is (1) an identified associated pathogen, (2) no critical or impending threat to the organ involved, and (3) no history of kinetically aggressive preceding behaviour of the disease in the local site.

Guideline — Low-grade lymphoma — extra-gastric marginal zone lymphoma — pathogen treatment urgency	Level of evidence	Refs
Where an identified pathogen is associated with extra-gastric marginal zone lymphoma, and there is no clinical urgency to obtain immediate disease regression, eradication therapy directed against the identified pathogen is recommended.	III	95, 96

Localised disease

Approximately 60–75% of these cases of extra-gastric marginal zone lymphoma are anatomically localised (stage I–II disease).[99,100] Where there is no associated infective agent identified, or successful eradication of an identified agent is not associated with disease regression, or there is clinical urgency to achieve disease regression, localised irradiation using 25–35 Gy is highly effective, depending upon the specific location and the relative risk of adverse effects on surrounding

normal tissues,. There are a number of large retrospective series describing complete remission rates of 95–100% with external beam XRT in this dose range[93,101,102], and long-term local disease-control rates of 95–100%. The rate of local relapse appears to be higher with external beam RT doses of <25 Gy.[93] Although patients with nodal marginal zone lymphoma will more rarely have localised disease (<30%[103]), the approach to their management should be similar to patients with other stage I–II 'low-grade' lymphomas.

Guideline — Low-grade lymphoma — extra-gastric marginal zone lymphoma — durable local control	Level of evidence	Refs
Where there is no associated infective agent identified, successful eradication of the agent is not associated with disease regression, or there is clinical urgency to achieve disease regression, localised irradiation using 25–35 Gy is highly effective in achieving durable local control for extra-gastric marginal zone lymphoma (nodal and non-nodal).	III	93, 101, 102

Depending upon the adequacy of initial staging, length of follow up and patient selection, approximately 20–30% of patients will develop disease recurrence outside the irradiated field, with the contralateral paired organ at moderate risk (~ 10% long-term). The long-term rate of disease-free survival is approximately 75% at 5–10 years.[93,100]

Disseminated disease

Where disease is disseminated at diagnosis, recurs within prior radiotherapy fields, or radiation cannot be delivered, a range of chemotherapy and immunotherapy strategies have shown activity in phase II studies. However, it should be emphasised that the durability of local control appears to be inferior to that achieved with XRT[94,104], and systemic chemotherapy is not recommended in circumstances where local XRT can be safely delivered for the treatment of localised disease. Agents with established activity include rituximab[105], 2-CdA[106], cyclophosphamide[104], and fludarabine.[107] Oral chlorambucil (15 mg/m^2/day) and prednisolone (100 mg/day) each given for five days every 28 days also has similar levels of activity to the listed agents, with no evidence of benefit (as measured by either response rate, CR rate, FFS or overall survival) for the addition of epirubicin.[108] With any of these agents, initial response rates are high (50–90%), and there are no comparative data that allow meaningful comparisons of efficacy. Choices for treatment should be based on patient acceptance and tolerance of the anticipated adverse effects of the agents under consideration.

Disseminated disease (stage III or IV) is incurable with available therapies. However, patients with stage IV disease due to the bilateral involvement of paired organs (which is extremely rare) should be treated with local XRT with curative intent. The reported median survival is 7–10 years.[109,110] Asymptomatic patients may be observed without therapy, as there is no evidence that this strategy impairs their long-term outcome.[110] Similarly, the available non-randomised data[99,109,110] do not suggest the superiority of combination chemotherapy (e.g. CHOP) over single-agent alkylating agents (cyclophosphamide or chlorambucil). The one available randomised trial of the addition of an anthracycline (epirubicin) to alkylating agent therapy (chlorambucil) did not show any benefit in terms of either overall response rate or overall survival.[108] There is a continuing randomised study by the International Extranodal Lymphoma Study Group (IELSG) of chlorambucil ± concurrent rituximab.

Guideline — Low-grade lymphoma — extra-gastric marginal zone lymphoma — therapeutic options	Level of evidence	Refs
Patients with asymptomatic disseminated marginal zone lymphoma may be observed without initial therapy.	III	110
Patients with symptomatic or progressive disseminated marginal zone lymphoma should be treated with single-agent chemotherapy (alkylating agents/nucleoside analogues/rituximab have similar levels of activity).	III	104–107
There is no apparent benefit from the use of combination chemotherapy regimens (e.g. CHOP) as initial therapy.	III	99, 109, 110
There is no benefit from the addition of anthracylines to alkylating agents (e.g. chlorambucil).	II	108

Transformation to aggressive lymphoma

The lifetime risk of developing histological transformation to a histologically aggressive NHL is approximately 10–20%, and is influenced by the presence or absence of the t(11;18)(q21;q21) translocation. The relative frequency of this translocation varies according to the organ involved.[99]

12.7 B-cell monoclonal lymphocytosis

There are recent data that a small proportion of elderly patients with normal numerical peripheral blood parameters have a detectable monoclonal B-cell population in the peripheral blood by sensitive flow cytometry, with a phenotype consistent with extra-nodal marginal zone lymphoma.[111] These patients should not be treated unless symptoms develop, or there is evidence of progressive lymphocytosis with haematopoietic impairment. These disorders have been given the label of B-cell monoclonal lymphocytosis and their clinical significance is yet to be determined, but it appears that the annual risk of progression to a recognisable lymphoproliferative disorder is about 1%.[112]

12.8 Nodal marginal zone B-cell lymphoma

Summary of clinicopathological findings

Clinical	Localised or generalised lymphadenopathy, without extranodal or splenic disease.
Morphology	Perifollicular and interfollicular infiltration by centrocyte-like or monocytoid cells. May resemble extranodal marginal zone or splenic marginal zone lymphoma. Plasmacytic differentiation common.
Immunphenotype	Similar to extranodal marginal zone lymphoma, but some cases are IgD+, similar to splenic marginal zone lymphoma.
Genetics	None defined.

This is a very rare disorder. It is managed stage-for-stage in the same way as extranodal marginal zone lymphoma.

12.9 Lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia)

Summary of clinicopathological findings

Clinical	IgM paraprotein >3 g/dl. Hyperviscosity syndrome. Autoimmune disorders. Bone marrow, lymph nodes and spleen involvement.
Morphology	Monomorphous. Small lymphocytes, plasmacytoid cells and plasma cells. No features of marginal zone lymphoma, follicular lymphoma or chronic lymphocytic leukaemia. Dutcher bodies.
Immunophenotype	Surface and cytoplasmic IgM, IgG or IgA. IgD -ve. CD19, CD20, CD22, CD79a and CD38 +ve. CD43+/-. CD5, CD10, CD23 and cyclinD1 –ve.
Genetics	Post follicular, somatically rearranged VH genes. T(9;14)(p13;q32) (*PAX-5* encodes BSAP).

Waldenström's macroglobulinemia can manifest symptoms through any combination of:

- the physicochemical properties of the IgM paraprotein (hyperviscosity, peripheral neuropathy, cryoglobulinemia, cold-agglutinins, and amyloidosis)
- bone marrow infiltration with haematopoietic compromise
- extra-medullary infiltration (splenomegaly, lymphadenopathy, or rarely other organ infiltration)
- systemic paraneoplastic symptoms (fevers, sweats, weight loss), or
- immunological disturbance or compromise (autoimmune phenomena or immunosuppressive complications).[113]

Specific therapies may be employed to manage any of these individual manifestations, distinct from any systemic anti-neoplastic therapy.

12.9.1 Prognostic features

The major adverse prognostic features for overall survival are: age ≥65 years, serum albumin <40 g/L, and the presence of at least one, or two, lineage cytopenias (Hb <120 g/L, neutrophils <1.5 x 10^9/L, or platelets <150 x 10^9/L).[114] The five-year actuarial survival rates for patients with 0–1 risk factors is 90%, 2 risk factors 67% and 3–4 risk factors 37%. Patients who are asymptomatic and without evidence of progressive disease may be managed expectantly without therapy. There are no randomised studies evaluating immediate versus delayed therapy.

12.9.2 Hyperviscosity

For patients who present with hyperviscosity, plasmapheresis is an effective form of management, allowing systemic treatments time to control the disease. As well, plasmapheresis may be used in a palliative context in patients with advanced drug-resistant disease.[115] The required frequency of plasmapheresis depends on the production rate of the IgM and the threshold at which the individual patient becomes symptomatic, but is usually every three to eight weeks.[116]

12.9.3 Chemotherapy

Alkylating agents

Traditionally, alkylating agents, most commonly chlorambucil, have been used as the primary therapy for symptomatic patients. In one of the few randomised studies reported in this disease, Kyle

compared continuous chlorambucil 0.1 mg/kg/day with intermittent dosing 0.3 mg/kg/d for seven days every six weeks.[117] Based on a reduction in serum paraprotein of ≥50%, the response rate with continuous therapy was 75%, and for intermittent therapy 64%. These therapies were very prolonged, with a median time to achievement of response of 18 and 21 months, respectively. The median response durations were 26 and 46 months, respectively, and the median overall survival in both treatment arms was 65 months. None of these differences were statistically significant. These characteristics provide a basis for comparison with other therapies.

In the context of sequential studies at a single institution[118], there was no difference in response rate, or overall survival between patients treated with chlorambucil and prednisolone (57% response rate), intravenous (IV) CVP (cyclophosphamide/vincristine/prednisolone) (44% response rate) or CHOP (65% response rate). None of these differences were statistically significant, and the median overall survival of these cohorts again did not differ. Thus there is no additional benefit from the addition of corticosteroids to simple alkylating agents, nor are the more aggressive IV alkylating agent regimens, or anthracycline-containing regimens, superior to chlorambucil alone for initial therapy, based on this single institution retrospective comparison.

These and other studies have provided justification for using the attainment of an objective response as a surrogate endpoint for improving overall survival. In three studies, patients attaining an objective response have had greater median overall survival than non-responding patients; 49 months versus 24 months[119], 96 months versus 42 months[120] and 92.4 months versus 30 months.[118] Those rare patients attaining a complete response had a median overall survival of eleven years.[118]

Nucleoside analogues

As initial therapy, the nucleoside analogue class of drugs appear to be at least as effective single agents as alkylating agents, and have the advantage of requiring between three and six months of therapy, albeit parenteral in all published series, although oral fludarabine is now available and is pharmacokinetically equivalent to the IV form.[121] There are no comparative studies of the efficacy of IV versus oral fludarabine in this disease, but they are predicted to have equivalent efficacy. Cladribine (2-chlorodeoxyadenosine; 2-CdA) has achieved an overall response rate of 75% (reported range 44–90%) among previously untreated patients, with 12% attaining CR.[118] Fludarabine has achieved an overall response rate of 79%, with 5% attaining CR, and a median response duration of greater than three years for all responding patients.[107] The follow up of these studies at the time of reporting is inadequate as yet to draw any firm conclusion on any impact on overall survival.

Thus either single-agent oral alkylating agents (continuous or intermittent chlorambucil) or a nucleoside analogue (2-CdA or fludarabine) are recommended for the initial therapy of symptomatic patients. The continuing United Kingdom/ALLG randomised study of chlorambucil versus fludarabine in this setting is addressing the highly relevant question of the optimal initial therapy. It should be supported by both patients and clinicians. Combination therapies that are capable of achieving significantly higher rates of true complete remissions are required. This is a reasonable surrogate endpoint for the rapid assessment of efficacy in the context of exploratory phase II studies of novel combinations.

Guideline — Low-grade lymphoma — Waldenstrom's lymphoma — therapeutic options	Level of evidence	Refs
Patients with asymptomatic Waldenstrom's macroglobulinemia may be observed without initial therapy.	IV	113
Patients with symptomatic or progressive Waldenstrom's macroglobulinemia may be treated with plasmapheresis.	III	115, 116

Relapsed or refractory disease

In the context of relapsed/refractory disease, alkylating agent-based therapy (cyclophosphamide, adriamycin, prednisolone) has been compared with single-agent fludarabine.[122] Using conventional response criteria, the response rates were 11% and 30% respectively (P = 0.02), with median response durations of three months and 19 months respectively (P < 0.01), and superior event-free survival with fludarabine (P < 0.01). In spite of these differences, there was no difference in overall survival (P = 0.89). These response rates are supported by previous single-arm phase II studies of the nucleoside analogues in this context, where 2-CdA was able to induce responses in 45% of patients, and fludarabine in 31%.[113] There are no comparative studies of these two nucleoside analogue agents in this setting. Thus in the setting of relapsed or refractory disease, a nucleoside analogue, either fludarabine or 2-CdA, is clearly superior to alkylating agent therapy, and is recommended.

Guideline — Low-grade lymphoma — Waldenstrom's lymphoma — response to therapy	Level of evidence	Refs
In patients with relapsed Waldenstrom's macroglobulinemia, a nucleoside analogue (2-CdA or fludarabine) is associated with a higher response rate and more durable disease control than alkylating agent/anthracycline therapy.	II	122
Rituximab has useful activity as a single-agent in relapsed/refractory Waldenstrom's macroglobulinemia.	III	123–125
The combination of fludarabine and rituximab has high levels of activity in relapsed/refractory Waldenstrom's macroglobulinemia.	III	126

Thalidomide[127] has attained a response rate of 25%, but with very brief durations of response, making this therapy unattractive as a single-agent. Interferon-α has demonstrated modest activity[128] and can be considered as a maintenance therapy, provided it is well tolerated.

Monoclonal antibodies — rituximab

In previously untreated patients, MabThera (rituximab) has achieved a response rate of 35%.[125] In phase II studies in relapsed/refractory patients, MabThera (rituximab), has demonstrated a cumulative response rate of 36% (23/64), with median response durations of 7–15 months.[124–126] The combination of fludarabine and MabThera has shown marked activity and good tolerance in a phase II study in patients with relapsed/refractory disease, with an overall response rate of 65%[126]. Based on the established superiority of such combination strategies compared with fludarabine-containing chemotherapy alone in a broad range of indolent lymphoproliferative disorders, including Waldenström's macroglobulinemia, this combination is a very reasonable treatment for patients with relapsed/refractory disease.

Other management issues

Splenectomy can be effective in ameliorating symptomatic splenomegaly and can improve peripheral blood cytopenias due to splenic sequestration or autoimmune phenomena.

For patients with recurrent severe proven infections in the context of established hypogammaglobulinemia, regular replacement therapy with a pooled intravenous immunoglobulin preparation, such as Intragam, is recommended.

In the rare cases where it has been applied, high-dose therapy and either autologous stem-cell transplantation or allogeneic stem-cell transplantation have been able to achieve durable disease control, but with substantial morbidity and some mortality risk in this generally elderly patient group.[129] There are insufficient data to determine whether allogeneic stem-cell transplantation can

offer the prospect of cure for these patients, as is achievable in other 'low-grade' lymphoproliferative disorders.

Approximately 10% of patients ultimately develop a variety of forms of histologic transformation, with a poor outcome with conventional therapies.

12.10 Splenic marginal zone lymphoma

Summary of clinicopathological findings

Clinical	Spleen, splenic hilar nodes, bone marrow and blood. Bone marrow usually involved. Autoimmune thrombocytopaenia or anaemia common.
Morphology	Blood: villous lymphocytes +/- plasmacytoid forms. Spleen: Small round lymphocytes fill splenic marginal zone and replace mantle zone and germinal centres. Peripheral zone of slightly larger and paler cells. +/- plasmacytic differentiation. Red pulp involved. Lymph node: nodular pattern, replacement of follicles but no 'marginal zone' pattern. Sinuses dilated.
Immunophenotype	SIgM+ SigD+, CD19+, CD20+, CD79a+, CD5-, CD10-, CD43-, cyclinD1-, CD103-.
Genetics	Allelic loss of 7q21–32 t(11;14) and trisomy three may represent crossover with mantle cell and extranodal marginal zone lymphoma.

The median survival of patients is reported to be about thirteen years[130]. Adverse prognostic factors include: older age, anaemia, thrombocytopenia, and lymphocytosis.

Key points

Splenic marginal zone lymphoma

There are no prospective studies available to guide recommendations in this area. All available data are derived from retrospective cohort series. Within these limitations, the following recommendations can be made:

1 It is reasonable to follow, without active intervention, patients who are asymptomatic with stable lymphocytosis and minor, stable and asymptomatic cytopenias.[130,131]

2 It is recommended that patients be screened for hepatitis C. Where active hepatitis C is the underlying immunological precipitant for their lymphoma, specific treatment of the hepatitis C can be associated with significant regression of the lymphoma.[7]

3 Where patients have progressive or symptomatic splenomegaly, even in the context of significant marrow infiltration, splenectomy is the preferred therapy, where this can be performed safely.[130–132] Splenectomy results in favourable clinical response in ~90% of patients. About50% will never require any further therapy. Patients who are initially treated with splenectomy are reported to have a superior likelihood of survival than those initially treated with chemotherapy, although selection bias cannot be excluded in these retrospective comparisons.[130]

4 Where systemic chemotherapy is required for disease progression following splenectomy, or for symptomatic extra-splenic disease, either single-agent alkylating agents such as chlorambucil[131] or fludarabine[133,134] are reasonable choices, based on limited non-comparative data. CHOP does not appear superior to simpler alkylating agent therapy.[132]

Approximately 10% of patients ultimately develop various forms of histologic transformation with a poor outcome with conventional therapies.[135]

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CHAPTER 13 AGGRESSIVE LYMPHOMA

13.1 Introduction

This diverse group of lymphomas has in common an aggressive clinical behaviour. These lymphomas are very sensitive to chemotherapeutic agents, rendering them curable in a significant proportion of patients.

The pathological entities in this group of diseases are included in the mature B-cell and mature T-cell neoplasms in the WHO classification.[1]

They are:

- B-cell:
  1 Diffuse large B-cell lymphoma (DLBCL)
  2 Mantle cell lymphoma
  3 Mediastinal (thymic) large B-cell lymphoma
  4 Intravascular large B-cell lymphoma
  5 Primary effusion lymphoma
- T-cell:
  6 Angioimmunoblastic T-cell lymphoma
  7 Peripheral T-cell lymphoma, unspecified (PTCL)
  8 Extranodal NK/T-cell lymphoma, nasal type
  9 Hepatosplenic T-cell lymphoma
  10 Anaplastic large-cell lymphoma (ALCL)

13.2 Epidemiology

The aggressive lymphomas comprise about 50% of all lymphomas. The most common subtype is DLBCL, which constitutes 30–40% of all adult lymphomas.[2] The median age of patients is in the 60s, but the range is broad and the incidence increases with age.

The proportion of the specific subtypes according to the WHO classification is as follows:

DLBCL	30.6%
Mantle cell lymphoma	6.0%
Mediastinal LBCL	2.4%
PTCL	7.6%
ALCL	2.4%

13.3 Clinical presentation

Patients typically present with a rapidly enlarging mass at a nodal or extranodal site. Up to 40% of cases present with extranodal disease. The most common extranodal site is the gastrointestinal tract

(stomach or ileocaecal region). Virtually any extranodal site may be a primary location, including skin, bone, central nervous system, testis, and breast.

In general, DLBCL arises *de novo*, but in some cases, DLBCL arises as a result of transformation from an indolent lymphoma, for example, follicular lymphoma, CLL/SLL, marginal zone B-cell lymphoma, or nodular lymphocyte predominant Hodgkin lymphoma. Patients who are immunodeficient have an increased risk of developing DLBCL. In these cases the tumours are frequently positive for the Epstein-Barr virus (EBV).

13.4 Staging

The staging process is similar to that recommended for Hodgkin lymphoma (see Chapter 11):

1 History and Physical Examination

2 Radiology: chest x-ray, CT scan of chest, abdomen and pelvis

3 Pathology: full blood count, routine biochemistry including LDH and uric acid

4 Bone marrow biopsy

5 Diagnostic lumbar puncture in certain circumstances (paranasal sinus presentation, testicular lymphoma, involvement of bone marrow, more than two adverse parameters according to IPI)

6 Functional imaging — gallium and/or PET scanning. Evolving data suggest that PET scanning may be more sensitive than gallium scanning for the staging of patients with lymphoma[3]

7 MUGA scan or echocardiogram where appropriate

8 Stage according to Ann Arbor system (see Table 11.1)

13.4.1 International prognostic index

Pretreatment prognostic factors are critical in determining treatment and predicting outcome. The International Prognostic Index (IPI) was developed from a study of 2031 patients with aggressive lymphoma treated with a doxorubicin-based chemotherapy regimen. Five pre-treatment characteristics were found to be independent predictors. These are: age (≤60 versus >60), stage I or II versus stage III or IV, number of extranodal sites involved (≤1 versus >1), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus ≥2), serum LDH (normal versus greater than normal).[4]

Table 13.1 demonstrates the value of the index, which should be determined for each patient prior to treatment.

Table 13.1 International Prognostic Index

Risk group	Number of risk factors	% of patients	CR rate (%)	5-year survival (%)
Low	0–1	35	87	73
Low–intermediate	2	27	66	51
High–intermediate	3	22	54	43
High	4–5	16	34	26

Recently, cDNA microarray profiling has been shown to predict treatment outcome through the identification of specific patterns of gene expression.[5] DLBCL can be divided into prognostically significant subgroups with germinal centre B-cell-like (GCB), activated B-cell-like (ABC), and type 3 gene expression profiles.[6,7]

The GCB group has significantly better survival than the ABC group. The type 3 is heterogeneous, but has a poor outcome similar to the ABC group. Recently, immunostains have been used to determine the GCB and non-GCB subtypes of DLBCL and predict survival similar to the cDNA microarrays.[8]

13.5 Treatment of aggressive lymphoma

13.5.1 General principles

Where feasible, patients should have their treatment planned in a multidisciplinary process. This should comprise, at a minimum, haematologist/medical oncologist and radiation oncologist.

The treatment plan should reflect histological subtype, stage, IPI, age, co-morbidities and performance status.

The treatment strategy in patients with aggressive lymphoma, where feasible, is to cure the patient with initial therapy. The main treatment modality is combination chemotherapy, while in some patients the addition of radiation therapy provides additional benefit. Surgery has little role in this disease.

Relapse or failure to achieve complete response to therapy is associated with a poor outlook.

13.6 Diffuse large B-cell lymphoma (DLBCL)

Summary of clinicopathological findings

Clinical	Nodal or extranodal (any site). Rapidly expanding mass at any site. Often disseminated.
Morphology	Diffuse or partial, may be interfollicular or sinusoidal. *Variants*: centroblastic (inc. multilobated form), immunoblastic, T-cell/histiocyte-rich, anaplastic.
Immunophenotype	Mostly SIg+(M>G>A), cytoIg+ in plasmacytic/immunoblastic types. CD19+, CD20+, CD22+, CD79a+. CD30+ in most anaplastic cases and some non-anaplastic cases. Occasionally CD5 or CD10+ve. *Bcl-2* +ve in minority of cases. Bcl-6 +ve. Proliferation index (Ki-67) is high, >90% in rare cases. *Variants*: (a) Plasmablastic EBER+, CD20-, CD45-, CD138+. (b) DLCL with expression of full length IgA+, SIg+, ALK-, CD30-, CD45+/-, EMA+, CD4+, CD57+.
Genetics	Mostly post germinal centre t(14;18) in 20–30% bcl-6 gene involved in 30% These have prognostic significance.

The management of DLBCL has provided a model for curative cancer therapy integrating chemotherapy and radiotherapy. The following principles of management may also be applied to the other aggressive lymphoma entities.

13.6.1 First-line treatment of patients with DLBCL

Early-stage disease

About 15–20% of patients with DLBCL present with localised disease defined as stage I or II. Before 1980, radiation therapy alone was used as the primary treatment for patients with localised DLBCL. Approximately 50% of patients with stage I and 20% of patients with stage II disease were alive without recurrence at five years.[9] In a retrospective study from Stanford University, local control rates of 70–80% were achieved at doses ranging from 20 Gy to 50 Gy.[10] In patients with limited disease and normal LDH, local radiotherapy alone is reported to produce 70–80% five-year freedom from progression, and can be considered in patients unsuitable for chemotherapy. Most relapses occur outside the radiation field.[11]

Several large phase II trials have shown that combined-modality therapy using chemotherapy in addition to involved-field radiotherapy produced high, long-term, disease-free survival rates. In most of these studies, the radiation fields were reduced and the doses of radiation were also lower than when radiation is used as the sole treatment modality. The largest series, using a combination of doxorubicin-based chemotherapy regimens and involved-field radiation, produced complete remission rates of close to 100%, and five-year survival rates of over 80%.[12,13]

Several prospective randomised trials have been performed by cooperative groups addressing the role of radiation therapy in localised DLBCL. The Southwest Oncology Group (SWOG) randomised 401 patients with stage I and non-bulky stage II aggressive lymphomas (75% DLBCL) to three cycles of CHOP followed by involved-field radiation therapy to a dose of 40–55 Gray or to eight cycles of CHOP alone.[14] Both the PFS and OS at five years were superior in the combined modality arm (PFS 77% versus 64%, P=0.03; OS 82% versus 72%, P=0.02). Severe toxicity and cardiac toxicity were higher in the patients receiving CHOP alone. In an update of this study, with a median follow up of eight years, the authors reported a higher relapse rate and lymphoma-related deaths occurring between five and ten years for the combined modality arm, such that the curves overlap at seven years for FFS, and at nine years for OS.

The Eastern Cooperative Oncology Group (ECOG) treated 352 patients with stage I (bulky >10 cm mass or extranodal) or stage II disease with eight cycles of CHOP. The 215 patients achieving a CR were randomised to no further treatment or involved-field radiotherapy to a dose of 30 Gy for patients in CR or 40 Gy for those in PR. The disease-free survival and overall survival at five years were superior for the combined chemoradiotherapy arm (73% versus 58%, P=0.03 and 84% versus 70%, P=0.06) respectively. At ten years, the DFS was in favour of the combined therapy arm (P=0.05), but there was no difference in OS, P=0.24.[15,16]

The Groupe d'Etudes des Lymphomes des l'Adultes (GELA) reported a study in patients >60 years with stage I and II aggressive lymphoma and an age-adjusted IPI of zero. Patients were randomised between four cycles of CHOP versus four cycles of CHOP plus involved-field radiation therapy to 40 Gy. There were no differences in CR rates, five-year EFS or OS. However, for patients older than 70 years, the overall survival was better in the group receiving CHOP alone.[17]

Another study from GELA compared three cycles of CHOP followed by 30–40 Gy involved-field radiotherapy with the chemotherapy regimen ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), followed by consolidation chemotherapy with methotrexate, ifosfamide, etoposide and cytarabine. In 631 patients with low-risk, localised aggressive lymphoma EFS and OS were 74% and 80% for CHOP plus radiation versus 83% and 89% for the complex sequential chemotherapy regimen (P=0.004 and P=0.02 respectively.[18]

Guideline — Recommended treatment for localised aggressive lymphoma	Level of evidence	Refs
Patients with non-bulky stage I, with normal LDH and ECOG PS ≤1, should be treated with three cycles of CHOP and involved-field radiation therapy to a dose of 30–40 Gy.	II-III	9–14
Patients with bulky stage I, stage II, high LDH, ECOG ≥2 and/or three or more disease sites should be treated with 6–8 cycles of CHOP followed by involved-field radiation to 30–40 Gy.	II	15, 16
Radiotherapy may be unnecessary in elderly patients with localised aggressive lymphoma.	II	17
Patients with low-risk localised aggressive lymphoma may be treated with more intensive sequential chemotherapy, omitting radiation therapy.	II	18

Initial treatment of advanced-stage DLBCL

For patients with advanced-stage disease (stages III and IV), combination chemotherapy with curative intent is the most effective treatment. Prior to the development of multi-agent chemotherapy, the median survival of patients with DLBCL was less than one year.

Combination chemotherapy has been shown to have high efficacy in aggressive lymphoma. The CHOP regimen was first described in 1975. It has been studied extensively in single arm and randomised clinical trials. The standard CHOP regimen consists of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (capped at 2.0 mg), and prednisone (or prednisolone) 100 mg/day for five days (no standard dose, some trials use 40 mg/m^2). Treatments are given every 21 days.[19]

Attempts were made to increase the CR rate and decrease the relapse rate by developing second and third generation regimens based on the concept of dose intensity. They were designed to deliver the greatest number of active drugs (generally six to eight) at the highest possible drug dose per unit time. These regimens included m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, followed by cytarabine, bleomycin, vincristine and methotrexate), and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin). However, randomised trials comparing CHOP to second and third generation regimens failed to show any benefit of the newer regimens. The landmark intergroup SWOG/ECOG phase III trial comparing the above four regimens showed no difference in CR, progression-free (estimated five year of 33–38%) or overall survival (estimated five year of 45–46%).[20] A meta-analysis of these trials confirmed the equivalence of CHOP to other regimens.[21]

There are no randomised trials comparing the efficacy and toxicity of six versus eight cycles of CHOP. A common practice is to give two further cycles of CHOP after documentation of CR, with a minimum of six cycles, as most patients achieve CR after four.

Modified CHOP regimens

Modified CHOP regimens (CHOP-like) have generally attempted to reproduce or improve on the efficacy of CHOP with a reduction in toxicity. In these regimens, doxorubicin in CHOP was substituted by either another anthracycline or the anthracenedione mitoxantrone. A number of randomised phase III trials comparing these regimens to CHOP have shown equivalent efficacy and toxicity.[22–24]

Guideline — Recommended treatment for advanced-stage DLBCL	Level of evidence	Refs
CHOP chemotherapy is equivalent in outcome to other chemotherapy regimens with decreased toxicity.	II	19–24

Rituximab with standard CHOP

Rituximab is a chimeric human/murine IgG1 monoclonal antibody that binds specifically to the B-cell surface antigen CD-20. It acts by inducing both complement-mediated and antibody-dependent cytotoxicity. It also induces apoptosis and sensitised chemoresistant human lymphoma cell lines to cytotoxic chemotherapy.[25]

Rituximab alone at a dose of 375 mg/m^2 per week has a response rate of 31% in relapsed DLBCL.[26]

The addition of rituximab to CHOP has been widely explored in clinical trials. High response rates have been reported in phase II studies. In a phase II trial of 33 patients treated with R-CHOP for six cycles, the CR rate was 76%, with 88% progression-free at a median follow up of 31 months.[27]

The GELA group performed a randomised phase III trial in 399 elderly (age range 60–80 years), previously untreated patients with advanced-stage DLBCL of standard-dose CHOP given every 21 days, versus the same regimen plus rituximab (375 mg/m^2) on day one of each of eight cycles of treatment (R-CHOP). Patients were stratified by age-adjusted IPI scores (0–1 versus 2–3). The CR/CRu rate increased from 63% to 76% (p=0.005). The EFS was significantly longer in the R-CHOP arm as a result of lower rates of relapse and progression (P<0.001). The two-year OS was 57% in the CHOP arm and 70% in the R-CHOP arm (P=0.007). No increase in toxicity was noted and the addition of rituximab did not compromise the dose-intensity of CHOP. The benefit of R-CHOP was consistent across all subgroups of patients tested, including both low-risk (IPI 0–1) and high-risk (IPI 2–3) patients, but was greatest in patients with low-risk disease. An update of this trial presented at the ASH meeting in December 2003 showed that the results hold up with longer follow up. Whether these results can be extrapolated to young patients with advanced-stage disease, or to patients with early-stage disease, will require further clinical trials.[28,29]

The addition of rituximab to chemotherapy appears to have the greatest impact in DCBCL that over-expresses *bcl-2*. Several studies have implicated *bcl-2* over-expression as a poor prognostic factor in DLBCL. In the GELA study, two-year EFS and OS rates improved from 32% to 58% and from 48% to 67% respectively in the R-CHOP arm. There was no difference in EFS or OS rates between CHOP and R-CHOP in *bcl-2* negative patients.[30]

A second large randomised study was presented by Haberman et al. at the ASH meeting in December 2003.[31]

This was a North American intergroup study in 632 patients older than 60 years who were randomised to either R-CHOP or CHOP, followed by a second randomisation in patients achieving CR or PR to observation or maintenance rituximab. The overall response rates (ORR) were 77% with R-CHOP and 76% with CHOP (P=0.76). With a median follow up of 2.7 years, the TTF favoured R-CHOP (P=0.025), but there was no difference in OS (P=0.25). TTF also favoured maintenance rituximab (P=0.01), but there was no difference in OS (P=0.67). The schedule of rituximab used in this study differed from those in the GELA study. Patients received fewer courses of rituximab during induction CHOP. These factors may account for the differences in results between this study and the GELA study.

Guideline — Recommended treatment for advanced-stage DLBCL	Level of evidence	Refs
The addition of rituximab to CHOP is superior to CHOP in patients older than 60 years.	II	25–31

Dose intensified CHOP-like regimens

High-dose CHOP or CHOP-like regimens

Few studies have looked at increasing doses of the drugs in the CHOP regimen. The Australasian Leukaemia and Lymphoma Group (ALLG) performed a randomised trial in patients with aggressive lymphoma, stage I bulky, II–IV, comparing CEOP (cyclophosphamide 750 mg/m^2 epirubicin 75 mg/m^2), to high-dose CEOP (cyclophosphamide 1500 mg/m^2 epirubicin 150 mg/m^2) with G-CSF. In a study of 250 patients, there was no difference in CR rate, failure-free or overall survival, despite a mean 78% increase in dose intensity of the two drugs, cyclophosphamide and epirubicin.[32]

Guideline — Chop chemotherapy	Level of evidence	Refs
Dose escalation of CHOP or CHOP-like regimens does not improve overall survival.	II	32

Dose-dense regimens (including CHOP-14 and R-CHOP-14)

Gisselbrecht and colleagues treated 162 poor-prognosis patients with the LNH-84 induction regimen (cyclophosphamide, vindesine, bleomycin, prednisone, and methotrexate) and either doxorubicin or mitoxantrone. By using higher doses of cyclophosphamide and doxorubicin, and reducing the interval between cycles to two weeks, this regimen represents a two-fold increase in relative dose intensity over CHOP. Patients randomised to receive adjunctive G-CSF (5 µg/kg/day) were less likely to experience neutropenia or documented infections, and received significantly greater dose intensity, compared with patients not treated with G-CSF (93% versus 80%; p=0.0001). However, the CR rate and three-year survival were similar between the two groups. Adjunctive use of G-CSF facilitates the use of dose-intensified chemotherapy regimens.[33]

The results from two (NHL-B1 and NHL-B2) German High Grade Non-Hodgkin's Lymphoma Group studies have recently been published. Dose intensification was achieved by reducing the interval (dose-dense) between doses or by adding an extra drug to a combination regimen.

The data from NHL-B2 study suggest that reducing the interval between doses yields improved survival in elderly patients (61–75 years) with aggressive lymphoma. Final results were reported on 689 eligible patients of all IPI risk groups, who were randomised to the standard three-weekly CHOP regimen (CHOP-21), CHOP plus etoposide (CHOEP-21), or either regimen administered every two weeks (CHOP-14 or CHOEP-14) in all arms for six cycles. Shortening the treatment interval to two weeks was facilitated by the use of adjunctive G-CSF. Six hundred and eighty nine (689) patients were available for analysis. CR rates favoured CHOP-14. Five-year EFS and OS were 32.5% and 40.6%, respectively for CHOP-21, and 43.8% and 53.3% respectively for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 (p=0.003) for EFS and 0.58 (p<0.001) for OS.[34]

The results of the NHL-B1 are also available. This study looked at patients between 18 and 60 years with good prognosis lymphoma (normal LDH) and randomised them equally to CHOP-21, CHOEP-21, CHOP-14, CHOEP-14, for six cycles, as per NHL-B2. Shortening of the treatment interval to two weeks was facilitated by the use of adjunctive G-CSF. Seven hundred and ten (710) patients were available for analysis. CHOEP achieved better CR rates (87.6% versus 79.4%: p=0.003) and five-year

EFS (69.2% versus CHOP 57.6%; p=0.004), while interval reduction (i.e. 14-day regimens) improved OS (p=0.05; p=0.044) in the multivariate analysis.[35]

Guideline — CHOP Chemotherapy and Etoposide	Level of evidence	Refs
Etoposide added to CHOP therapy in low-risk patients younger than 60 years is superior in time to treatment failure than CHOP.	II	35

Gregory et al. in 2002 demonstrated in 120 patients (18–84 years) that CHOP-14 could be administered every fourteen days with prophylactic G-CSF support. Eight five per cent of the planned cycles were given on time at full dose. Haematologic toxicity was significant, but the tolerable with no treatment-related deaths and responses rates were comparable to CHOP-21.[36]

Wolf and Bentley[37], in Australia, have also demonstrated that pegfilgrastim can be used safely and efficaciously to support CHOP-14.

At the 2003 meeting of ASCO, the Senior Adult Care Task Force of the National Comprehensive Cancer Network (NCCN) advisory panels, Hotta et al. presented the Japan Clinical Oncology Group phase III study, JCOG9809, in which patients with advanced aggressive lymphoma were randomised between standard CHOP (S-CHOP) and CHOP given every two weeks (Bi-CHOP). Both arms received eight cycles of chemotherapy. There was no improvement in two-year progression-free survival or overall survival. The trial was terminated early after the first 286 patients were enrolled. It is not clear why this trial should have shown conflicting results to the German trial, as the full study has not been published. Patients' ages ranged from 17 to 69 years (median 57), and both normal and high LDH were included. The actual delivered dose intensity in the Bi-CHOP arm is uncertain.[38]

The GELA group has recently reported a study comparing eight cycles of CHOP to ACVBP (doxorubicin 75 mg/m^2 day one, cyclophosphamide 1200 mg/m^2 day one, vindesine 2 mg/m^2 days one and five, bleomycin 10 mg days one and five, every two weeks for four cycles, followed by sequential consolidation therapy (methotrexate with leucovorin, ifosfamide, etoposide and ara-C). There were 635 eligible patients aged 60–69 years, with at least one adverse prognostic factor by age-adjusted IPI. Despite higher toxicity, the ACVBP regimen was superior to standard CHOP in both event-free and overall survival. The CR rate was similar (56 versus 58%), but the EFS and OS at five years were better in the ACVBP arm (39 versus 29% and 46 versus 38% respectively).[39]

These studies of increased dose density represent methods in which dose-intensity chemotherapy can be delivered by decreasing the interval between cycles. The administration of dose-dense chemotherapy requires haematopoietic growth factor support from the first cycle of chemotherapy and every subsequent cycle.

Key point

It is difficult to offer a definitive guideline given the rapidly emerging new information about the adoption of dose-dense CHOP-like regimens with haemopoietic growth factor support. Participation is recommended in clinical trials where possible, or development of treatment policies in specialised units as new information becomes available.

Role of consolidative radiotherapy

Several retrospective studies have examined the impact of involved-field radiotherapy in patients with advanced-stage aggressive lymphoma who responded to CHOP or CHOP-like chemotherapy. These studies suggest that radiotherapy improved local control and freedom from progression in patients with tumour size of larger than 4–6 cm. One prospective, randomised trial in patients with stage IV

diffuse large-cell lymphoma and tumour masses >10 cm showed an improvement in disease-free (five-year rates 72% versus 35%, P<0.01) and overall survival (five-year rates 81% versus 55%, P<0.01).[40,41]

Use of haemopoietic growth factors

A 2004 report from the Cochrane Database entitled 'Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma' reviews 12 randomised studies with 1823 patients. This review concludes that when G-CSF given prophylactically does not affect tumour response, time to treatment failure or overall survival, there is a statistically significant reduction in the risk of neutropenia, febrile neutropenia and infection rates, leading to a potential positive impact for patients.[42]

However, as new information emerges from the dose-dense studies described above, recommendations for the use of G-CSF in these circumstances will need to be revised. This issue is discussed further in the next section.

Special populations — the aged

Balducci and Repetto report in 2004 that the benefits of prophylactic use of G-CSF in managing neutropenia in elderly patients with lymphoma have been shown in four studies. In these studies, a total of 656 patients receiving CHOP or CHOP-like therapy were randomised to G-CSF or placebo. The primary endpoints of these studies were grade 3/4 neutropenia and incidence of infection. The results in all four studies showed statistically significant reduction in grade 3/4 neutropenia and infection rates in the G-CSF treated groups.[43]

In a trial performed by the Dutch haemato-oncology association (HOVON) group in patients aged 65–90 years with stage II–IV aggressive lymphoma, patients were randomised between standard CHOP every 21 days and CHOP plus GCSF on days 2–11 of each cycle. In 389 eligible patients, the relative dose intensities (RDIs) of cyclophosphamide and doxorubicin were significantly higher in the G-CSF arm (96% versus 94% and 95% versus 93% respectively). However, there was no significant difference in CR rate (55 versus 52%) or OS at five years (22 versus 24%). There was also no difference in the incidence of infections or duration of hospitalisation. Thus, based on this study, the prophylactic use of G-CSF with standard CHOP is not justified.[44]

Published practice guidelines recognise the elderly as a population at increased risk for chemotherapy-induced neutropenia. ASCO and the European Organisation for Research and Treatment of Cancer (EORTC) recommend the use of prophylactic colony-stimulating factor (CSF) in elderly cancer patients receiving myelosuppressive chemotherapy.

In a published letter to the Journal of Clinical Oncology, Balducci and Lyman identified elderly (≥70 years) patients as a special population at risk for chemotherapy-induced neutropenia.[45]

The ASCO 2000 guidelines for the use of CSFs recommend that prophylactic CSFs be considered in certain circumstances in patients who are at higher risk for chemotherapy-induced neutropenia infectious complications. In addition to older age, risk factors include pre-existing neutropenia due to disease, extensive previous chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; history of recurrent febrile neutropenia while receiving chemotherapy of similar or lower dose intensity; or potentially enhancing the risk of serious infection (e.g. poor performance status and more advanced cancer, decreased immune function, open wounds, or active tissue infections).[46]

The EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer conclude:

> …the Working Party recommends the use of prophylactic G-CSF to support the administration of planned doses of chemotherapy on schedule and reduce the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infections in elderly patients receiving myelotoxic chemotherapy.[47]

Key points

Special populations — the aged

Prophylactic G-CSF should be considered in elderly patients and also in patients thought to be at high-risk, which is defined as:

- pre-existing neutropenia due to disease
- extensive previous chemotherapy or significant previous radiation therapy
- history of recurrent febrile neutropenia while receiving chemotherapy of similar or lower-dose intensity
- at risk for serious infection (e.g. poor performance status, decreased immune function, open wounds, or active tissue infection)

Careful consideration should be given in the use of anthracyclines in this group of patients with potential cardiac dysfunction.

Front-line high-dose therapy with stem cell support

Early attempts at utilising high-dose chemotherapy (HDCT) and autologous stem cell transplantation derived from observations from the PARMA study in which patients with relapsed aggressive lymphoma salvaged with HDCT and ASCT demonstrated improved survival rates compared to those who had received conventional salvage chemotherapy.[48] This study defined high-dose therapy as the treatment of choice for patients with relapsed aggressive lymphoma sensitive to salvage chemotherapy.

A number of studies have examined the role of high-dose therapy to consolidate an initial response to chemotherapy. These studies have been characterised by significant variability with respect to the timing of the HDCT, the amount of induction therapy administered (i.e. abbreviated or full-course induction), and in their recruitment of different IPI risk cohorts. Accordingly, the studies have yielded conflicting results.

The LNH87-2 trial of the GELA group randomised 1043 patients less than 55 years of age to one of AVVB or NCVB followed by four additional cycles of cyclophosphamide, vindesine, bleopmycin, prednisone and intrathecal methotrexate. Patients achieving a CR were then randomised to either HDCT and SCT or additional cycles of sequential chemotherapy. In the initial analysis there were no differences in the three-year OS or DFS.[49] However, a subsequent retrospective analysis of 236 patients who were IPI high-intermediate or high-risk showed a superior eight-year DFS (55% versus 39%, P=0.02) and OS (64% versus 49%, P=0.04) for the high-dose therapy arm.[50]

In another GELA study reported by Gisselbrecht et al., 397 patients under 60 years of age with poor prognosis aggressive lymphoma and two to three risk factors were randomised to a five-drug chemotherapy regimen or a shortened treatment program with three cycles of escalated doses of cyclophosphamide, epirubicin, vindesine, bleomycin and prednisone followed by high-dose chemotherapy and autologous stem cell transplantation. The five-year DFS and OS was inferior for the group receiving transplantation.[51]

A recent meta-analysis of eleven randomised studies of autologous stem cell transplantation, suggested a benefit in terms of improved overall survival for HDCT/ASCT over and above

conventional therapy only among those patients with high or high–intermediate IPI, and who had received prior full-course (versus abbreviated) induction therapy.[52]

At present, up-front, high-dose therapy with autologous stem cell transplantation cannot be recommended, even for poor-risk patients, outside of a clinical trial.[53]

Guideline — Front-line high-dose therapy with stem cell support	Level of evidence	Refs
Up-front high-dose therapy with autologous stem cell transplantation cannot be recommended outside of a clinical trial.	II	48–53

Central nervous system prophylaxis

Central nervous system (CNS) relapse of lymphoma is usually fatal despite therapy, and effective prophylaxis is desirable. It occurs in between 5% and 30% of patients with aggressive lymphoma. The incidence is insufficient to justify universal CNS prophylaxis. Many attempts have been made to identify factors associated with a high rate of CNS relapse. There is general agreement that patients with testicular and paranasal sinuses involvement should receive prophylaxis. For other groups, there are two large retrospective studies for guidance. Involvement of more than one extranodal site and a raised LDH was the only independent predictor of CNS recurrence.[54] Patients with both risk factors had a 17.4% incidence of CNS recurrence at one year compared to a 2.8% incidence if one or neither of these factors was present. A study by the HOVON group reported the risk of CNS recurrence to be related to the IPI score. Low-risk patients had a 0% incidence; high-risk had a 27% risk of CNS recurrence.

The optimal prophylactic therapy is unclear. In most cases, intrathecal chemotherapy with methotrexate or cytarabine is used. However, a 26% rate of CNS relapse in high-risk patients given prophylactic treatment with intrathecal chemotherapy has been reported.[55]

Response assessment

1 Physical examination and appropriate radiological tests should be performed after 2–4 cycles of CHOP and 3–4 weeks after the last cycle to assess response.

2 If a bone marrow biopsy is initially abnormal it should be repeated at the end of treatment.

3 Standard response criteria should be used to assess response categories.

4 The use of functional imaging (gallium-59, or FDG-PET) is often of value in assessing response, particularly in the evaluation of a residual mass after chemotherapy.

5 Many residual abnormal masses on CT scan do not contain any viable tumour tissue. If clinically indicated, biopsy of a residual mass should be considered. A percutaneous fine-needle aspirate or core biopsy under radiological guidance is often of value in this situation. It is possible that PET scanning may avoid this issue.

6 Patients who have not achieved a complete response (CR) should be evaluated for early salvage treatment regimens. Evolving opinions suggest that PET scanning, even after as few as one to two cycles, may predict likelihood of CR. This is an area for continuing study.

Follow up

There are few studies examining the value of follow-up strategies on the early detection and treatment of recurrence of lymphoma. The European Society of Medical Oncology recommends the following follow-up schedule.[56]

1 History and physical examination every three months for two years, every six months for three more years, and then annually. High-risk patients may require more frequent assessments.

2 Blood count and LDH at three, six, twelve and twenty-four months, the subsequently only if there is clinical suspicion of relapse.

3 Evaluation of thyroid function (TSH) in patients receiving neck irradiation at one, two and five years.

4 Screening for breast cancer in women who received chest irradiation at a premenopausal age, starting at 40–50 years.

5 Adequate radiological examinations at six, twelve and twenty-four months, by CT scan when indicated by site of disease.

There is little evidence to support these recommendations for follow-up procedures. In the retrospective studies that have been reported in the literature, only a minority of recurrences were detected by routine laboratory or radiologic studies.

13.6.2 Treatment of patients with relapsed aggressive lymphoma

More than 50% of patients with aggressive lymphoma are either primary refractory or, more often, relapse after a complete response to their initial treatment. For these patients, high-dose therapy with stem cell transplantation has been demonstrated to have the greatest potential for cure.[48] However, this treatment approach is generally restricted to patients who are sensitive (achieve a CR or PR) to second-line or salvage chemotherapy. In general, patients who are refractory to second-line chemotherapy should not be offered stem cell transplantation except in the context of a clinical trial. These patients have a very poor prognosis.

Where relapse occurs late (more than twelve months after initial treatment) patients should, wherever possible, have a repeat biopsy to exclude the possibility of a follicular lymphoma. Early relapse does not generally require a rebiopsy.

Staging procedures should follow the guidelines for newly diagnosed disease. The IPI should be calculated, as this has prognostic value. The cumulative dose of anthracyclines used during first-line therapy should be calculated. If further anthracyclines are to be used, an echocardiogram or MUGA scan for the quantification of the left ventricular ejection fraction should be done.

There are no randomised trials comparing salvage regimens. Commonly used regimens studied in phase II trials are dexamethasone, high dose cytarabine and cisplatinum (DHAP or DHAC), etoposide, cisplatinum, high dose cytarabine and methylprednisolone (ESHAP), ifosfamide, carboplatin and etoposide (ICE), and etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin (EPOCH). Response rates to salvage chemotherapy generally range between 45% and 70%, with CR rates of 25–40%. In the absence of a clinical trial, the choice of salvage regime is up to the individual physician. Some regimens, for example, ICE, also enable the collection of adequate numbers of peripheral blood stem cells.

Recently, many salvage regimens have incorporated the anti-CD20 monoclonal antibody rituximab. In one study, the CR rate in patients treated with R-ICE was significantly higher than with historical controls treated with ICE.[57]

There is no current established role for allogeneic stem cell transplantation in relapsed or refractory aggressive lymphoma. This procedure could be considered in individual patients with relapsed disease, who are young and have a histocompatible donor.

13.7 Mantle cell lymphoma

Summary of clinicopathological findings

Clinical	Older patients, male predominance, stage III or IV. Hepatosplenomegaly, lymphadenopathy and marrow involvement. GI involvement common.
Morphology	Mantle zone, nodular or diffuse patterns. No proliferation centres. Monomorphous small to medium-sized cells with irregular nuclear contours. Absence of large follicle centre cells, prolymphocytes, immunoblasts or para-immunoblasts. Scattered epithelioid histiocytes. Variants: blastoid; (classic, lymphoblastoid and pleomorphic)
Immunophenotype	SIgM and IgD+. CD5+ in most cases, CyclinD1+, CD43+, FMC7+, *bcl-2*+. CD23-, CD10-, *bcl-6*-,CD21, CD23OR CD35 dispersed FDC meshworks reflecting architectural pattern.
Genetic	Pre-germinal centre cell. t(11:14)(q13;q32) in most cases (PRAD1, *bcl-1*). Other cytogenetic changes often associated with blastic variants.

13.7.1 Prognosis

Mantle cell lymphoma (MCL) was recognised as a distinct clinicopathological entity in 1991.[58] It is now accepted that this form of lymphoma has among the poorest long-term outcome of all B-cell lymphomas. However, a small proportion of patients with MCL may have an indolent course, and not initially require therapy. Attempts at prediction of outcome are under investigation with the use of new prognostic markers.[59–63]

Key point

Identification of indolent subgroups of mantle cell lymphoma using appropriate indices and markers is emerging as an important issue.

13.7.2 Non-intensive therapy

The BNLI report of 65 cases of MCL treated with non-intensive therapy (radiotherapy, COP, or chlorambucil) showed that such approaches were associated with median progression-free (PF) and overall survival (OS) times of 2 and 4.75 years respectively. Forty of these patients received second-line therapy, with a median overall survival of 25 months. None were alive at ten years.[64]

The rare patient with localised disease may, however, be cured by involved-field radiotherapy alone.[64]

These poor results have led to the investigation of novel treatment strategies in MCL.

The addition of anthracyclines appears to add little, with CR rates of 20–30% and similar over-all outcomes reported in a number of phase II studies.[65–67]

13.7.3 Role of rituximab

The addition of rituximab to CHOP and the fludarabine, cyclophosphamide and mitoxantrone (FCM) regimen have been reported to improve responses in recently reported randomised studies.

The German Low Grade Lymphoma Study Group (GLSG) performed a prospective randomised trial of CHOP versus CHOP plus rituximab (CHOP-R) in 122 patients with newly diagnosed stage III or IV MCL. CHOP-R was superior to CHOP in terms of overall response rate (94% versus 75%), CR rate (34% versus 7%), and time to treatment failure (median 21 months versus 14 months), but not

progression-free or overall survival.[68] The authors suggest that CHOP-R may serve as a new baseline for advanced-stage MCL. They acknowledge, however, that post-induction therapy needs to be further improved given the lack of impact on overall survival.

A second prospective randomised study of the GLSG compared FCM with rituximab FCM in patients with relapsed or refractory MCL and follicular lymphoma. Only 48 patients with MCL could be evaluated. This study showed the FCM plus rituximab regimen was superior in terms of overall response (58% versus 46%), CR (29% versus 0%), progression-free survival and strikingly, overall survival.[69]

Both studies suffer from their small size and the low CR rates in the standard arms. Their findings need to be confirmed.

Phase II studies of novel agents such as thalidomide and the proteosome inhibitor bortezomib have suggested significant activity in MCL.[70–72]

Intensification of chemotherapeutic regimens has been investigated using a variety of approaches. Such strategies have limited applicability, given the age of patients with MCL —the median is 60–65 years.[64]

13.7.4 Intensive and high-dose chemotherapy

The hyper-CVAD regimen produced a 68% CR rate in a small single institution study of newly diagnosed patients over the age of 65 years.[73]

A number of phase II studies utilising autologous transplantation have been reported.[74–84]

Three recently published studies are described below:

- A French multicentre study enrolled 28 patients with newly diagnosed MCL into a program of sequential CHOP, DHAP and then TBI-cytarabine-melphalan-conditioned peripheral blood stem cell autologous transplant (auto-PBSCT). A high CR rate (84%) and long PFS (75% at a median follow up of four years) were reported.[74]

- An Italian multicentre study enrolled 28 newly diagnosed patients to receive an intensive regimen following standard induction. The R-HDS regimen included cyclic high-dose cyclophosphamide (7 gm/m^2), high-dose cytarabine (24 gm/m^2) and two cycles of high-dose melphalan (180 mg/m^2). The program was supported by auto-PBSCT and six doses of rituximab were administered. Once again, a high CR rate (100%) and high OS and EFS at 54 months of 89% and 79% were seen.[75]

- A small study utilising I-131-labeled anti-CD20 antibody followed by high-dose cyclophosphamide and etoposide supported with the infusion of autologous PBSC reported similar response and survival rates.[76]

These studies suggest that the use of HDT with auto-PBSCT may prolong survival in MCL. A similar conclusion was drawn from a registry-based analysis of 195 patients with MCL transplanted and reported to the European Group for Blood and Marrow Transplantation and the International Bone Marrow Transplant Registry. Best outcomes were seen with patients transplanted in first CR or those with responsive disease.[85]

A single phase III study addressing the role of autologous transplantation has been reported. This study, performed by the European MCL network, randomised newly diagnosed responsive patients to receive either two cycles of Dexa-BEAM followed by a Cy/TBI-conditioned auto-PBSCT, or a total of eight cycles of CHOP followed by interferon maintenance. One hundred and twenty two (122) patients were randomised. While response rates were higher and PFS was longer in patients randomised to the HDT arm, OS at three years was not prolonged.[86]

Taken together, these data suggest that selected patients may benefit from autologous transplantation but this strategy cannot be recommended as part of standard therapy at this time. Data confirming that increased response rates translate to prolongation in survival are awaited.

The role of allogeneic transplantation remains uncertain.

The experience with myeloablative allo-HSCT is limited to case reports or small series. Long-term survival has been reported.[87]

The data concerning non-myeloablative allografts allow the conclusion that there seems to be a graft versus MCL effect. The durability of responses is unclear, as is the optimal transplant protocol.[87]

Key point

The optimal therapy of patients with mantle cell lymphoma is unclear at present. Given the poor outcomes with conventional therapy, novel approaches should be considered and implemented preferably in the context of clinical trials. Such patients should optimally be managed in specialised centres.

13.8 Mediastinal (thymic) large B-cell lymphoma

Summary of clinicopathological findings

Clinical	Female predominance, third to fifth decades. Localised anterior mediastinal mass. Dissemination is extranodal: kidney, adrenal, liver skin and brain.
Morphology	Diffuse, sclerotic and compartmentalised like carcinoma. Large cells with clear cytoplasm.
Immunophenotype	CD19+, CD20+, CD45+. Ig and HLA-DR may be –ve. CD5-, CD10-. Often CD30 weakly +ve.
Genetics	Hyperdiploid, gains in 9p and *REL* amplification. Over-expression of *MAL* gene.

Primary mediastinal B-cell lymphoma (PMBCL) with sclerosis is a distinctive subtype of non-Hodgkin's lymphoma. It has unique clinicopathologic aspects and aggressive behaviour. This is a subtype of DLBCL arising in the mediastinum of putative thymic B-cell origin. It typically arises in relatively young patients (20–50 years), with a female preponderance. Patients present with localised disease and clinical features related to a large anterior mediastinal mass, sometimes with superior vena caval syndrome. The cells express B-cell markers such as CD19 and CD20. CD10 and CD5 are usually negative.

In a large retrospective review by the International Extranodal Lymphoma Study Group of 426 patients from 20 institutions with PMLCL, the authors found that MACOP-B appeared superior to other chemotherapy programs, including CHOP.[88] This retrospective study strongly suggests that MACOP-B (or similar third-generation chemotherapy regimens such as VACOP-B) plus radiation therapy represents the best therapeutic option for most of these patients. The long-term overall survival is as high as 70–75%. On the other hand, patients with predictive factors of poor outcome are likely candidates for high-dose sequential chemotherapy plus autologous stem cell transplantation.

13.9 Treatment of aggressive T-cell lymphoma

T-cell lymphomas are uncommon in Western countries, and constitute about 15–20% of the aggressive lymphomas. They are more common in Asia. Most patients present with nodal

involvement, but any site can be affected. Patients often have generalised disease with infiltrates in the bone marrow, liver, spleen and extranodal tissues.

There are no standard treatment protocols for aggressive T-cell lymphomas. In general, treatment approaches similar to those used for aggressive B-cell lymphomas have been used. Several studies have reported inferior outcome for patients with aggressive T-cell lymphomas when compared to B-cell lymphomas when stratified for IPI. However, other studies have found that, stage for stage, the outcome of T-cell and B-cell diffuse large-cell lymphomas was similar.[89–92]

More intensive therapies are under investigation.

Summary of clinicopathological findings: peripheral T-cell NOS

Peripheral T-cell lymphomas that are not otherwise specified (peripheral T-cell NOS) are the most common form of T-NHL (~50%) in Western countries.

Clinical	Adults > children. Often disseminated nodal disease +/- extranodal, including skin, marrow. Aggressive, <30% five-year survival.
Morphology	Medium to large cells, some with clear cytoplasm; prominent venules; admixed inflammatory cells. Some have mainly atypical small cells. Variants: Lennert's lymphoma (epithelioid histiocyte-rich) and T-zone lymphoma with preserved follicles.
Immunophenotype	CD3+, variable pan-T loss, most CD4+, CD30+/- mainly in large-cell type; CD56+ and cytotoxic phenotype rare. EBV+/- in bystander cells or large B cells.
Genetics	Clonal rearrangements of TCR genes. No consistent cytogenetic abnormalities; complex karyotypes.

13.10 Anaplastic large-cell lymphoma

There are clinico-epidemiological differences between ALK protein positive (ALK+) or negative (ALK-) cases. This category specifically describes cases of T-cell or null cell anaplastic large-cell lymphoma (ALCL).

Clinical	Bimodal age distribution. ALK+ cases first three decades of life, M>F; ALK- cases in later life. Most have B symptoms but low IPI scores, stage III or IV disease involving nodes and extranodal sites (chiefly skin, bone, soft tissue, lung, liver, gut; marrow involvement subtle — up to 30% if immunostains used). Excellent prognosis — 75% overall survival and 56% failure free survival for all ALCL-T/null cases in the Lymphoma Classification Project, the best overall survival and failure-free survival of any large-cell lymphoma. ALK+ ALCL has better survival than ALK- ALCL.[93]
Morphology	Cohesive growth of cells, diffuse and sinusoidal distribution. 'Hallmark cell' present in all morphological variants — large cell, eccentric reniform or horseshoe-shaped nucleus, prominent but not 'inclusion-like' nucleoli, paranuclear eosinophilic region. Common (70%), lymphohistiocytic (10%) and small cell (5–10%) variants recognised, among other less common forms.
Immunophenotype	T-cell or null-cell phenotype and CD30+ are definitional. ALK protein+ (60–85%) in nuclear and cytoplasmic, cytoplasmic only, or membrane-restricted pattern. Extensive pan-T antigen loss; CD3e+/-; CD2+/-, CD4+/-; usually EMA+, CD45+, CD45RO+ and CD43+; Cytotoxic protein+ in >50%; clusterin+.
Genetics	Up to 90% have clonally rearranged TCR genes. EBER negative. Several cytogenetic abnormalities involving the ALK gene (2p23) described. t(2;5)(p23;q35) most common involving nuclephosmin gene. Other partner genes may be TPM3 (1q25), TFG (3q21), ATIC (2q35), CLTCL (17q11-ter), MSN (Xq11–12).

13.11 Other variants of aggressive T-cell lymphomas

Rare entities include angioimmunoblastic T-cell lymphoma, hepatosplenic gamma/delta T-cell lymphoma and enteropathy-type (intestinal) T-cell lymphoma. At present, there are no data to support an approach different from that recommended for B-cell lymphomas. If possible, these patients should be entered into clinical trials.

13.12 References

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CHAPTER 14 HIGH-GRADE LYMPHOMA

14.1 Introduction

The high-grade lymphomas (HGL) are a small group of histologically diverse tumours with a number of biological and clinical features in common. The entities included in this chapter are:

- Burkitt lymphomas (BLs)
- lymphoblastic lymphomas (LLs) of precursor-T and B-cell types.

These are rare lymphomas, affecting predominantly younger people, and characterised by very high growth rates. Patients frequently present with rapidly growing tumours that interfere with or obstruct vital organ function. For example, the mediastinum is a common site of presentation of LL, leading to superior vena cava obstruction, tracheal compression, or pericardial effusion, frequently presenting as an acute medical emergency. Similarly, ureteric obstruction may result from a rapidly enlarging retroperitoneal mass due to BL. Efforts at diagnosis are often compromised or truncated because of the rapid development of medical complications from the underlying disease. The high-grade lymphomas have a high propensity to disseminate into bone marrow, central nervous system (CNS) and other sanctuary sites, a feature that shapes the treatment strategy for these patients.

The rarity of these lymphomas, the frequency of complications related to early disease and treatment, and the complexity of protocols for curative therapy, argue in favour of these patients being treated by experienced specialist teams.

14.2 Epidemiology

There are few epidemiological reports on the incidence of HGL in Western populations. Lymphoblastic lymphoma accounts for one third of lymphoma in children, but only 3–5% of lymphoma in adults. That equates to about 160 cases per year for the whole of Australia.[1]

In adults, the median age at diagnosis for precursor T-LL is in the early 20s, though some reports suggest that precursor B-LL occurs in older patients.[2–4] T-LL is much more common in males than females, with male:female ratios ranging from 2:1 to 4.5:1.[4,5]

14.3 Comments on diagnosis and staging

14.3.1 Burkitt and Burkitt-like lymphoma

Summary of clinicopathological features

Clinical	Rapid onset of bulky disease due to short doubling time. May present as acute leukaemia with blood and bone marrow involvement (L3/ALL). Tumour lysis syndrome seen in treatment of bulky disease. Clinicopathological variants: *Endemic*: African, 4–7 years, male predominance. Involves jaws, facial bones, orbit. Less often: ileum, caecum, ovaries, breast or kidneys. *Sporadic*: children and young adults, male predominance. Ileocaecal mass. Less often: ovaries, breast or kidneys. *Immunodeficiency associated*: usually HIV associated.
Morphology	Monotonous, intermediate to size cells with multiple nucleoli, basophilic, often vacuolated cytoplasm. High turnover with apoptosis, tingible body macrophages and abundant mitoses. *Variants*: BL with plasmacytoid differentiation; atypical Burkitt/Burkitt-like.
Immunophenotype	IgM, CD19+, CD20+, CD22+, CD79a+, CD10+, *bcl-6*+, CD5-, CD23-, *bcl-2*-, TdT-. Endemic: CD21+, sporadic CD21-. A high-growth fraction (Ki-67) of 100% is required, but not specific.
Genetics	Somatic Ig VH rearrangement t(8;14). *Variants*: t(2;8), t(8;22) EBV+ in virtually all endemic cases, 25–40% of immunodeficiency-related cases. A diagnosis of Burkitt-like lymphoma requires specific evidence for *c-myc* dysregulation.

Burkitt and Burkitt-like lymphoma have been and to some extent remain a source of confusion in relation to clinicopathological definitions, pathological characteristics (both at light and ultrastructural levels), and clinical behaviour. Burkitt lymphoma is defined pathologically by the t(8;14), t(2;8), or t(8;22) chromosomal translocations involving the *c-myc* gene, whereas the diagnosis of Burkitt-like lymphoma (BLL) has been considerably less precise.[6]

From the epidemiological standpoint, Burkitt lymphoma exists as three distinct variants:

- *endemic BL*, which occurs in equatorial Africa and New Guinea
- *immunodeficiency-associated BL*, which occurs most frequently in association with human immunodeficiency virus infection
- *sporadic BL*, which accounts for approximately 2% of all lymphomas in developed countries.

The accompanying recommendations apply only to sporadic BL and BLL.

Within the defined pathological group of Burkitt lymphoma, BLL, and B-cell acute lymphoblastic leukaemia (ALL) (L3) is a clinical entity characterised by a short history of rapidly developing symptoms and signs, and which without treatment, results in life-threatening complications within days to weeks. This clinical entity has now been most reliably defined pathologically as a malignant lymphoma exhibiting essentially 100% positivity for the proliferation marker Ki-67.

The pathological diagnosis can be made on biopsy of nodal or extra-nodal tissue, or on bone marrow aspirate and trephine biopsy in leukemic patients. For the purpose of these guidelines, the finding of 100% Ki-67 positivity on immunostaining is required for the diagnosis of BL or BLL.[7] All such cases should be referred to a specialist lymphoma histopathologist for diagnostic confirmation.

With regard to staging investigations, patients with suspected or confirmed BL or BLL should have full staging procedures preferred, including a complete blood count, bone marrow aspiration and

trephine biopsy, full biochemical profile, including LDH and uric acid, and serum protein electrophoresis. Viral serology for HIV, hepatitis B and C, and EBV should be performed. CAT scans of neck, chest, abdomen and pelvis should be carried out. A CSF sample should be obtained by lumbar puncture, and where clinically indicated, CNS imaging by CAT scans or MRI may be necessary.

14.3.2 Lymphoblastic lymphomas

Summary of clinicopathological features: precursor T lymphoblastic leukaemia/lymphoma

Clinical	Mediastinal mass, respiratory embarrassment, pleural effusion, +/- high WCC and marrow involvement. Other sites of predilection — CNS and gonads in addition to lymph nodes, spleen, liver, skin, Waldeyer's ring. Outcome similar to B-ALL.
Morphology	Diffuse nodal involvement +/- follicular sparing; 'starry-sky' appearance; medium-sized lymphoblasts; nuclei round or convoluted; finely granular chromatin; nucleoli typically inconspicuous.
Immunophenotype	TdT+; variably express CD1a, CD2, CD3, CD4, CD5, CD7, CD8; CD4/8 may be co-expressed; CD10 variable; pan-B antigen negative; high proliferation index (Ki-67+).
Genetics	Clonal rearrangements of TCR genes; IgH clonally rearranged in up to 20% cases; TAL-1 microscopic deletion 25% cases; del(9p) 30% cases; one third have rearrangements involving TCR genes and a variety of partner genes.

Summary of clinicopathological features: precursor B lymphoblastic leukaemia (B-ALL) or lymphoma (B-LBL)

Clinical	B-ALL: predilection for CNS, lymph nodes, spleen, liver and gonads. Present with bone marrow failure. B-LBL: skin, bone, soft tissue and lymph nodes.
Morphology	B-ALL: small to intermediate-sized cells with dispersed, fine chromatin, multiple, variable nucleoli, blue–grey cytoplasm. Occasionally hand-mirror cells, coarse azurophilic granules (t(9;22)(q34;q11.2)). B-LBL: diffuse, rarely partial effacement. Small to intermediate-sized cells with rounded, variable convoluted nuclei, dispersed chromatin, moderate mitotic activity. Often 'starry sky' appearance. Resembles T-precursor neoplasms. May form 'Indian file' pattern resembling lobular carcinoma of breast.
Immunophenotype	TdT+; HLA-DR+; CD19+, cCD79a+. CD10+ and CD24+ except in variant (4;11)(q21;q23). CD20, CD22 and CD45 variable. CD13 and CD33 may be expressed in B-ALL/LBL. CD10 and cIg expression define level of maturation. SIg usually absent except some cases of pre-BALL/LBL. CD43 often positive. Moderately high proliferation index (Ki-67).
Genetics	*Good prognostic groups:* Hyperdiploid >50 (DI 1.16 to 1.6) t(12;21)(p13;q22) (*TEL/AML1* fusion) *Intermediate prognostic groups* Hyperdiploidy<51 Near triploidy del(6q); del(9p); del(12p) *Poor prognostic groups:* t(9;22)(q34;q11.2) (*BCR/ABL* fusion with age-related variants) t(4;11)(q21;q23) (*AF4/MLL*) t(1;19)(q23;p13.3) (*PBX/E2A*) Hypodiploidy

Comments on diagnosis and staging

The lymphoblastic lymphomas form a second group of high-grade NHL with discrete cytological, histological, and clinical features. The predominant type is T-cell lymphoblastic lymphoma (T-LL), a tumour derived from immature thymocytes and closely related to the T-cell variant of acute lymphoblastic leukaemia (T-ALL). B-cell LL is a very rare and clinically more heterogeneous syndrome that requires separate consideration.

The defining pathological features of T-LL are the cytological findings of medium to large lymphoblasts, often with convoluted nuclei, and the characteristic immunophenotype, with expression of early T lineage antigens. In certain circumstances, the finding of these two characteristics on needle biopsy may be sufficient to make a confident diagnosis of T-LL.

Patients with T-LL frequently present with rapidly progressive supra-diaphragmatic lymphadenopathy, or with symptoms relating to superior vena caval obstruction, tracheal compression, or pleural or pericardial effusions. These clinical symptoms may rapidly evolve into medical emergencies, requiring rapid diagnosis, staging and management. Early involvement of bone marrow and/or CNS is a frequent event.

The distinction between T-LL and T-ALL is often contentious. Both disease entities are closely related, being derived from malignant transformation of cortical thymocytes. While the genetic and cytogenetic abnormalities observed in T-ALL and T-LL are more diverse than in the Burkitt

lymphomas, there is a similar distribution of these molecular changes, and overlapping cytological and immunophenotypic findings. Both diseases involve the bone marrow. A consensus cut-off of 25% has been applied, therefore, to distinguish T-LL (<25% marrow blasts) from T-ALL (>25% blasts).

Aside from the issue of marrow involvement, it is recommended that where possible, patients with suspected or confirmed T-LL have full staging procedures carried out, including complete blood count, biochemical profile including LDH and uric acid, radiological staging with chest X-ray and CAT scans of chest, abdomen and pelvis, and CSF examination by lumbar puncture. A formal tissue biopsy of nodal or extra-nodal tissue should be performed unless precluded by clinical circumstances.

Guideline — High-grade lymphoma — specialist pathologist, bone marrow and cerebrospinal fluid assessment	Level of evidence	Refs
Biopsies of tissues suspected to be Burkitt or other high-grade lymphoma should be referred for review by a pathologist skilled in lymphoma diagnosis.	IV	3
Patients with newly diagnosed high-grade lymphoma should have mandatory assessment of bone marrow and cerebrospinal fluid.	IV	8

General comments on management

In general, the same management principles apply to high-grade NHL as to all other lymphomas: accurate diagnosis based on adequate tissue biopsy, full staging of the disease clinically, pathologically and radiologically, and appropriate treatment delivered by an experienced clinical team. There are, however, a number of special circumstances that warrant the management of cases of high-grade NHL within clinical teams with particular expertise in the treatment of high-grade haematological malignancies. These factors include:

- the relative youth of these patients compared to the average age of onset of other forms of NHL
- the relatively high potential of curability with appropriate care
- the frequent difficulty in obtaining an adequate diagnostic biopsy
- the rapid pace of the disease and the frequency of serious medical complications related to intra-thoracic, abdominal, CNS and bone marrow involvement
- the risk of serious metabolic complications, such as hyperuricemia, hyperkalemia, and acute renal failure early after commencing chemotherapy, due to tumour lysis
- the complexity of combined chemotherapy and radiation therapy protocols.

Guideline — High-grade lymphoma — multidisciplinary care	Level of evidence	Refs
Patients with newly diagnosed high-grade lymphoma should ideally be managed in specialist units experienced in treating these disorders.	IV	9, 10

14.4 Burkitt lymphoma

Standard treatment programs in use for intermediate-grade NHL have been demonstrated to be unsuitable for the curative treatment of patients with BL and BLL.

Due to the relative rarity of these tumours, large randomised trials have not been conducted in BL and BLL. However, a small number of phase II studies have been reported in the past decade, demonstrating high response rates and improved cure rates with short-term high-intensity regimens.[8,11–15]

Table 14.1 Treatment results in adult Burkitt's lymphoma

Study	Protocol	Number of patients	Results
McGrath et al. 1996[11]	CODOX-M/IVAC NCI 89-C41	41 (20 adults)	2yr EFS 92%
Mead et al. 1996[12]	CODOX-M/IVAC (UKLG)	52 (all adults)	2yr EFS Low risk 83.3% High risk 59.5%
Patte et al. 1991[8]	LMB	34 (some stage IV DLCC)	35-month DFS 68%
Schwenn et al. 1991[13]	HiC-COM	20	2yr EFS 75%
Thomas et al. 1999[14]	Hyper-CVAD	26 (all adults)	3yr OS 49%
Reiter et al. 2000[16]	BFM 86	151 (all children, some large-cell NHL)	7yr EFS 81%

The general principle behind these studies is the intensified use of several chemotherapeutic agents, particularly methotrexate, cyclophosphamide, an anthracycline, and cytarabine, used in repeated short courses, with treatment lasting less than six months and not followed by maintenance therapy. The selection of drugs with excellent CNS penetration, such as methotrexate and cytarabine, appears to obviate the need for prophylactic CNS radiation therapy.

Guideline — Intensive treatment of Burkitt lymphoma	Level of evidence	Refs
Adults with Burkitt lymphoma should be treated, where possible, with intensive combination chemotherapy of relatively limited duration, according to one of the recently published treatment regimens.	III	8, 11–15

14.5 Lymphoblastic lymphoma

The optimal treatment for adults with T-LL has not been defined.

Early assessment of the results of combination chemotherapy protocols originally designed for treatment of intermediate-grade lymphoma, incorporating an anthracycline, vincristine and prednisone, plus other drugs, produced unsatisfactory results. In one study, the complete response rate was only 53%. Almost half of the patients not receiving CNS prophylaxis developed CNS disease, and only 20% were long-term survivors.[17] Although no randomised clinical trials have been conducted, CHOP-like regimens without CNS treatment and longer-term maintenance therapy appear to be inadequate therapy for T-LL.[4,17–20]

Following improved results in paediatric patients with protocols designed for management of ALL (intensive multi-drug induction and consolidation therapy, prophylactic CNS treatment, and prolonged maintenance therapy), similar treatment strategies have been applied in adults with T-LL.[19,21–35] The results from larger, recently reported phase II studies are shown in Table 14.2.

Table 14.2 Results of ALL-like regimens in adults with T-lymphoblastic lymphoma

Study	Number of cases	Regimen	CNS therapy	% CR	% DFS	% Survival
Slater et al. 1986[24]	51	L2 L10 or modified L17 or modified	IT	78	75 at 5yr (60 if leukemic)	45 at 5yr
Coleman et al. 1986[25]	44	Cy, Dox, VP, Lasp, MP, MTX	CNS RT, IT	95	35	40 at 5yr
Morel et al. 1992[19]	30	LNH-84	IT	83	44	60
	22	FRALLE	CNS RT, IT	91	52	65
	7	LALA	CNS RT, IT	86	33	57
Bouabdallah et al. 1998[33]	50	LALA or BFM	CNS RT, IT	89	45 at 5yr	49 at 5yr
	12	Various NHL		58		
Thomas et al. 1999[34]	24	Hyper CVAD	CNS RT, IT	96	72 at 3yr	80 at 3yr
Hoelzer et al. 2002[35]	45	GMALL 04/89, 05/93	CNS RT, IT	93	62 at 5yr	51 at 5yr

While initial complete response rates of up to 96% have been reported, systemic and CNS relapse rates have been high, and long-term disease-free survival rates of 45–72% have been described. These results are equivalent to those observed in ALL. Important prognostic factors reported in adult T-LL include age, serum LDH, and presence of bone marrow involvement. Differences in results reported in different series may reflect variability in patient composition based on these prognostic factors.

Although no comparative clinical trials have been conducted, the balance of opinion would favour the use of one of the ALL regimens, using at least four-drug-combination induction chemotherapy with prophylactic intrathecal treatment, intensive consolidation chemotherapy, further prophylactic treatment to the CNS with intrathecal therapy, high-dose systemic methotrexate, or cranial irradiation, followed by prolonged maintenance treatment with antimetabolite agents.

Guideline — Lymphoblastic lymphoma — intensive treatment	Level of evidence	Refs
Adults with lymphoblastic lymphoma should be treated with a regimen designed for therapy of acute lymphoblastic leukaemia.	III	19, 21
This must include CNS prophylaxis.	III	36

14.5.1 Prophylaxis and treatment of sanctuary sites

There is a high rate of relapse in the CNS during or after systemic treatment with chemotherapy for high-grade NHL (HGNHL). Patients with a high LDH or involvement of head and neck sites have been reported to be at greater risk.[36] Prophylactic treatment of the CNS is mandatory.

Radiotherapy and chemotherapy give equivalent results in terms of survival, but in one study, irradiated patients had significantly fewer episodes of CNS relapse.[37] Prophylaxis given early in the course of systemic treatment may be more effective.[25] In order to avoid late complications, chemotherapy is preferred in children. In adults, the risks of late complications are much less and radiotherapy is an alternative when there is a contraindication to chemotherapy.

The combination of radiotherapy and chemotherapy is used to treat established CNS involvement.

There is no role for prophylactic treatment of the testes.

14.5.2 Management of early treatment complications

Tumour lysis

Because of the high cellular proliferation rate, patients may present with hyperuricaemia and hyperphosphatemia, or develop it after the first dose of chemotherapy due to rapid tumour lysis. All patients should be assessed for hyperuricaemia and renal impairment prior to treatment. Prophylaxis with allopurinol and double maintenance fluids should be given before commencing chemotherapy.

Therapy with urate oxidase (now available) should be considered in patients with large tumour burden, as this agent rapidly decreases uric acid to undetectable levels by converting it to allantoin — a very high water-soluble compound. The use of urate oxidase dramatically reduces metabolic complications of tumour lysis. Hyperuricaemia should be corrected with hydration and alkalinisation and a good urine flow established before chemotherapy is given, to reduce the risk of renal failure from tumour lysis.

Hyperphosphataemia is managed with parenteral fluids, diuresis and oral calcium carbonate. (Note that sevelamer hydrochloride as a new oral intestinal phosphate-binding agent may become available.) Excessive alkalinisation of urine should be avoided. If hypophosphatemia is profound there is usually coexistent hypocalcaemia. Calcium replacement is *not* recommended unless the patient is symptomatic. In acute tumour lysis, there is a substantial risk of hyperkalaemia and risk of death. Potassium replacement must be avoided. If, despite supportive measures, metabolic disturbances or fluid balance cannot be controlled, haemodialysis will be necessary. The calibre and type of monitoring needed for patients with acute tumour lysis requires management in critical care units.

14.5.3 Complications caused by lymphoma

Airways obstruction, SVC obstruction, cardiac tamponade

Large mediastinal masses may cause severe airways obstruction at presentation. The problem may be acute because of the very rapid cell turnover in HGNHL. Appropriate respiratory support and cytotoxic treatment should be given as an emergency measure. Because of the unique chemosensitivity of T-LL, rapid responses are seen with chemotherapy. Radiotherapy may also give rapid tumour response and small doses may achieve significant tumour shrinkage. However, all patients will need to start chemotherapy within a few days and the concurrent use of mediastinal radiotherapy and anthracycline chemotherapy may cause severe mucosal reactions.

Cardiac tamponade requires prompt initiation of specific therapy together with pericardial paracentesis. SVC obstruction, although not uncommon in this setting, is not usually life threatening.

Abdominal complications

Massive abdominal involvement (commonly with ascites) is most usually due to Burkitt's lymphoma, and may be responsible for perforation and/or obstruction of bowel (including intussusception), GI haemorrhage, obstruction of ureters, IVC and lymphatics. GI haemorrhage or obstruction may require surgical intervention. Initial treatment should also include specific treatment for the lymphoma.

Ureteric obstruction may require initial management with surgical stents or nephrostomy tubes and the prompt institution of therapy. Such obstruction carries added significance in the presence of a high tumour burden, as treatment will require the establishment of diuresis, and management of hyperuricemia and hyperphosphatemia to avoid or minimise acute renal failure.

Neurological complications

Neurological emergencies include paraplegia, cranial nerve palsies, meningeal disease and intracerebral tumour. In general, excellent responses are obtained with chemotherapy. Extradural disease is the cause of paraplegia and responds promptly to systemic therapy. Delay in institution of treatment can lead to irreversible paraplegia due to compromise of the external blood supply to the cord.

Guideline — Lymphoblastic lymphoma — specialist care	Level of evidence	Refs
Patients with lymphoblastic lymphoma should be managed in units with experience in dealing with the early complications of the disease and its treatment.	IV	19, 21
Prophylaxis with fluids and allopurinol should be given before starting therapy.	IV	36

14.5.4 Assessment of response

Janicek et al. reported that early restaging gallium scans can be predictive of outcome in patients treated on CHOP regimens.[38] This may not apply to children, who have vastly superior outcome with current intensive therapy. Monitoring response with gallium scans is not recommended.

Second-look surgery is not recommended, based on the evidence presented by the Berlin-Frankfurt-Munster (BFM) Group.[15] For patients with high-risk disease who are already receiving intensive regimens, the identification of residual disease late in therapy is of limited value, as few therapeutic options remain (but might include high-dose therapy and stem cell rescue).

The early identification of slow responders with second-look surgery may be beneficial if the patient was initially assigned to a low-risk regimen because it would provide an opportunity to intensify therapy.

The role of surveillance scanning at the end of therapy is questionable because early detection of relapse is unlikely to affect outcome.

The role of new imaging modalities such as PET scanning in the follow-up surveillance of patients treated for HGNHL remains to be determined.

14.5.5 Role of adjuvant radiotherapy for sites of bulky disease

While radiotherapy improves survival in bulky intermediate-grade lymphoma, there is no evidence that it improves outcome in HGNHL. A randomised trial in children showed no survival benefit and increased acute toxicity when radiotherapy was given to large mediastinal masses.[39] The combination of radiotherapy and anthracycline-based chemotherapy increases the acute side effects of radiotherapy, particularly skin and mucosal reactions within the radiation field.

Radiotherapy may be considered in the management of residual gallium avid masses, but given the small number of such cases, there is no strong evidence of benefit. Radiotherapy may also be considered when there is airways compromise at presentation, although there is no evidence that the response to radiotherapy is any faster than that to chemotherapy.

Guideline — Radiation therapy and bulky disease	Level of evidence	Refs
Adjuvant radiotherapy is not indicated in treatment of sites of original bulk disease in high-grade lymphoma.	II	39

14.5.6 Bone marrow and stem cell transplantation

High-dose chemotherapy with autologous stem cell rescue

A number of studies have examined the role of early high-dose therapy with chemotherapy and/or total body irradiation for patients with T-LL in first complete response, followed by hematopoietic stem cell rescue with cryopreserved bone marrow or peripheral blood stem cells. Initial results suggested durable responses in up to 75% of cases, while a large series of cases collected by the EBMT showed a 63% probability of DFS at six years. One small randomised trial comparing standard chemotherapy with autologous stem cell transplantation has been reported.[42] A total of 65 patients were randomised, 31 to transplant and 34 to chemotherapy. The three-year relapse-free survival figures of 24% for chemotherapy and 55% for transplant arm were not significantly different. Other smaller phase II studies are listed in Table 14.3.[33,40,41,43–46]

Table 14.3 Results of high-dose therapy and autologous stem cell transplantation in adults with T-lymphoblastic lymphoma in first remission

Study	Number of cases	% TRM	% DFS	% survival
Milpied et al. 1989[43]	13	0	70	80 at 4yr
Santini et al. 1989[44]	12	0	75	NR
Verdonck et al. 1992[40]	9	0	67	NR
Baro et al. 1992[45]	14	9	77	85
Sweetenham et al. 1994[46]	21	14	NR	63
Jost et al. 1995[41]	12	0	42	NR
Bouabdallah et al. 1998[33]	18	0	NR	50 at 5yr
Sweetenham et al. 2001[42]	31	3	50 at 2yr	NR

At present, high-dose therapy with stem cell rescue for adult T-LL in first complete response appears to be effective therapy, but it has not been demonstrated to be superior to maintenance chemotherapy.

Allogeneic bone marrow transplantation

The role of allogeneic bone marrow transplantation in the early phases of therapy for adult T-LL has not been defined. Several small phase II studies have been reported.[33,43,47,48]

Although toxicity appears to be higher for patients receiving allografts, long-term results do not appear different from those of patients receiving autografts.

Table 14.4 Results of allogeneic bone marrow transplantation for adults with T-lymphoblastic lymphoma in first remission

Study	Number of cases	% TRM	% DFS	% survival
Phillips et al. 1986[47]	2	0	NR	NR
Ernst et al. 1986[48]	8	23	NR	69
Milpied et al. 1989[43]	12	17	67	80
Bouabdallah et al. 1998[33]	11	17	NR	78 at 5yr

Guideline — High-dose chemotherapy and autologous stem cell support	Level of evidence	Refs
High-dose chemotherapy with autologous stem cell support is effective therapy for patients with lymphoblastic lymphoma in first remission, but it has not been proven to produce superior disease-free survival. Ideally, it should be used only in the context of a clinical trial.	III	40, 41

14.5.7 Follow up and management of late effects of therapy: importance of multidisciplinary approach

Long-term follow up requires (a) that the patient eventually takes responsibility for his or her medical care and (b) the identification of a regular/consistent family medical practitioner supported by a specialist centre.

Specific issues

- fertility
- puberty delayed — rare
- growth — if CNS prophylaxis includes radiotherapy, more marked if includes spine/pituitary
- second malignant neoplasms — brain tumours cranial irradiation; myelodysplasia, AML
- hypothyroidism — scatter effect of radiotherapy
- IQ performance and psycho-social adjustment
- cardiac-anthracyclines — long-term follow up shows cardiac failure even with low doses of anthracycline

Treatment of relapse

The prognosis for patients with systemic relapse of HGNHL is poor. Responses to intensive salvage chemotherapy may be achieved, but rarely will be durable. Small case series of successful treatment of relapsed HGNHL with either autologous or allogeneic stem cell transplantation have been reported, although the proportion of long-term disease-free survival in these patients is low.

Isolated CNS or other extramedullary site relapse may be treated with local radiotherapy, but subsequent systemic relapse is usual.

14.5.8 Management of B-lineage lymphoblastic lymphoma

This accounts for 15% of lymphoblastic lymphomas in childhood. ALL-type therapy is regarded as optimal treatment.[49,50]

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CHAPTER 15 CHILDHOOD LYMPHOMA

15.1 Introduction

The majority of children with lymphoma have high-grade disease. Most key management principles apply to both children and adults.

All patients should be treated at paediatric oncology centres and entered into clinical trials where possible. This is feasible as all centres in Australia are associated with the United States Children's Oncology Group (COG).

15.2 Epidemiology

Lymphoma makes up about 7–8% of childhood cancers. About 40–50 new cases are diagnosed in Australia each year.[1] There is a male predominance that is most marked in lymphoblastic lymphomas. Apart from the role of EBV in Burkitt's lymphoma, aetiology for the majority is unclear. Genetic DNA fragility disorders such as ataxia telangiectasia account for very few cases.

15.3 Diagnosis and staging

The recommendations from Chapter 13 regarding the management of highly aggressive lymphomas in adults are equally relevant to children.

The four major subtypes of childhood lymphoma are defined as:

- small non-cleaved cell (Burkitt and Burkitt-like) (40%)
- lymphoblastic (30%)
- B-cell large-cell lymphoma (30%)
- anaplastic large-cell lymphoma (10%)

Childhood lymphoma is usually extranodal at presentation. A majority (75%) present with advanced disease. The key clinical features of these subtypes are summarised in Table 15.1.[2]

Table 15.1 Lymphoma in children

Histology	%	Immunophenotyping	Clinical presentation
Small non-cleaved (Burkitt and Burkitt-like)	40	B-cell 100%	Abdomen, head, neck, BM, CNS
Lymphoblastic	30	T-cell 90%	Mediastinum, lymph nodes
		B-cell 10%	CNS, BM, bone
Large cell	20	B-cell 100%	Mediastinum, abdomen
Anaplastic large cell	10	T-cell 70%	Skin, mediastinum, liver, spleen
		Null 20%	Abdomen
		B-cell 10%	

Source: Cairo[2]

Currently, there are several staging systems for childhood lymphoma: St. Jude, Children's Cancer Group, French Society of Pediatric Oncology (SFOP), and United Kingdom Children's Cancer Study Group (UKCCSG).[2] These reflect the diverse presentation, relatively small number of patients, and escalating cure rate in recent times.

15.4 Management strategies

Children with lymphoma uniformly have rapidly growing tumours with frequent visceral spread and involvement of the bone marrow and central nervous system. The high tumour burden places the child at high risk of serious metabolic complications even before therapy has commenced. The generally prompt response to therapy, although gratifying, can lead to serious life-threatening tumour lysis. The management of this issue and other complications arising during the early stages of therapy are discussed in Chapter 13. The complexity of current modern protocols, together with the need to have prompt and responsive teams to deal with acute complications, demands that children be managed in specialised units.

15.5 Burkitt and Burkitt-like lymphomas

In Burkitt lymphoma, short duration, intensive chemotherapy has been shown to be superior to less intensive, longer duration therapy as used in the treatment of ALL.[3] The mainstay of therapy in these protocols is cyclophosphamide, high-dose methotrexate, high-dose cytarabine, doxorubicin, vincristine, etoposide and steroids.

The role of surgery in modern treatment regimens is limited to obtaining adequate biopsy and management of acute emergencies (e.g. bowel obstruction). In selected patients, complete resection of small localised tumours (e.g. stage I or II abdominal masses) may be appropriate, providing it can be undertaken with minimal morbidity.[4]

The SFOP LMB 89 and the German BFM 90 protocols are the most effective reported. They have been used on large numbers of patients, with EFS rates of more than 90% for all patients; 80–90% for patients with stage IV Burkitt lymphoma and B-cell leukaemia, and 98–100% for stage I and II patients.[5,6] With such therapy, the significance of most prognostic factors has disappeared.

Table 15.2 Results of various protocols in the treatment of paediatric B-cell lymphomas

Study	Group	No. patients	3yr event-free survival (%)
Patte et al. 2001[5]	LMB 89		
	Stage I and II patients	122	96±4
	Stage III patients	280	93±3
	Stage IV	97	95±4
	Leukemic patients	67	79±8
Reiter et al. 1999[6]	Berlin-Frankfurt-Munster		
	Stage I	49	95±5
	Stage II	114	98±1
	Stage III	171	86±3
	Stage IV	23	83±8
	Leukemic patients	56	76±8
Link et al. 1997[7]	Paediatric Oncology Group protocols		
Brecher et al. 1997[8]	Stage I and II	>100	88
Bowman et al. 1996[9]	Stage III	64	79±6
	Stage IV	59	79±9
	Leukemic patients	74	65±5
McGrath et al. 1996[10]	US National Cancer Institute 89-C-41		
Adde et al. 1998[11]	Low-risk patients	18	100
	High-risk patients	66	85
Gairo et al. 2003[12]	Children's Cancer Group		
	Disseminated Disease		
	CCG 551, -503, -552	424	54 *(4yrs)*
	CCG 5911	46	80 *(4yrs)*

CNS prophylaxis is a crucial part of therapy. The use of high-dose systemic chemotherapy and intrathecal agents (MTX and Ara-C) has obviated the need for cranial or cranio-spinal radiotherapy. Indeed, some studies show that radiotherapy in Burkitt lymphomas is ineffective.[13,14]

Patients with completely resected stage I or II tumours (that are not in the head or neck, or epidural region) should not receive CNS prophylaxis, as the risk of CNS spread is very low.[6]

The prognosis for patients with CNS disease, previously poor, has dramatically improved with the above treatment approach.

Guideline — Combination chemotherapy for Burkitt lymphoma	Level of evidence	Refs
Paediatric patients with Burkitt lymphoma require intensive combination chemotherapy of relatively short duration.	III	3

Guideline — CNS chemoprophylaxis — advanced lymphoma	Level of evidence	Refs
Central nervous system (CNS) chemoprophylaxis is mandatory for all patients with advanced-stage disease, and for those with localised head and neck disease.	III	13, 14

15.6 Lymphoblastic lymphomas

15.6.1 Chemotherapy

For children with T-LL, an ALL regimen is considered standard therapy. This principle arose from the results of a randomised Children's Cancer Group Study.[3]

Treatment intensity for children with LL is adapted to the risk of relapse. All children require prolonged therapy irrespective of their risk classification. Those with extensive disease are best treated with a high-risk ALL-type regimen for a prolonged period (two years). Those with limited-stage disease also benefit from a longer duration of treatment but with a regimen for low-risk ALL. Optimal duration of therapy for patients with localised LL has not yet been defined.[7,15] Survival rates for young patients with LL treated with ALL-based protocols ranges from 80% to 90%.[16–22]

15.6.2 Radiotherapy

Radiation therapy does not have a role in frontline therapy if effective combination chemotherapy is used. This applies to patients with localised or advanced and disseminated disease.[7,15] Radiotherapy might be indicated in certain selected situations such as spinal cord compression or thoracic outlet obstruction. However, even in such emergencies, initial treatment with chemotherapy is recommended given the unique chemosensitivity of LL (and the deleterious effects of external beam radiation on growing tissues). Local radiotherapy does not appear to benefit patients with overt testicular or bone disease.

Radiotherapy does have a role in the treatment of overt CNS disease. In certain centres and cooperative groups, it is also used for CNS prophylaxis. CNS prophylaxis is an integral component of therapy for children with T-LL. Intrathecal therapy with MTX and ARA C is considered standard therapy. In patients with extensive T-LL, cranial radiotherapy is currently used for prophylaxis, but the importance of its use is yet to be adequately established.[21,22] Patients with CNS disease at diagnosis require cranio-spinal radiotherapy.

15.6.3 Surgery

Surgical resection or debulking of lymphoma is no longer used or recommended. The main determinant of outcome is the tumour bulk at presentation, not the extent of surgical resection. This principle, first clearly established in Burkitt lymphoma, has been extended successfully to patients with LL.[12,23,24] Surgery has a clear role in selected patients who present with significant symptoms (GI obstruction/acute abdomen).

Table 15.3 Treatment results in paediatric T-LL

Study	Protocol/group	No. of patients	Results
Reiter et al. 2000[21] Grenzebach et al. 2001[25]	BFM 90	101	5yr EFS 92%
Anderson et al. 1993[3]	LSA2L2/CCG	164 (advanced stage)	5yr EFS 64%
Hvizdala et al. 1988[26]	LSA2L2/POG	76	3yr EFS 58%
Patte 1992 et al. [19]	LSA2L2 (Goustave-Roussy)	84	5yr EFS 78%
Amylon et al. 1999[27]	POG 8691-8704	195(advanced stage)	4yr EFS 78%
Eden et al. 1992[22]	UKCCG8503	95(advanced stage)	4yr EFS 65%
Reiter et al. 1995[20]	BFM-85/BFM	77	7yrEFS 78%
Tubergen et al. 1995[28]	CCG 502	281	5yr EFS 84% (localised) 67% (advanced)
Millot et al. 2001[29]	EORTC 58881	60 (advanced stage)	6yr DFS 76%

Guideline — Management of lymphoblastic lymphoma	Level of evidence	Refs
Children with lymphoblastic lymphoma should be treated with a chemotherapy regimen designed for the therapy of acute lymphoblastic leukaemia (ALL).	III	3
The duration of treatment may be able to be adjusted, based on risk factors.	III	3, 7, 15
Treatment must include central nervous system (CNS) prophylaxis.	III	21, 22
Patients with central nervous system (CNS) disease at diagnosis require cranio-spinal radiotherapy.	IV	7, 15

15.7 B-lineage lymphoblastic lymphoma

This uncommon subtype accounts for 15% of lymphoblastic lymphoma in children. ALL-type therapy is the optimal treatment.[16,30]

15.8 Large-cell lymphoma (LCL)

15.8.1 B-cell LCL

Limited stage

Children with localised B-cell LCL have an excellent (90–95%) five-year event-free survival as demonstrated by cooperative group regimens.[5,6,15,31]

Table 15.4 Treatment and outcome of limited-stage (localised) B large-cell lymphoma in children and adolescents

Variable	CCG[31]	POG[15]	SFOP[5]	BFM[6]
Subjects (n)	52	27	52	71
Treatment	COMP	COMP	COPAD	CP, DX, FROS, MTX, Ara-C, VP-16, DX, MTX, CTX, DOX
Length (months)	6	8	1.5	3
5-year EFS (estimated)	95%	88%	99%	100%

These studies established that cure in the majority of children with limited-stage disease can be achieved with therapy that is intensive, of short duration (2–6 months), and does not require radiotherapy, surgery, or extensive CNS prophylaxis. Although several effective regimens have been identified, randomised comparison trials have not been undertaken to define a standard treatment.

Advanced stage

Event-free survival of 90% is achieved using intense regimens originally developed for patients with small non-cleaved cell (Burkitt's) lymphoma.[5,6,32,33]

Table 15.5 Treatment and prognosis of advanced B large-cell lymphoma in children and adolescents

Variable	CCG[32]	POG[33]	SFOP[5]	BFM[6]
Subjects (n)	18	33	62	56
Treatment	Orange	APO +	LMB	BFM
Length (months)	6	12	6	5
3-year EFS (estimated)	90%	78%	90%	95%

Guideline — Management of localised large-cell lymphoma and advanced-state disease	Level of evidence	Refs
Children with localised large-cell lymphoma require intensive short-term therapy.	III	1, 5, 6, 15, 31
Children with advanced-stage disease require intensive Burkitt-style therapy.	III	5, 6, 15, 32, 33

15.8.2 Anaplastic large-cell lymphoma (ALCL)

The optimum therapy for this subtype of NHL has not been defined for children. Recommended regimens are based on high-grade peripheral B-cell (SNCL [Burkitt's]) lymphoma protocols.[34–36]

Table 15.6 Anaplastic large-cell lymphoma — results of treatment with Burkitt cell regimens

Study group	Number of patients	CCR %	EFS %	S %	Ref	Median follow up (yrs)
High-grade B-cell regimen	82	95	66 (3yrs)	83 (3yrs)	34	4.1
BFM high-grade B-cell regimen	89		76 (all) 100% (localised) 73–79% (advanced)		35	5.6
UKCCSG high-grade B-cell regimen	72	82	59 (5yrs)	65 (5yrs	36	4.3

Guideline — Treating anaplastic large-cell lymphoma	Level of evidence	Refs
Therapy for anaplastic large-cell lymphoma should be based on SNCL (Burkitt's) protocol until optimum therapy is defined.	III	34–36

15.9 Low or intermediate-grade lymphomas

Such lymphomas are rare in childhood, making incidence and frequency estimates unreliable.[37,38] Most patients present with localised disease, often in the cervical legion, respond promptly to therapy, and have an excellent five-year event-free survival (greater than 90%). There is a male predominance. Histologically, both follicular and diffuse patterns of lymph node involvement are relatively common. This is referred to in Chapter 12. Optimum therapy is not defined. Conservative therapy for localised disease may be appropriate, but cannot yet be recommended.[39]

15.10 Late effects: follow up and management — a multidisciplinary approach

End-of-treatment surveillance and late effects are discussed in Sections 15.12.10 and 15.12.12 respectively.

15.11 Salvage therapy

Children within initially localised lymphoma who subsequently experience a local recurrence can be rescued with intensive re-treatment programs. However, relapses in children are generally systemic and rarely localised. Salvage therapy with intensive chemotherapy regimens is usually not successful. High-dose chemotherapy regimen with stem cell rescue offers a small but significant chance of long-term disease-free survival for children with large-cell lymphoma.

15.12 Hodgkin lymphoma

15.12.1 Introduction

Hodgkin lymphoma in children is a highly curable malignancy. Biologically, there is little to distinguish the behaviour of the disease and its response to therapy between adults and children. The earliest paediatric treatment regimens were modelled on those developed for adults. The recognition that the quality of long-term survival could be severely compromised by the late sequelae of therapy led to significant modifications of treatment strategies for children. There remains, however, considerable overlap with adult practice in the way paediatric patients are evaluated and in the

principles of therapy that are applied. This reflects the common basic biology of the disease (see also Chapter 11).

15.12.2 Epidemiology

Each year in Australia, approximately 30–40 children under the age of 15 years are diagnosed with Hodgkin lymphoma.[40] The incidence in the 10–15 year age group is more than double the rate under ten years of age.[41] The bimodal age distribution in Australia is typical of developed countries, with an early peak in the incidence of the disease between 20 and 30 years. Within this peak there is variability in the features of the disease. For example, there is a marked male predominance (4:1) under the age of ten years, which gives way to an equal male and female incidence in adolescents and young adults.[42,43] Although the nodular sclerosis variant is the most common histological subtype in children overall, this is not the case for those under ten years of age, for whom mixed cellularity is the predominant variant. There is also significant ethnic and geographical variation in the distribution of histological subtypes.[44]

Lower socioeconomic status is associated with children presenting under the age of ten years. Conversely, a higher socioeconomic background is associated with Hodgkin lymphoma in older children and adolescents.

15.12.3 Pathogenesis and aetiology

Hodgkin lymphoma is a B-cell malignancy. The strong association of Epstein Barr virus (EBV) with HL in adults is also present in the children. Distinctive features of the association with EBV in the paediatric age group include a high incidence in Asian children, in those with the mixed cellularity variant, and in the younger age group (less than ten years). Children with genetic (e.g. ataxia telangiectasia) and acquired (e.g. HIV) immunodeficiency disorders have a higher incidence of HL. The influence of genetic factors is also seen in the increased risk faced by first-degree relatives and especially, identical twins.[45,46]

Malignant cells in involved nodes or tissue in HL account for less than 1% of the total cell population. This feature that makes it imperative that adequate tissue (by excision or open biopsy) is obtained for diagnostic purposes. Core biopsy is usually inadequate for this purpose.

Disease classification is the same for children and adults.

Overall in children, the nodular sclerosis variant is the most common, accounting for 60% of cases (40% of diagnoses under the age of ten years, and 70% of older children and adolescents). Children with the mixed cellularity subtype make up 30% of the total, and these patients are more likely to present with advanced disease. Lymphocyte predominant subtypes are relatively uncommon, making up about 10% of the total. Lymphocyte-depleted HL is rare in childhood.

15.12.4 Clinical features

The most common presentation is with cervical and/or supraclavicular masses that are otherwise asymptomatic. Two thirds of children have mediastinal involvement. Subdiaphragmatic presentation is rare. Rarely, patients present with signs of auto-immune haemolytic anaemia or thrombocytopaenia.

15.12.5 Staging

The staging system is the same as used in adults. Modern treatment and imaging modalities have virtually eliminated staging laparotomy.

15.12.6 Evaluation

Patient evaluation is essentially similar to that recommended for adults: bone marrow biopsy (bilateral) in any patient with B symptoms, or those with stage III or IV disease. The yield in children with localised disease (without B symptoms) is very low. Marrow biopsies will require a general anaesthetic in children.

Malignant cells in involved nodes or tissue in HL account for less than 1% of the total cell population. This makes it imperative that adequate tissue (by excision or open biopsy) is obtained for diagnostic purposes. Core biopsy is usually inadequate for this purpose. Twenty per cent of core biopsies give false negative results.[47]

It is important to consider fertility preservation after diagnosis is confirmed, by either sperm storage (pubertal) or ovarian biopsy and storage (any age).

PET scan detects more sites than gallium, and is better to assess residual disease. PET scan, however, can be too sensitive and positive regions might need to be assessed by biopsy, especially when the scan is performed to assess early response or after completion of therapy.[48–51]

Guideline — Open biopsy to ensure less diagnostic error	Level of evidence	Refs
Open biopsy to ensure sufficient tissue for analysis is the procedure of choice to minimise diagnostic errors (see Chapter 10 — Surgical biopsy in lymphoma).	III	47

15.12.7 Principles of therapy

All patients should be treated at paediatric oncology centres and entered into clinical trials where possible. This is feasible, as all centres in Australia are associated with the United States Children's Oncology Group (COG).

1. With modern treatment, overall survival of children with HL is 90%.[52] However, the late effects of therapy (second malignancies) are directly responsible for a large proportion of patient deaths.[53] Newer therapies developed over recent years focus on preventing long-term toxicity.[54] Late sequelae of full-dose radiotherapy has resulted in a shift to using combined therapy (chemotherapy with lower-dose radiotherapy).

High cure rates can be achieved with programs ranging from single modality radiotherapy to varying combined modality regimes. These options vary in terms of rates of relapse, chance of salvage therapy, and toxicity. Parents, as well as older children when adequately informed, may express a preference for the type and style of therapy.

15.12.8 Treatment of localised disease

In selected (but not all) centres in Australia, therapy with chemotherapy alone for all patients has been the standard treatment for many years. Such protocols were established to avoid the effects of radiotherapy, and in a desire to eliminate staging laparotomy as a diagnostic/prognostic tool. However, there are few studies that demonstrate the value or superiority of this approach for all patients. Both the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) have conducted randomised studies comparing chemotherapy alone with combined modality treatment (chemotherapy reduced dose, involved-field radiotherapy) in patients with intermediate to advanced disease stages.[55,56] In these two sets of studies, the overall survival was equivalent in both treatment arms. However, in the CCG study, low-dose involved-field radiotherapy improved the event-free survival (EFS). In the POG study, the addition of radiotherapy made no difference, but both groups

received a heavy chemotherapy schedule. Similarly, the German paediatric cooperative group evaluated a chemotherapy-alone approach in patients who achieved a complete remission (CR), and compared this to patients who had not achieved CR after the same chemotherapy and who went on to receive involved-field radiotherapy. Again, both groups had equivalent overall survival, but the group receiving chemotherapy alone had a lower EFS (81% versus 92%, P= 0.01).[57]

Chemotherapy-only programs for patients with localised or bulky disease have not yet been adopted as standard therapy by larger national cooperative children's cancer groups in the United States or Europe. Rather, such groups continue to explore in randomised studies the selected use of chemotherapy alone in discrete, well-defined cohorts of children. This approach highlights the clear move by the groups towards limiting radiotherapy as well as reducing chemotherapy exposure, particularly in patients with localised disease. In addition, these clinical studies are evaluating 'response-based' therapies with the aim of limiting treatment exposure in children.

Guideline — Low or intermediate-risk disease — combined-modality therapy	Level of evidence	Refs
Children with localised low-risk or intermediate-risk disease (that is, they have adverse prognostic factors, for example, mediastinal mass, bulky disease, B symptoms) are best treated with combined-modality therapy.	II	55, 56

15.12.9 Treatment of advanced disease

The treatment regimens adapted from adult trials (MOPP[1], ABVD[2]) have been shown to have significant late sequelae. Over the past 15 years, concerted attempts have been made through clinical trials to diminish this late toxicity yet still maintain the excellent cure rate.[52] There are now numerous highly effective chemotherapy regimens for patients with advanced disease.[54] No one regimen is clearly superior. Recent results from the German-Austrian Hodgkin Lymphoma Group are amongst the best reported.[58] Regimens developed for adults such as BEACOPP[3] or escalated BEACOPP are dose-intensive programs that may offer further improvements in outcome for children with advanced high-risk disease.[59]

It is recommended that radiation alone is not a treatment option for children with classical HD, even for those with localised disease. For adults (and hence for children), radiation therapy alone is no longer the treatment of choice in most centres in the United States and Europe.[60]

Most children with nodular lymphocyte predominant HD present with localised disease. They have an excellent prognosis. Whether patients with stage I-A need therapy beyond surgical excision is not yet known. In patients for whom growth of tissues is not an issue (adolescents), local radiotherapy for this unique subgroup might be appropriate.

Aspects of radiotherapy are discussed in Sections 11.14–17.

[1] MOPP: nitrogen mustard, vincristine, prednisone, procarbazine.
[2] ABVD: adriamycin, bleomycin, vincristine, OTIC
[3] BEACOPP: bleomycin, etoposide, adriamicin, cyclophosphamide, vincristine, prednisone, procarbozine.

Guideline — Multidisciplinary treatment for advanced lymphoma	Level of evidence	Refs
For patients with advanced disease, intensive risk-adapted chemotherapy represents standard therapy. Patients who achieve prompt complete remission may not require radiotherapy. For patients who have a partial response, involved-field radiotherapy to areas of bulk disease is of benefit.	II	55, 56

15.12.10 Post treatment surveillance

Most children who relapse do so within two years of completing treatment. It is not known whether the early detection of recurrent disease alters outcome. Nevertheless, it is standard practice in many units to follow patients with serial CT and gallium scans (PET scans in the future) every three months for two years. Thereafter, follow up is designed to monitor the patient for late effects of therapy.

15.12.11 Salvage therapy

Determining appropriate salvage therapy depends very much on factors such as the nature of therapy the patient received previously, the duration of remission, the site of relapse, and changes to the underlying histology. Conventional treatment programs may prove effective in patients who have had minimal prior therapy. However, standard care for most patients who experience an early relapse associated with B symptoms, or have a stage II or greater late relapse, is autologous stem cell transplantation.[61,62]

15.12.12 Late effects

All paediatric oncology units in Australia have a comprehensive program of following children and adolescents who are long-term survivors of childhood cancer. Specific late effects for long-term survivors of HL include:

- soft tissue and bone growth abnormalities including avascular necrosis (steroid effect)
- pulmonary complications (bleomycin, radiation)
- cardiovascular sequelae (anthracyclines, radiation)
- endocrine abnormalities including hypothyroidism, infertility
- second malignant neoplasms

15.13 References

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CHAPTER 16 IMMUNODEFICIENCY ASSOCIATED LYMPHOMA

16.1 Introduction

It has long been recognised that disturbances of the immune system may be associated with an increased incidence of lymphoma. The extent to which this occurs varies according to the specific underlying immune disturbance and has been documented with variable clarity and certainty.

The WHO[1] classification is:

1 Lymphoproliferative diseases (LPDs) associated with primary immune disorders

2 Human immunodeficiency virus-related lymphomas

3 Post-transplant lymphoproliferative disorders

4 Methotrexate-associated lymphoproliferative disorders

Lymphomas occurring in these settings share a number of features that differ from those occurring in the general population. These include the distribution of specific histologies, the incidence of extranodal disease, the greater frequency of Ebstein Barr virus (EBV) integration in the lymphoma, and importantly, the potential for disease regression without specific therapy when manipulation of the immune system is possible, for example, by the withdrawal of immunosuppressive drugs. These features are common to the four subtypes of immunodeficiency-associated LPDs, although to greater and lesser extents. In counterpoint to these broad similarities are the many specific differences, as illustrated by the heterogeneity among LPDs, complicating the many rare but distinct primary immunodeficiency syndromes. In this chapter, generalisations are made where applicable but are not intended to obviate the need to consider each entity and clinical scenario independently. Where management recommendations are the same as for lymphomas occurring in the non-immunocompromised host, they are cross-referenced.

16.2 Lymphoproliferative diseases associated with primary immune disorders

16.2.1 Predisposing conditions

There is good epidemiologic evidence that patients with a variety of primary immunodeficiency syndromes are at risk for the development of lymphoma. It has been difficult to quantitate that risk accurately, with a variety of estimates based on case series published in the literature. These range from as little as 1.4% to one series reporting that 25% of patients with genetically determined immunodeficiencies will develop primary B-cell lymphomas in their lifetimes.[2–6]

The predisposing conditions are[2,4,7,8]:

- ataxia telangiectasia (AT)
- Wiskott-Aldrich syndrome (WAS)
- common variable immune deficiency (CVID)
- severe combined immune deficiency (SCID)
- x-linked lymphoproliferative disorder (XLP or Duncan syndrome)
- Nijmegen breakage syndrome (NBS)

- hyper-IgM syndrome (HIM)
- autoimmune lymphoproliferative syndrome (ALPS)

While the evidence of increased risk of lymphoma is firm, the benefit of early detection and intervention is less well documented. The presumption that surveillance for lymphoma and early intervention is beneficial is an extrapolation from general cancer medicine principles.

16.2.2 Clinical presentation

The clinical presentation commonly involves extranodal sites of disease, predominantly gastro intestinal tract (GIT), central nervous system (CNS), lung and kidney.[2,3] Presenting symptoms may resemble infection and commonly include fevers, infectious mononucleosis-like syndrome, and fatigue. Benign lymphoid hyperplasia may precede the development of lymphoma[2], as may the development of monoclonal gammopathy.[9]

16.2.3 Management

Management of the primary immune disorder usually entails consideration of allogeneic bone marrow transplantation (BMT) from a sibling donor.[10] The clinical decision to proceed to transplant depends on the severity of the clinical phenotype, including the perceived risk of developing lymphoma. BMT is, in general, curative of the underlying disorder, and appears to reduce the risk of developing lymphoma.[11]

Diagnosis and staging of lymphoma follows standard guidelines (see Chapter 8). Special considerations include:

- monoclonal B-cell populations may be self limited in some primary immune disorders (PIDs) (e.g. in CVID) and are not diagnostic of lymphoma[12]
- some non-clonal proliferations of B-cells (e.g. in XLP) or plasma cells (e.g. in hyper IgM syndrome) may be fatal
- extranodal sites may require specific investigations

It is unknown whether standard risk factor assessment or evaluation of IPI are helpful in the setting of PID-related lymphoma. The underlying immune status is an important predictor of outcome. T-cell count and T-cell function correlated with outcome in a series of 18 patients with PID and LPD.[13]

The most common histologic subtype is DLBCL, although polymorphic LPDs also occur frequently. Rarely described are Burkitt's lymphoma, follicular lymphoma, peripheral T-cell lymphoma, and Hodgkin lymphoma.[2–6]

There is a paucity of data documenting the treatment and outcome of PID patients with lymphoma. Retrospective analyses of case reports predominate.[7,14,15] There are no randomised controlled trials within this rare patient group to provide evidence for specific recommendations. More recent data suggest that standard treatment with curative intent, stratified along the currently recommended lines according to histology and prognostic index, be attempted in patients with PID[16], although confirmation of this approach is needed. As PID lymphoma usually occurs in paediatric patients, the specific approach should be appropriate to the paediatric patient.

Special considerations include continuing specific treatment of the underlying immunodeficiency, for example, immunoglobulin replacement, antibiotic prophylaxis, etc. The option of allogeneic BMT should be considered and fully explored, if not already done in the context of the primary disorder. Toxicity from standard lymphoma therapies may be considerably greater than in the non-

immunocompromised lymphoma patient population and strict attention to supportive care measures must be maintained.

Guidelines — Immune deficiency — treatment	Level of evidence	Refs
Patients with primary immune deficiency (PID) should be under close clinical surveillance for the development of lymphoproliferative disease. Maintain a high index of suspicion with prolonged symptoms of unidentified infection; symptoms referrable to common sites of extranodal lymphoma; and precursor lesions such as lymphoid hyperplasia and monoclonal gammopathy.	V	2, 3
Standard curative intent therapy appropriate for the specific lymphoma should be administered, with special attention to supportive care for expected treatment-related toxicity.	IV	16
Primary immune deficiency (PID) patients with lymphoma should be assessed for potential allogeneic bone marrow transplant.	opinion	10, 11

16.2.4 Recommendations for future research

- Cancer registries should prospectively collect data on lymphoma patients to document the incidence of underlying PID and determine the outcome for this subset of patients.
- PID-related lymphoma patients should be eligible to participate in the large lymphoma clinical trials, and identified as a specific subset for the prospective collection of information on outcomes and comparison with the non-immunocompromised lymphoma patient. Ideally, laboratory information including EBV status should be incorporated into such trials.

16.3 Management of lymphomas associated with infection by the human immunodeficiency virus (HIV)

16.3.1 Background

Lymphoma is a common complication of HIV infection, correlating with both the degree and duration of immunosuppression. Incidence rates vary from 1.6% to 6% per year.[17] The introduction of highly active anti-retroviral therapy (HAART) has seen a reduction in the incidence of lymphoma, particularly primary CNS lymphoma.

16.3.2 WHO classification

The WHO categories are as follows:

- Lymphomas also occurring in immunocompetent patients
  - Burkitt lymphoma
    - Classical
    - With plasmacytoid differentiation
    - Atypical
  - Diffuse large B-cell lymphoma

    - Centroblastic
    - Immunoblastic
  - Extranodal marginal zone B-cell lymphoma (MALT lymphoma) (rare)
  - Peripheral T-cell lymphoma (rare)
  - Classical Hodgkin lymphoma
- Lymphomas occurring more specifically in HIV-positive patients
  - Primary effusion lymphoma
  - Plasmablastic lymphoma of the oral cavity
- Lymphomas also occurring in other immunodeficiency states
  - Polymorphic B-cell lymphoma (PTLD-like)

16.3.3 Clinical

The lymphomas are predominantly aggressive B-cell lymphomas[18], most commonly Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma (PEL) and plasmablastic lymphoma of the oral cavity. EBV positivity is higher than in the same entities in the non-HIV lymphomas. It varies from 30% to 100%, depending on the specific histology and site.[18] In general, pathologic features are similar to the non-HIV counterparts. Burkitt lymphoma with plasmacytoid differentiation, PEL, and plasmablastic lymphoma of the oral cavity are rarely reported outside the HIV setting. PEL has been associated with Kaposi's sarcoma and HHV8 infection. Primary CNS lymphoma is more common in HIV-lymphoma than in non-HIV lymphomas, although the incidence has fallen dramatically since the introduction of HAART (see Chapter 2).

The incidence of Hodgkin lymphoma also increases in the HIV population in the order of eight-fold.[18] There is a predominance of the poorer prognostic histological subtypes (lymphocyte depleted and mixed cellularity) and presentation is usually with advanced-stage disease. It is almost always EBV positive and is associated with a poorer prognosis than in HIV-negative patients.

16.3.4 Therapy for systemic NHL

Chemotherapy

There have been three prospective randomised trials in HIV-positive lymphoma patients, all conducted in the pre-HAART era (see Table 16.1). These studies examined dose intensity. The AIDS Clinical Trials Group compared standard-dose mBACOD with reduced dose of the same protocol (mostly 50%) and were unable to demonstrate any benefit for response or survival for either group.[19] Toxicity was greater in the standard-dose arm despite the routine use of GM-CSF.

Table 16.1 Randomised chemotherapy trials for HIV lymphoma

Study	Number	Regimens	Median CD4 cells/ul)	CR rate	Survival
Kaplan et al. 1997[19]	94 98	100% mBACOD 50% mBACOD	100	45 40	7.2m (median) 8.2m
Tirelli et al. 1999[20]	80 79	ACVB CHOP	200	65 56	51% at 2yr 43% at 2yr
Tirelli et al. 1999[20]	59 51	100% CHOP reduced CHOP	60	63* 39*	35% at 2yr 28% at 2yr

*statistically significant

The French–Italian Co-operative Group stratified patients according to adverse prognostic factors defined as prior history of AIDS, CD4 <100 cells/uL, and ECOG performance status of two or more.[20] In 159 patients with no adverse factors, full-dose CHOP was compared to a more intensive regimen (ACVB). All patients were given G-CSF support. There were no significant differences for response, event-free or overall survival. There was greater haematological toxicity in the ACVB group but no difference in death rate. For patients with one adverse factor, standard-dose CHOP was compared to reduced-dose CHOP (50% doxorubicin and cyclophosphamide). The complete response rate was significantly better in the full-dose CHOP arm at 63%, compared to 39% for the reduced dose (p = 0.001), but there was no difference in overall survival.

Preliminary evidence suggests that infusional therapy may be a promising approach in primary and salvage treatment of patients in the HAART era.[17] Two regimens have shown promising results, CDE[21] and EPOCH.[22] In 39 patients EPOCH was reported to achieve an impressive 74% complete response rate, 92% disease free survival and 60% overall survival with median follow up beyond four years. However there are no randomised data comparing infusional to standard therapy.

Since CHOP is equivalent to more intensive regimens in lymphoma patients who are HIV negative[23], it is reasonable to expect the same for patients with HIV-related lymphoma. Consequently, CHOP could be considered the standard of care. This is supported by the French–Italian Group study. Whether all patients should be treated with full-dose CHOP is not clear. The French–Italian Group study suggests full dose is more likely to be effective even in patients with poor prognostic factors.[20] It is recommended that full-dose CHOP be given with HAART to maximise response and reduce secondary complications of immune failure. An infusional regimen such as EPOCH may be a reasonable alternative, however, randomised comparative studies with CHOP are needed in the HAART era. There are no current data for accelerated CHOP (CHOP 14) or CHOP with rituximab specific to the HIV population.

CNS prophylaxis

This has not been extensively studied in the context of HIV-related lymphoma. However, a high incidence of CNS involvement has been reported from early studies and some treatment centres recommend all patients receive CNS prophylaxis.[17] It is recommended in the absence of specific data that guidelines for similar lymphoma subtypes in the non-HIV population be adopted.

Rituximab

One preliminary study of CDE and rituximab in 29 patients has reported an 86% complete response rate and 80% actuarial two-year overall survival.[24] The AIDS Malignancy Consortium completed a randomised study of CHOP plus rituximab compared to CHOP alone, in September 2002. The results are awaited with great interest.

Highly active anti-retroviral therapy (HAART)

To date, there have been only preliminary studies of the interaction of chemotherapy and HAART. The EPOCH study demonstrated that didanosine used with chemotherapy was associated with reduced haematological toxicity.[22] The AIDS Malignancy Consortium studied the HAART combination of stavudine, lamivudine and indinavir with either low or standard-dose CHOP, and found no increase in toxic side effects.[25] Cyclophosphamide clearance was reduced by 50% compared to historical controls, with no difference in expected clearance of doxorubicin or indinavir. Zidovudine should be avoided in HAART protocols because of its well recognised haematological toxicity.[21,25] Since HAART substantially reduces morbidity and mortality of AIDS complications, and pre-HAART studies of chemotherapy for HIV-related NHL demonstrated as many as 25% of complete remission patients dying of these complications, it is recommended that HAART be given either during or after the completion of chemotherapy. A number of recent small prospective studies have demonstrated improved survival for patients on HAART. One non-randomised study has reported an improvement in median survival from 8.2 months to 17.8 months for patients with HIV-related NHL treated in the post-HAART era.[26] This study demonstrated a CR rate of 71% for HAART responders compared to 30% for non-responders. In another study, HAART treatment was associated with improved survival, with an 84% reduction in risk of death.[27] A retrospective risk factor study in more than 200 patients found response to HAART was independently associated with improved survival.[28]

It is therefore recommended AIDS–lymphoma patients should receive HAART or have their existing antiretroviral therapy changed to maximise improvement in immune function.

16.3.5 Therapy for primary CNS lymphoma

Before the introduction of HAART, the prognosis for patients with primary CNS lymphoma was exceptionally poor, with many patients too ill to consider either radiotherapy or chemotherapy. The introduction of HAART has led to a number of anecdotal reports of improvement in prognosis. Hoffman et al. reported dramatic improvement in survival of these patients when HAART achieved immune recovery.[29] In general, treatment guidelines should follow those for patients without HIV infection.

16.3.6 Therapy for Hodgkin lymphoma

There are no randomised treatment studies. Most reports have only small numbers of patients and describe clinical experience with well-known protocols such as ABVD. Since the introduction of HAART, more intensive protocols have been tried. Recently, successful and safe use of the Stanford V regimen has been reported.[30] If immune reconstitution can be achieved with HAART, then treatment guidelines similar to those for HIV-negative patients with Hodgkin lymphoma may be considered.

Stem cell transplantation

The success of immune reconstitution using HAART has led to the investigation of high-dose chemotherapy and stem cell transplantation as salvage therapy for patients with refractory or relapsed lymphoma. The prognosis for these patients is very poor. Gabarre et al. reported the results of autologous marrow and blood stem cell transplants in eight such patients, with five achieving a CR and survivals reported from 5 to 15+ months.[31] Krishnan et al. reported nine similar patients, with seven achieving CR and median survival 19 months. These modest results represent a remarkable improvement on the previously expected results for such patients.[32]

Allogeneic stem cell transplantation has generally been unsuccessful, with one case report of a relapsed lymphoma patient surviving in remission after a syngeneic transplant.[33] Non-myeloablative allogeneic stem cell transplantation has been reported in two patients, one with lymphoma and one

with acute myeloid leukaemia.[34] Both survived the therapy. The lymphoma patient died of relapsed disease at one year; the other patient remained in remission at two years.

Extra-nodal lymphoma

This is a more common presentation in HIV–lymphoma and should be managed according to the site-specific requirements for the non-HIV population.

Guidelines — Management for lymphomas associated with HIV	Level of evidence	Refs
Full-dose CHOP should be considered the current standard of care for HIV-related lymphoma, although new data are awaited.	IV	19, 23
Highly active anti-retroviral therapy (HAART) should be commenced or maximised in patients with HIV-related lymphoma.	III	22, 26
Hodgkin lymphoma should be managed as for non-HIV patients, with the addition of HAART.	III	30

Key point

Primary CNS lymphoma should be managed as for non-HIV patients with the addition of highly active anti-retroviral therapy (HAART).

16.4 Post-transplant lymphoproliferative disorder

16.4.1 Background

Post-transplant lymphoproliferative disorders (PTLDs) occur as a consequence of immunosuppression in the recipient of an allograft. They encompass a spectrum of specific pathologies well described in the WHO classification.[35] The incidence of PTLD varies considerably between 1% and 20% or more, depending on a number of variables that are discussed below. PTLD may be of early (within the first year after transplant) or late onset (any time thereafter). PTLD has been associated with solid organ transplants of all types and also in bone marrow or stem cell recipients. Recognition of patients at high risk for the development of PTLD is an important element of organ transplantation management.

16.4.2 WHO classification

The WHO categories are as follows:

- Early lesions
  - Reactive plasmacytic hyperplasia
  - Infectious mononucleosis-like
- Polymorphic PTLD
- Monomorphic PTLD (classified according to lymphoma classification)
  - B-cell neoplasms
    - Diffuse large B-cell lymphoma
    - Burkitt/Burkitt-like lymphoma

- Myeloma
- Plasmacytoma-like lesions

– T-cell neoplasms
  - Peripheral T-cell lymphoma unspecified
  - Other types
  - Hodgkin lymphoma

16.4.3 Clinical features

The clinical presentation is highly variable, correlating to some extent with the risk factors discussed below, as well as the specific morphologic subtype of PTLD. Early-onset PTLD commonly presents with an infectious mononucleosis-like syndrome, with cervical lymphadenopathy and tonsillar enlargement, or simply pyrexia of unknown origin. Late-onset PTLD, like other immunodeficiency lymphomas, commonly present with extranodal disease that may manifest as organ dysfunction, often including the allograft.

Key point

Patients with post-transplant lymphoproliferative disorder (PTLD) should undergo standard diagnostic and staging procedures with special attention to extranodal sites including the allografted organ and/or gut, lung, central nervous system, kidney.

16.4.4 Risk factors

Nearly all the current knowledge pertaining to risk factors for PTLD is derived from retrospective observational cohort studies. All of these studies suffer from one or more significant limitations, including small numbers, short follow-up times, recall bias, co-intervention bias, solid organ heterogeneity, non-uniformity of diagnosis, or inclusion of only early-onset PTLD. Nonetheless, some consistent observations have been made.

Risk factors include:

- serological status for EBV and CMV of the donor and recipient
- immunosuppressive therapy
- recipient age
- underlying disease
- type of organ transplant
- miscellaneous factors

Serological status for EBV and CMV of the donor and recipient

EBV is implicated as an essential cofactor for the development of PTLD. An EBV seronegative recipient (R-) may acquire EBV from a seropositive donor (D+). Pre-transplant EBV seronegativity increases the incidence of PTLD 10- to 75-fold over that of EBV-seropositive recipients (R+) of organs from seropositive donors.[36] The majority of PTLDs in this setting derive from donor EBV. In R+, EBV reactivation is usually the mechanism.

Cytomegalovirus (CMV) seromismatch (R-, D+) has been associated with up to a 7.3-fold risk of PTLD in several studies[36,37], although was not confirmed in a small study of paediatric lung transplants.[38] Reactivated CMV infection may play a role in PTLD, but is difficult to separate from its collinear relationship with higher levels of immunosuppression. CMV seromismatch exerts an important synergy with EBV seromismatch and OKT3 therapy in promoting PTLD.[36]

Immunosuppressive therapy

The degree and duration of immunosuppression as well as the specific agents are important, recognised risk factors for PTLD.

Specific agents

OKT3

This has been associated with greatly increased risks of early onset, extensive-stage and fatal PTLD.[36,39–43] Swinnen et al.[39] first reported the increased (nine-fold) prevalence of PTLDs in cardiac transplant recipients who received greater than a 10 mg cumulative dose of OKT3. Higher doses were associated with increased risk, with 6.2% of patients receiving ≤75 mg developing PTLD, and 35.7% receiving >75 mg developing the disorder ($p<0.001$). The reported multivariate-adjusted relative risk of PTLD following OKT3 therapy has ranged between 1.8- and nine-fold.[36,39,44,45] The relative risk of PTLD is synergistically increased four to six-fold by the combination of OKT3 therapy with other risk factors such as EBV and CMV seromismatch (D+, R-). All three risk factors together have been associated with over a 500-fold increased risk (95% CI 324–862) of PTLD compared with the absence of all three factors.[39] The median time to development of OKT3-associated PTLD has been reported between four and seven months after transplant but generally occurs within the first year.[36,39,44,46] Two studies[47,48] have not been able to confirm a high incidence and early onset of PTLDs in OKT3-treated transplant recipients, but insufficient statistical power and high baseline immunosuppression confound the interpretation of these.

Calcineurin inhibitors (cyclosporin and tacrolimus)

These have been associated with a one to five-fold risk of PTLD. Multivariate analysis of the large Collaborative Transplant Study database (45,141 kidney and 7634 heart transplant recipients) suggested that triple therapy containing a calcineurin inhibitor was associated with a 1.5-fold relative risk of PTLD compared to dual therapy or cyclosporin alone.[45] This finding was confirmed in a single centre Australian study of 2030 renal transplant patients.[46] The relationship between cyclosporin levels and PTLD has not been fully established.[47,49] The incidence of PTLD associated with cyclosporin appears to be comparable to that associated with tacrolimus therapy in adults.[46,50]

In paediatric patients, tacrolimus therapy increased the risk of PTLD up to 11-fold (absolute risk 11–20%) relative to non-contemporaneous patients treated with cyclosporin.[47,51,52] Higher tacrolimus levels were a significant risk factor for lymphoma on multivariate logistic regression in a paediatric liver transplant population.[51] There are insufficient data, however, for specific recommendations.

Mycophenolate mofetil

This has not been shown to be associated with a statistically significant increased risk of PTLD in several short-term, multicentre, randomised control trials.[53–55] They were not adequately powered, however, to reliably assess the effect.

Interleukin-2 receptor antibody (basiliximab, daclizumab)

Induction with this agent[56–59] does not appear to be associated with an enhanced risk of early PTLD in short-term (one-year) randomised controlled trials. Pooled data from two randomised, placebo-controlled trials of daclizumab (n=535) showed no increased risk of PTLD over placebo after three years.[58]

Sirolimus and RAD

Sample sizes and follow-up times have been too small to determine precisely the risk of PTLD from these agents.[60,61] The macrolide immunosuppressant, RAD (everolimus, an analogue of rapamycin/sirolimus), has been shown to inhibit the growth of human EBV-transformed B lymphocytes *in vitro* and *in vivo*[62], indicating that it may be effective in the prevention and treatment of PTLDs. However, there has been insufficient clinical experience with this agent to test this possibility.

Antithymocyte globulin (ATG)

This has been reported to increase[45,51,60,63] or have no effect[38,46,64] on the occurrence of PTLD in small observational cohort studies. All of the studies reporting a deleterious effect of anti-lymphocyte antibodies on PTLD risk have lumped patients receiving ATG with those receiving OKT3 and have not analysed ATG administration as a separate covariate. Thus the risk of ATG may have been overestimated. On the other hand, the negative studies had a relatively small number of cases (up to 29) and may have been inadequately powered.

Duration and intensity of immunosuppression

PTLD can present as early as less than a month to as late as many years after transplantation. The incidence of PTLD is highest in the first year, which is the time of most intense immunosuppression (approximately 100 cases/10^5 patient-years), and falls by about 60% thereafter (approximately 40 cases/10^5 patient-years).[36,45,46,65]

More intensive immunosuppression is associated with an earlier onset of PTLD. Penn[44] reported mean lag times between solid organ transplantation and PTLD diagnosis of seven months for OKT3, 15 months for cyclosporin, and 48 months for patients treated with azathioprine/cyclophosphamide. In a large renal transplant cohort, median lag times were six months for OKT3, 48 months for triple therapy calcineurin inhibitor/prednisolone/azathioprine ormycophenolate), and 168 months for dual therapy (prednisone + azathioprine).[42]

Early onset PTLDs are much more likely to be EBV-related than late onset PTLDs. In one series, 50% of EBV-positive PTLDs had arisen within six months of transplantation, whereas 50% of EBV-negative PTLDs had not occurred until five years after transplantation.[66]

Late-onset (several years) PTLD is less strongly associated with potent immunosuppression.[46,67,68] Some of this association, however, may represent a bias of the shorter follow-up periods of studies involving newer, more potent, immunosuppressive therapies. PTLDs of T-cell origin are uncommon and may also arise later in the post-transplantation course.[69]

Recipient age

Paediatric patients have higher frequency of PTLD than adult recipients of similar allografts. Contributing to this is a higher percentage of EBV- and CMV- seronegative recipients. Zangwill et al. reported an overall PTLD occurrence rate of 26% among 50 paediatric heart transplant recipients (mean follow up 3.3 years), with risk related to EBV status: 0% in persistently R-, 5% in R+, and 63% in patients who seroconverted after transplantation.[70]

Ho reported similar findings in a series of paediatric kidney transplant recipients.[71] Rates in seronegative adults are comparatively much lower.[71,72]

Older recipient age appears to be a risk factor for the development of late-onset (>1 year) PTLD. The Collaborative Transplant Study observed that the incidence of late-onset PTLD in 7634 cardiac transplant recipients was significantly higher in individuals over the age of 49 years compared with those less than 20 years (480 versus 99 cases/10^5 patient-years respectively).[45] A similar, non-significant trend was observed in 45,141 renal transplant recipients.

Underlying disease

Hepatitis C infection has been implicated as a risk factor for PTLD to complicate liver transplantation in two small retrospective studies using either contemporaneous or historical controls (11% versus 2% and 7% versus 1%, p<0.05).[73,74] However, these studies performed univariate analyses, which did not adjust for potential confounders, such as background immunosuppression. A similar finding has been reported for PTLD in cardiac transplant recipients (HCV positive 8% versus HCV-negative 2%, p=0.01).[75]

A striking association was reported in one series of patients who underwent liver transplantation for treatment of Langerhans cell histiocytosis. Two thirds of patients developed PTLD.[76]

Children with cystic fibrosis receiving lung allografts have been reported to have a higher frequency of PTLD (23% versus 4% for other indications, adjusted odds ratio 11.0, 95% CI 2.7–55.7) in one (n=128) retrospective, single-centre cohort analysis.[38]

Type of organ transplant

The risk of PTLD appears to be strongly influenced by the type of organ transplanted. The risk is lowest in bone marrow transplant and renal and pancreatic transplant recipients (1–2%)[45,46]; intermediate in liver and cardiac transplants (2–4%)[45,77]; and highest in lung and intestinal transplants.[74,78–81] The incremental risk may be partly due to variations in immunosuppressive burden (where lower immunosuppression is employed in renal and pancreatic transplants because rejection and graft loss is not generally immediately life-threatening). Moreover, the large lymphoid populations transferred with lung or intestinal transplants facilitate EBV transmission.[67,82]

The allografted organ is at specific risk of involvement in patients with PTLD. The Collaborative Transplant Study demonstrated that renal lymphoma developed in 14.2% of renal transplant recipients versus 0.7% of heart transplant recipients. Allograft involvement is particularly common (≥80%) in lung and intestinal transplant patients with PTLD.[38,67,79–81,83]

In HLA-matched sibling bone marrow transplants, the incidence of PTLD is generally less than 1%.[84–86] Several risk factors are associated with a much higher incidence.[87–89] These include non-HLA identical transplants, T-cell depletion of the graft, severe graft versus host disease (GVHD), and in common with solid organ transplant recipients, EBV seronegativity and the use of antithymocyte globulin.

Miscellaneous risk factors

- Immunologic profile: a small, prospective, single-centre, nested case-control study found that a high absolute count of activated NK cells (CD56+ DR+) at baseline was a significant, independent predictor of PTLD development.[90]
- Cytokine gene polymorphisms: preliminary data suggest that the development of PTLD is linked with low-producing polymorphisms of interferon-γ (80% versus 12%)[91] and tumour necrosis factor-α.[92]
- Caucasian race, cadaveric donor[47] and adenotonsillar hypertrophy[93] have each been implicated as PTLD risk factors in small, single studies of paediatric transplant populations.
- The degree of HLA mismatching does not appear to influence the risk of PTLD in recipients of solid organ transplants, in contrast to bone marrow transplantation.[67]

What do other guidelines say?

ASTS/ASTP EBV-PTLD Task Force and Mayo Clinic Organized International Consensus Development Meeting

The three identified epidemiological risk factors for PTLD are EBV seronegativity pretransplantation (R-), CMV disease in a CMV mismatch (D^+/R^-) patient, and high doses of antilymphocyte antibodies or over immunosuppression.

Guidelines — Post-transplant lymphoproliferative disorder (PTLD) — risk factors	Level of evidence	Refs
Two of the major known risk factors for the development of PTLD are Epstein-Barr virus (EBV) sero-mismatch and cytomegalovirus (CMV) sero-mismatch (R-, D+).	III-2	36, 37

Key point

Before transplant, the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) status of recipient and donor should be determined to identify patients at high risk of developing post-transplant lymphoproliferative disorder (PTLD).

Guidelines — Post-transplant lymphoproliferative disorder (PTLD) — risk factors	Level of evidence	Refs
Use of OKT3 is the third powerful known risk factor for PTLD.	III-2	39

Key point

Post transplant use of OKT3 should be minimised and recipients should be identified as patients at high risk for the development of post-transplant lymphoproliferative disorder (PTLD).

Recommendations for future research

- National registries (such as ANZDATA) should prospectively collect detailed clinical data, including demographics, immunosuppression, EBV and CMV status, and other potential risk factors in all transplant recipients and identify PTLD cases.
- Uniform practices of testing EBV and CMV serologies in both donors and recipients prior to transplantation should be promoted. This would help to identify at-risk patients and may influence subsequent decisions regarding maintenance and anti-rejection immunosuppression.
- Trials of newer immunosuppressive agents and subsequent post-marketing surveillance should specifically evaluate whether or not PTLD risk is modified.

16.4.5 Surveillance

Monitoring the EBV viral load

Measuring the EBV viral load in plasma and peripheral blood mononuclear cells has been used to identify patients at risk of developing PTLD. Studies are hard to compare because study design as well as EBV detection methods and analysis are highly variable. In the majority of cases, however,

EBV viral load is increased in patients with PTLD compared to patients without disease. There is overlap, however, with evidence that two-thirds of transplant recipients become persistent viral load carriers without evidence of PTLD. More recent studies utilising quantitative real-time PCR show the potential to identify threshold EBV levels above which patients are at greatly increased risk of developing PTLD.[94–96]

Viral load monitoring can be used to follow patients with PTLD and, along with other parameters, to provide an assessment of the effectiveness of therapeutic protocols.

CMV monitoring

There is no evidence pertaining to the usefulness or otherwise of CMV monitoring (e.g. PP65 antigenaemia, serology, polymerase chain reaction) in a PTLD surveillance program.

Monoclonal gammopathies

The best available evidence addressing the value of gammopathy monitoring by serum protein electrophoresis for PTLD surveillance is a prospective cohort study by Lemoine et al.[97] Nine hundred and eleven (911) consecutive liver transplant recipients underwent serum protein electrophoresis prior to transplantation, twice in the first post-transplant year and then annually thereafter. Gammopathy was observed in 114 patients overall, and in 18 out of 21 PTLD patients before the development of PTLD (therefore, positive predictive value = 16%). The adjusted relative risk of gammopathy for PTLD was 65.3. For diagnosis of PTLD remission, the positive and negative predictive values of gammopathy disappearance (on monthly serum electrophoresis monitoring) were 91% and 100% respectively. Gammopathy disappearance preceded the radiologic diagnosis of complete remission by a mean of four months.

Badley et al[98] observed the presence of monoclonal gammopathy in 5 of 7 (71%) patients with PTLD and 52 of 194 (27%) patients without PTLD (positive predictive value 9%, negative predictive value 99%) in a small (n=201), single-centre, retrospective cohort analysis. Numbers were too small to permit a multivariate analysis.

What do the other guidelines say?

ASTS/ASTP EBV-PTLD Task Force and Mayo Clinic Organized International Consensus Development Meeting

Quantitative EBV polymerase chain reaction technology is a promising innovation that may allow for an earlier diagnosis of PTLD and identification of those patients likely to develop PTLD. However, additional study is required before recommending it for routine clinical use.

Guidelines — Surveillance of post-transplant lymphoproliferative disorder (PTLD) patients	Level of evidence	Refs
Monitor EBV viral load serially by quantitative real-time PCR in plasma (preferably in the context of ongoing research).	IV	94–96
Monitor for the development of monoclonal gammopathy.	IV	98

Recommendations for future research

- The major future goal will be to standardise EBV-DNA quantitation using real-time PCR in order to generate comparable data and to establish threshold values to identify patients at high risk of developing PTLD.
- Concurrent evaluation of EBV-DNA load and gammopathy monitoring in prospective studies is needed, particularly in high-risk groups (e.g. EBV and CMV seromismatch, OKT3 therapy).

16.4.6 Therapy of PTLD

There is no standard approach. Early diagnosis and use of appropriate therapies is essential to the successful treatment and management of PTLDs. Treatment should be tailored to the specific form of disease in the individual patient. Most centres follow a step-wise approach, with the initial intervention influenced by the extent of disease and the degree of acute illness of the patient. This results in a diversity of modifications and makes it difficult to compare therapies.

Therapy for PTLD includes:

- reduction of immunosuppression
- antiviral therapy
- cytokine therapy, for example, interferon
- conventional chemotherapy
- monoclonal antibody
- surgical excision
- radiotherapy
- cellular immunotherapy

Reduction of immunosuppression

There are no randomised controlled trials evaluating this well-established approach. The available studies are all retrospective and often limited by recall, co-intervention and selection biases. The infrequent reporting of standardised prognostic markers, such as the International Prognostic Index, make it difficult to generalise results to clinical practice.

Reduction or cessation of immunosuppression is almost universally reported in the therapy of PTLD. However, there has been no standardised approach to immunosuppression management, and treatment has often been combined with other therapies in an *ad hoc* fashion. Thus it is not possible to make evidence-based recommendations regarding the extent to which immunosuppression should be curtailed, or for how long. Most studies have suggested major reductions with cessation of azathioprine or mycophenolate mofetil and reduction of calcineurin inhibitors by at least 50%.[67–89] Prednisone dosage is usually reduced to 10 mg or below. Patients with kidney or pancreas transplants (where loss of the organ is not immediately fatal) may have all immunosuppressive agents ceased except for a maintenance dose of steroids to avoid Addisonian crisis.[46,99]

Regression of PTLD after immunosuppressant dose reduction ranges from 23% to 63%.[68,99] Reported subsequent allograft rejection rates have ranged between 0% and 74%.[46,68,99,100]

Risk factors for non-response to reduction of immunosuppression have been analysed in a retrospective study of 42 PTLD patients. These were elevated lactate dehydrogenase, organ dysfunction and involvement of at least two organs.[99] The respective complete or partial response rates for 0, 1 or >1 risk factors present were 89%, 60% and 0%. The median time to documented radiologic complete or partial remission was 3.6 weeks (range 1.7–14.6 weeks). Other retrospective studies have suggested that patients with late-onset (>1 year post-transplantation) PTLD are unlikely to respond to immunosuppression reduction alone.[46,78]

Systemic antiviral therapy

The efficacy of antiviral therapy for treating PTLD has not been firmly established. Transformed B cells have a circular viral DNA that is not very susceptible to inhibition with thymidine kinase

inhibitors such as acylovir and ganciclovir.[101] However, there are anecdotal reports of PTLD regression with both acylovir and ganciclovir therapy.[102–108] Other authors have documented poor clinical outcomes with acylovir.[101,103,109] There are no randomised controlled trials. The limited data available are all retrospective.

Cytokine therapy

There are no randomised trials. All studies are retrospective and most are small.[110–113] Interferon alpha may succeed when no response has been seen with reduction of immunosuppression.[112,113] However, the risk of rejection is also present with the use of this agent. Ten of the 34 cases in the published literature had rejection of the allograft.[113] Complete response rates of up to 40% have been reported with interferon alpha.[111,113] Recombinant interferon-alpha has been given with IV immunoglobulin and induced remission in five patients, with three durable responses.[111]

Chemotherapy

Reported results of treatment of PTLD with conventional chemotherapeutic agents are conflicting.[102,103] Early attempts to use anti-lymphoma chemotherapy resulted in high mortality rates and response rates were highly variable. This may be related to the heterogeneity of PTLD, different chemotherapy regimens, the type of organ transplant, the variable degrees of immunosuppression, the timing of treatments, and concomitant therapies. Infectious and other complications of chemotherapy were less well managed and may also have contributed to the poor outcomes. Nonetheless, observed cure rates of 20%, 11% and 23% were documented.[41,103,114]

Davis et al.[113] reviewed the more recent literature (1994–2000) and found 67 of 202 patients were treated with chemotherapy. The patients were heterogenous and were treated with different cytotoxic regimens. Forty-six patients (22%) achieved CR, with a mortality of 11% during chemotherapy.

More encouraging results have been obtained in cardiac transplant recipients mainly treated with ProMACE-CytaBOM. CR was obtained in 75%, with mortality of 25%. No relapses were observed at a median follow up of 64 months.[115] An overall response rate of 80% (30 PR and 50% CR) was reported in ten selected patients with late onset (>1 year) PTLD post-renal transplant treated with CHOP chemotherapy.[116] Modified approaches with regimens used to both treat the tumour and maintain an immunosuppressed state to preserve the allograft have also been reported.[117–119] A case series from a single Australian centre with a treatment approach of initial reduction and eventual discontinuation of immunosuppression once established on CHOP chemotherapy reported an excellent outcome. Overall response rate was 100%, with CR in 93% and PR in 7%.[120]

Advances in supportive care (G-CSF, blood product support, antimicrobials, etc) for patients with haematological malignancies, have contributed to reduced morbidity and mortality from chemotherapy in more recent studies.

Monoclonal antibody therapy

Anti-B-cell antibodies have demonstrated efficacy in the treatment of PTLD. Early experience was with murine anti-CD21 and anti-CD24. Fifty-eight patients were treated, with CR of 61% and low relapse rate of 8%.[121] More recent experience has been with the humanised anti-CD20 monoclonal antibody, rituximab. Efficacy has been reported in a number of case reports and small case series.[122–125] In the largest cohort to date, Milpied reported a 69% response rate, with 73% projected survival at one year.[123] Similar response rates (66%) were reported in twelve children with PTLD post stem cell transplantation treated with rituximab.[124] Rituximab has been included in the European Best Practice Guidelines for the management of PTLD based on the growing evidence of efficacy and minimal toxicity.[126] The growing body of evidence supporting the use of rituximab in combination with chemotherapy in de novo aggressive lymphoma will influence the approach to patients with PTLD, although no data specific to this population are yet available.

Surgery

Data are anecdotal or retrospective case series. Surgical resection has been used and may be curable in the early limited stage, particularly in relatively slowly growing PTLD. In one series, 74% of patients survived.[115] However, another study reported a complete remission rate of only 31% in PTLD treated by surgery or radiotherapy.[103] Surgery has been used for resection of residual disease persisting after reduced immunosuppression or interferon therapy.[78,110]

Radiotherapy

There are no randomised trials. Most of the reports are retrospective studies with small number of patients, often citing combined therapy with surgery or chemotherapy. Survival rates of around 20% for radiotherapy have been documented in PTLD.[115] Radiotherapy has also been used in the treatment of CNS tumours and for control of localised disease elsewhere.[109]

Cell therapy

Expression of the full complement of EBV latent antigens in PTLD provides an ideal target for T-cell-based immunotherapy. There are two distinct categories of PTLD — those arising in bone marrow transplant patients where the proliferating B cells are exclusively of donor origin, and those arising in solid organ transplant patients where the proliferating B cells are generally of recipient origin. The importance of cytotoxic T cells (CTL) in controlling these B-cell expansions was first demonstrated in the case of PTLD in bone-marrow transplant patients transfused with EBV-specific CTLs.[127] In this case, adoptive transfer of EBV-specific CTLs from the bone marrow donors was successfully used to resolve PTLD in the recipient. To date, more than 60 bone marrow transplant patients have been infused with EBV-specific CTL lines as a prophylactic treatment. None of these patients has shown any symptoms of PTLD. Interestingly, many of these adoptively-transferred EBV-specific T cells can be detected 18 months after the infusion.

Although applying a similar rationale of adoptively transferring EBV-specific CTLs to resolve PTLD arising in solid organ recipients is an attractive idea, there are fundamental differences between bone marrow and solid-organ transplantation that pose a major challenge. These include:

- activating a CTL response in vitro in cells from patients receiving high levels of immunosuppressive drugs
- the risk of expanding allospecific CTLs that will threaten the integrity of the transplanted organ when adoptively transferred; and the efficacy of adoptively-transferred CTLs in the face of high levels of immunosuppression *in vivo*.

  One possible way to overcome these limitations is to use allogeneic CTL lines grown from healthy virus carriers who share MHC class I alleles with the patient.[128] Adaptation of this approach for wider clinical use has to proceed with some caution, however, because adoptive transfer of allogeneic T cells can be associated with allograft rejection. Ideally, the best strategy would be to expand autologous EBV-specific T cells from the patient. Such methodology is evolving. Indeed, a novel protocol has recently been developed for activating autologous EBV-specific CTL lines from solid-organ transplant patients.[129] This activation protocol involves co-cultivation of peripheral-blood mononuclear cells with autologous EBV-infected B-cell lines under conditions that favour expansion of virus-specific CTLs and hinder the proliferation of allospecific T-cells.

These CTLs consistently showed:

- strong EBV specificity, including reactivity through defined epitopes despite concurrent immunosuppressive therapy
- no alloreactivity towards donor alloantigens.

More importantly, adoptive transfer of these autologous CTLs into a single patient with active PTLD was coincidental, with a very significant regression of the PTLD. These results demonstrate that a potent EBV-specific memory response can be expanded from solid-organ recipients who have acquired their primary EBV infection under high levels of immunosuppressive therapy, and that these T-cells might have therapeutic potential against PTLD.

What do other guidelines say?

ASTS/ASTP EBV-PTLD Task Force and Mayo Clinic Organized International Consensus Development Meeting

The initial intervention in all patients should be a reduction in immunosuppression. However, how much reduction, for how long, and how to predict the response, is unknown.

Staged approach is recommended as follows:

1. reduce immunosuppression
2. IFN alpha
3. if no response to 1 and 2, proceed to chemotherapy.

The European Best Practice Guidelines for Renal Transplantation (Part 2)

Reduction of basal immunosuppression in all cases.[126]

In the case of EBV-positive B-cell lymphoma, antiviral treatment with acyclovir, valacyclovir or ganciclovir may be initiated for at least one month or according to the level of EBV replication

In the case of CD20-positive lymphomas, treatment with rituximab, a chimeric monocloncal antibody directed against CD20, should be carried out.

Recommendations for future research

- National registries (such as cancer registries and/or ANZDATA) should prospectively collect detailed information on identified PTLD cases regarding IPI, treatment and outcome.
- Pooled registry data (e.g. pooled Collaborative Transplant Study database) should be analysed to determine the extent and duration of immunosuppression reduction associated with the most favourable risk:benefit ratios in the therapy of PTLD.
- A randomised controlled trial of immunosuppression reduction in monitored, high-risk patients is needed to confirm the effectiveness of such a pre-emptive strategy, with clearly defined triggers for pre-emptive treatment (such as a defined EBV load).
- A large, multicentre, randomised controlled trial of antiviral therapy in high-risk patients is needed.
- The role of rituximab, both as a single agent and in combination with chemotherapy, needs to be systematically evaluated in randomised international studies, .
- The role of surgery and radiation therapy needs to be prospectively evaluated in international trials of patients with localised PTLD.
- Setting up a transplant-related lymphoma task force under the auspices of the ALLG may be a useful starting point to generate some of the clinical trial work needed.

Guidelines — Management of post-transplant lymphoproliferative disorder (PTLD) patients	Level of evidence	Refs
Management of PTLD patients All patients with PTLD should have baseline immunosuppression substantially reduced or ceased as the initial therapeutic strategy	IV	67, 68, 99
Consider early additional therapy in patients with risk factors for non-response to reduced immunosuppression (elevated LDH, end organ dysfunction, multi-organ involvement, late onset PTLD, rapidly progressive disease).	IV	46, 78, 99
Additional therapies that should be considered but the roles of which have not been clearly defined include systemic antivirals (ganciclovir, acyclovir)[102–105]05 and alpha interferon.[110–113]	IV	102–105, 110–113
Standard combination chemotherapy for aggressive lymphoma should not be delayed in patients who are not responding to initial strategies (see Chapter 13 — Aggressive lymphoma).	IV	115, 116

Key point

Standard chemotherapy should be considered as initial therapy in patients with extensive systemic or rapidly progressive disease, particularly with IPI >1.

Guidelines — Management of post-transplant lymphoproliferative disorder (PTLD) patients	Level of evidence	Refs
Rituximab is an active agent and should be considered as an additional therapeutic modality.	IV	122–125
Radiation may contribute to the management of PTLD and should be considered in the same settings as non-PTLD lymphomas.	IV	109, 115
Adoptive immunotherapy with allogeneic EBV-specific CTL should be considered in post-BMT PTLD.	IV	127
Adoptive immunotherapy with autologous EBV-specific CTL should be considered for solid organ PTLD patients in the context of continuing clinical research.	IV	128, 129

16.5 Methotrexate-associated lymphoproliferative disorders

16.5.1 Background

Lymphomas and LPDs may occur in patients immunosuppressed with methotrexate, most commonly in the setting of treatment for rheumatoid arthritis, psoriasis or dermatomyositis. More than 100 cases have been reported in the literature, over 85% in association with rheumatoid arthritis, which is itself associated with an increased risk of lymphoma.[130–135] There is no definitive epidemiological evidence, however, of the extent to which methotrexate increases the risk of lymphoma in such patients, if at all.[136–139] Important clinical observations regarding lymphoma in this setting justify its inclusion as a

separate entity, however. The histologies observed are variable and include DLBCL, Hodgkin lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma and polymorphous PTLD. EBV has been implicated in the pathogenesis in approximately 50% of cases. Extranodal presentations are common. There are no other discernibly different features from lymphoma in non-methotrexate treated patients.

16.5.2 Therapeutic considerations

The most important clinical observation with respect to these lymphomas has been regression on withdrawal of methotrexate in approximately 60% of cases.[140–142] The majority of these have been EBV positive. All evidence for this is in the form of case reports, but the observation is made repeatedly and consistently. The reported incidence of regression varies with the specific histology involved, with fewer Hodgkin and diffuse large B-cell lymphomas regressing than lymphoplasmacytic lymphomas.[142] While the majority of those reported in the literature regressed, non-reporting of those that did not regress may bias this literature.

Guidelines — Methotrexate and lymphoproliferative disorders	Level of evidence	Refs
Patients being treated with methotrexate should be monitored for the development of a lymphoproliferative disorder.	IV	130–135,
Methotrexate should be ceased in patients who develop lymphoma and observed for regression before administration of the appropriate lymphoma therapy, if clinically feasible. Methotrexate should not be reintroduced in such patients.	IV	140–142

16.5.3 Recommendations for future research

- National registries should record whether lymphoma patients were being treated with methotrexate.
- Registries of rheumatoid arthritis patients should identify those who develop lymphoma, and determine the relative risk associated with methotrexate therapy.
- The role of EBV should be explored in all patients with methotrexate-associated lymphoma, with a view to the potential for therapeutic intervention with EBV-specific adoptive immunotherapy.

16.6 References

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CHAPTER 17 GASTRIC LYMPHOMA

17.1 Introduction

The gastric lymphomas represent a wide spectrum of disease, ranging from indolent low-grade marginal-zone lymphoma to aggressive diffuse large B-cell lymphoma.

17.2 Summary of clinicopathological findings

These are described in Chapters 12 and 13.

17.3 Mucosal-associated lymphoid tissue (MALT) lymphoma

17.3.1 Aetiology and epidemiology

The aetiological link between *H.pylori* infection and the development of gastric lymphoma is discussed in Section 2.3.2.

17.3.2 Cytogenetic changes

In some 30–40% of cases, a cytogenetic anomaly reflecting a t(11;18) (q21;q21) translocation is detected. This t(11;18) translocation results in a chimeric transcript between the AP12 and MLT genes.[1] Patients with such an abnormality tend to have aggressive, more advanced disease, suggesting prompt treatment and close follow up. However, it appears that t(11;18) positive lymphomas do not respond to *Helicobacter Pylori* (*H-pylori*) irradiation therapy.[1–3] Therefore detection of the presence or absence of the translocation should assist in the clinical management of patients with gastric MALT lymphoma. By contrast, the t(11;18) negative MALT lymphomas show numerous allelic imbalances, some of them identical with aberrations seen in diffuse large B-cell lymphoma, suggesting that this group is the source of tumours eventually transforming into high-grade diffuse large B-cell lymphoma.[4]

17.3.3 Clinical presentation

There is generally an equal proportion of males and females at presentation, with median age in the mid-60s. Symptoms are usually non-specific indigestion and epigastric discomfort. The disease is multi-focal in about 30% of cases. The immunophenotyping and morphology is described above and in Chapter 5.

17.3.4 Diagnosis and staging

This should be carried out as recommended for lymphomas in general, as described in this and other chapters (e.g. see Chapter 8 and Section 9.7). The most appropriate staging systems are controversial and are described in Table 17.1.[5] Patients require testing for *H.pylori* infection.

Table 17.1 Staging of gastric MALT lymphoma: comparison of different systems

TMN Stage	Lugano staging system for gastrointestinal lymphomas	TNM staging system adapted for gastric lymphoma	Ann Arbor stage	Tumour extension
I	Confined to gastrointestinal tract (single primary or multiple, non-contiguous)	T_1 N_0 M_0	IE	Mucosa, submucosa
		T_2 N_0 M_0	IE	Muscularis propria
		T_3 N_0 M_0	IE	Serosa
II	Extending into abdomen			
	II1 = local nodal involvement	$T_{1–3}$ N_1 M_0	IIE	Perigastric lymph nodes
	II2 = distant nodal involvement	$T_{1–3}$ N_2 M_0	IIE	More distant regional lymph nodes
IIE	Penetration of serosa to involve adjacent organs or tissues	T_4 N_0 M_0	IE	Invasion of adjacent structures
IV	Disseminated extranodal involvement or concomitant metastases	$T_{1–4}$ N_3 M_0	IIIE	Lymph nodes on both sides of the diaphragm/distant (e.g. bone marrow or additional extranodal sites)
	Supradiaphragmatic nodal involvement	$T_{1–4}$ $N_{0–3}$ M_1	IVE	

Source: Yalhalom et al.[5]

17.3.5 Endoscopic ultrasound examination

Endoscopic ultrasound (EUS) may become a gold standard for accurately imaging and staging gastric lymphoma. EUS allows direct visualisation of the individual layers of the five-layered gastric wall and assessment of peri-gastric structures and lymph nodes. This accurate staging allows determination of the best therapy for individual patients.[6]

However, reports from several centres suggest that inter-observer agreement for staging by EUS is suboptimal. Others suggest that gastroscopy with biopsy seems sufficient for the routine follow up of patients with gastric lymphomas. Clearly, improvements in the accuracy of EUS need to be demonstrated before this can be recommended as a routine procedure. This may require operators to become more experienced in the technique.[7–9]

Guideline — Gastric MALT lymphoma staging and evaluation	Level of evidence	Refs
Patients should be staged as for lymphomas in general.	III	5
Endoscopic ultrasound should be included in the staging process if experienced operators are available.	III	6–9
Markers for the t(11;18) (q21; q21) translocation should be obtained on tumour biopsy samples.	III	1, 4

17.3.6 Role of antibiotics in *H.pylori* treatment

The concept for the use of antibiotics to eradicate *H pylori* was based on the assumption that *H-pylori* was evoking an immunological response, that is, that the tumour is antigen driven. The original report is based on six patients in whom biopsy showed histological and molecular genetic evidence of MALT lymphoma with *H.pylori* infection, and who were treated with antibiotics. In all cases, *H-pylori* was eradicated. In five patients, repeat biopsy showed no evidence of lymphoma.[10]

Confirmation of this observation came from Roggero in a series of 26 patients with localised primary low-grade gastric MALT lymphoma. *H.pylori* was completely eradicated in 25 of 26 patients, but four patients needed second-line antibiotic therapy. Disappearance or almost total regression of lymphomatous tissue was observed in 15 of 25 evaluable patients.[11] Several other series have confirmed these results. Standard antibiotic combination regimes are recommended.[12,13]

Similarly, Fischbach followed some 90 patients with stage I disease and *H.pylori* infection. The patients were treated with antibiotics. The *H.pylori* was eradicated in 88 patients. The long-term outcome was characterised by CR in 56 patients, minimal residual disease in 17 patients, and partial remission in 11 patients. There was no change in four patients, and progressive disease in two patients. Four patients with complete remission relapsed between six and 15 months, one revealing re-infection by *H.pylori*. The authors concluded that the majority of patients with low-grade MALT lymphoma treated by exclusive *H.pylori* eradication have a favourable long-term outcome offering a real chance of cure.[14]

17.3.7 Persistent evidence of disease after antibiotics

Despite complete remissions of low-grade gastric MALT lymphomas after cure of *H.pylori* infection, many patients display evidence of monoclonal B cells during follow up. Neubauer followed a series of 50 patients in which *H.pylori* was cured in all 50. Forty patients achieved complete remission of their lymphomas, but five subsequently relapsed. Among six patients whose lymphoma did not respond to *H.pylori* eradication, four revealed high-grade lymphomas. PCR indicated the presence of monoclonal B cells during follow up of 22 of 31 assessable patients in complete remission.[12]

Thiede's group in Germany followed 97 patients, of whom 77 achieved complete endoscopic and histological remission. Twenty of 24 patients with PCR monoclonality at diagnosis and with sufficient molecular follow up displayed monoclonal bands for a median time of 20 months after CR. The authors suggest that patients with monoclonal PCR should be observed closely, whereas long-term PCR negativity may indicate cure of the disease.[15]

Further evidence of the presence of molecular disease following complete clinical and pathological remission came from Bertoni's group. At an interim analysis in a large series, some 105 of 189 patients had achieved a complete histological remission after anti-*H.pylori* treatment. Gastric biopsies from a subset of the patients were analysed by PCR targeted to IgG heavy-chain genes as a molecular marker for minimal residual disease. Some 44 cases were monoclonal by PCR diagnosis. Of these, 42 achieved histological complete remission. Of 34 cases undergoing molecular follow up, some 15 (44%) were in molecular remission, with a median follow up of two years after antibiotic treatment. Therefore, less than half of the patients with MALT lymphoma can achieve sustained molecular remission after anti-*H.pylori* therapy. The authors concluded that the presence of molecular disease in the absence of histological disease does not appear to be associated with histological relapse, but given the indolent nature of MALT lymphomas, a longer follow up is needed.[16]

17.3.8 Prognostic factors

Cytogenetic markers

The t(11;18) translocation marker will predict resistance to antibiotic therapy. Liu et al. screened for the AP12/MLT fusion transcript as a marker for t(11;18) in ten antibiotic responsive and 12 non-responsive gastric MALT lymphomas. The AP12/MLT transcript was detected in nine of 12 patients non-responsive to antibiotic therapy, but none in responsive patients. Therefore, most *H.pylori*-associated gastric MALT lymphomas that do not respond to antibiotic therapy are associated with the t(11;18) translocation.[1]

Similarly, Starostik has shown that the patients with the t(11;18) transcript do not transform to high-grade diffuse large B-cell lymphomas.[4]

Lui et al. have further investigated the relationship between t(11;18) as a marker for all stage gastric MALT lymphomas that will not respond to eradication of *H.pylori*. The t(11;18) translocation was detected in two of 48 complete regression cases and those positive cases showed relapse of lymphoma in the absence of *H.pylori* re-infection. In contrast, the translocation was present in 42 of the 63 non-responsive cases, including 26 of 43 at stage IE. They concluded that t(11;18) positive tumours, independent of early stage, do not respond to *H.pylori* eradication.[2]

Inagaki's group in Japan have taken this observation further in a molecular and clinicopathological study of 115 patients. All eradication responsive cases were devoid of the AP12/MLT fusion product. All tumours positive for the fusion product and as well negative *H.pylori* infection were non-responsive to eradication. They consider that gastric MALT lymphomas can be divided into three groups:

- Group A — eradication responsive and fusion negative,
- Group B — eradication non-responsive and fusion negative
- Group C — eradication non-responsive and fusion positive.

Group A tumours were characterised by low clinical stage and superficial gastric wall involvement, and Group C tumours by low *H.pylori* infection rates, advanced clinical stage and nuclear-10 expression. All group C tumours showed exclusively low-grade histology. Group B tumours, which have not been well recognised, frequently showed nodal involvement, deep gastric wall involvement, advanced clinical stage and sometimes an increased large-cell component. Multivariant discriminate analysis revealed that responsiveness to eradication could be predicted accurately by negative AP12/MLT fusion product, positive *H.pylori* infection, low clinical stage and superficial gastric wall invasion.[17]

Endoscopic ultrasound

EUS has predicted outcome of treatment of MALT lymphoma following simple eradication therapy of *H-pylori*. Thus patients with disease limited to the mucosa and/or submucosa at EUS will show complete remission rates up to 100%, whereas very few patients with a more extensive infiltration will show complete remission. The TNM classification appears to be more appropriate for staging lesions by EUS.[6]

Caletti's group in Bologna, Italy, evaluated 51 patients in stage T= $-T_2$, N_0 $-N_1$. Some 66% of T_1N_0 patients achieve CR, compared with only four of eight patients with T_1N_1, and one of four patients with T_2N_0 staged disease. None of the patients in stage T_2N_1 achieved complete response.[6]

This group concluded EUS is the most accurate imaging modality for staging infiltrating gastric lesions, allowing determination of the best modality of therapy for individual patients. The early-stage T_1 lesions are likely to regress after anti-*H-pylori* therapy, while more advanced lesions (T_2–T_4) may require more aggressive treatment protocols. They also note that patients who continue to have a thickened gastric wall on EUS after antibiotic therapy may be considered for other treatment modalities, even if endoscopic biopsies are negative. Many of these patients have persistent lymphoma.

17.3.9 Gastric MALT lymphoma treatment

Antibiotic therapy for *H.pylori* is regarded as standard primary treatment. There are many series documenting histological regression after successful eradication. A standard course of triple therapy should be used.[1–5,18]

Given that more than 90% of cases are associated with *H.pylori*, it is reasonable to treat all patients with a course of eradication therapy at the outset. Patients who are truly *H.pylori* negative will not

respond to this approach, and occasional patients have false negative testing. As well, patients with more advanced-stage disease and the t(11;18) translocation are unlikely to respond to *H.pylori* eradication. It has been recommended that a trial of eradication therapy is worthwhile, as a minority of such patients will have lymphoma regression.[18]

It is suggested that endoscopy be repeated at two months after the completion of eradication assessment, and that patients with complete regression be monitored yearly with endoscopy and biopsy. Patients with no response are considered for alternate therapies, and patients with partial regression should undergo continued monitoring until regression is complete or it is clear that it will not occur.[18]

17.3.10 Management of patients unresponsive to *H.pylori* eradication

Radiation therapy

Schechter showed in a series of 17 patients without evidence of *H.pylori* infection or with persistent lymphoma after antibiotic therapy, that all patients achieved a biopsy-confirmed complete response following a total radiation dose of 30 Gy delivered in 1.5 Gy fractions. At a median follow-up time of 27 months, event-free survival was 100%.[19]

Similarly, the Princess Margaret Group in Toronto treated 70 patients between 1989 and 1998. Included in this group were 15 patients with gastric involvement. Complete response was seen in 66 of 69 patients. No relapses were observed in patients with stomach lymphoma. The group concluded that localised MALT lymphomas have an excellent prognosis following moderate-dose RT. Median radiotherapy dose of 30 Gy. They reported a further series of patients, including 17 with gastric MALToma treated from 1989 to 2000. Again, no relapses were observed in patients with stomach lymphoma.[20,21]

Guideline — Treatment of gastric MALT lymphoma	Level of evidence	Refs
Standard triple therapy should be used in all patients (*H-pylori* positive and negative).	III	1–5, 18
Patients require endoscopic follow up with biopsy initially, at two months after eradication, and then yearly.	III	18
Patients failing to respond to eradication therapy may require radiation therapy.	III	19–21

Diminishing role for surgery in gastric lymphoma

Following excellent results achieved with radiotherapy, a surgical approach has been questioned in recent years. The German Multicentre Study Group compared the treatment of patients with gastric lymphoma with a combined surgical and conservative treatment versus conservative treatment alone. They were concerned that a truly randomised study would not be accepted by physicians, and the decision as to whether surgery or conservative management was carried out was left to the discretion of each participating centre.[22]

For low-grade lymphomas, if patients had had gastric resection, patients with stage IE and IIE were treated by extended-field radiotherapy with total abdominal radiation of 30 Gy. Without resection, patients with stages IE and IIE received extended-field radiotherapy as above and, in addition, patients with stage IIE received six cycles of COP chemotherapy. Patients with high-grade lymphoma received, in addition, CHOP chemotherapy whether or not resection had been performed. Between 1992 and 1996, some 106 patients had conservative treatment only. The survival rate after five years was 84.4% ,and was influenced neither by patient characteristics nor stage of histological grade.

Seventy-nine patients had combined surgical and conservative treatment, and at five years, their survival was 82%. They concluded that a gastric conservative approach should be favoured.[22]

Yoon and colleagues reviewed the changing role of surgery. In a review of a Medline search (1984 to 2003), they note that 40% of gastric lymphomas are low-grade and nearly all classified as MALT lymphoma. The remainder are high-grade lesions with or without a low-grade MALT component. They note that for the low-grade MALT lymphomas confined to the gastric wall without certain negative prognostic factors, *H.pylori* eradication was highly successful in causing lymphoma regression. The more advanced low-grade lymphomas, or those that did not regress with antibiotic therapy, could be treated with a combination of *H.pylori* eradication, radiation therapy and chemotherapy. By contrast, the high-grade lymphomas could be treated with chemotherapy and radiation therapy according to the extent of the disease. They note that surgery for gastric lymphoma was reserved for patients with localised residual disease after non-surgical therapy or for rare patients with complications.[23]

Guideline — Lack of role for surgery	Level of evidence	Refs
In general, patients with gastric MALT lymphoma do not require surgery, because results of radiotherapy and/or chemotherapy are superior.	III	22, 23

17.4 Diffuse large B-cell lymphoma of the stomach

17.4.1 Aetiology

Molecular evidence now suggests that diffuse large-cell lymphoma (DLCL) may originate either by transformation of a gastric MALToma that is negative for the t(11,18) translocation, or as a *de novo* tumour with other genetic aberrations.[4]

17.4.2 Staging

It now appears to be well established that such lymphomas should be managed according to the principles established for the treatment of nodal DLBCL.[23] The patients are clinically staged as such, obviously including gastroscopy and endoscopic ultrasound where available.

17.4.3 Diminishing role for surgery

Over the last decade or so, the treatment has changed, with virtual elimination of the need for gastrectomy. This change is based not so much on randomised clinical trials, but on analysis of outcome in cohort studies.[23]

The Princess Margaret Hospital (Toronto) saw 122 patients with DLCL lymphoma between 1967 and 1996. Previous treatment of partial gastrectomy followed by radiation therapy led to an overall ten-year survival of 66% and cause-specific survival of 88%. In the past decade, for combination chemotherapy (CHOP) followed by radiation therapy, the overall five year rate was 87% and cause specific survival 95%.[24]

Similarly, in Taiwan, some 38 patients with DLCL were treated with anthracycline containing combination chemotherapy, or curative surgery followed by adjuvant chemotherapy. There were 38 patients in the first group and 21 in the second. The projected five-year relapse-free survival and overall survival were 86% and 73% respectively in the group receiving chemotherapy alone, while in the group with surgery and chemotherapy, the five year relapse-free survival and overall survival were 78% and 78% respectively, that is, not significantly different from group A.[25]

A randomised trial has been done in terms of the role of surgery in primary gastric lymphoma. Avials in Mexico randomised 589 patients with primary gastric diffuse large-cell lymphoma in early-stages IE and II. One hundred and forty-eight patients were randomised to surgery, 138 to surgery plus radiotherapy, 153 to surgery plus chemotherapy, and 150 patients to chemotherapy alone. Radiotherapy was at a dose of 40 Gy, and chemotherapy was CHOP at standard doses. Actuarial overall survival at ten years was for surgery 54%, surgery plus radiotherapy 53%, surgery plus chemotherapy was 91%, and chemotherapy alone 96%. They therefore concluded that chemotherapy should be considered the treatment of choice in this patient setting. It was interest that there was not a chemotherapy plus radiotherapy arm.[26] Similarly studies in Japan demonstrated that patients who received non-surgical treatment showed a better overall survival than those treated by surgery.[27]

17.4.4 Systemic chemotherapy

These data suggest that systemic chemotherapy alone is a reasonable alternative treatment for stage I and stage II DLCL (see Chapter 13). Resection of the primary tumour before systemic chemotherapy does not appear to improve the cure rate of this group of patients.

Guideline — Treatment of gastric and diffuse large-cell lymphoma (DLCL)	Level of evidence	Refs
Patients are managed as for DLCL as described elsewhere with CHOP chemotherapy.	I–III	23–27

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CHAPTER 18 PRIMARY CUTANEOUS LYMPHOMAS

18.1 Epidemiology

Primary cutaneous lymphomas comprise both T-cell (75%+) and B-cell lymphomas. They are rare conditions representing 2% of all lymphomas, with an annual incidence of 0.3–1 per 100,000.[1,2] The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF), which is typically found in adults of 40–60 years of age, in all races, with men afflicted by the disorder twice as commonly as women. Primary cutaneous B-cell lymphomas (PCBCL) comprise the second largest group of extranodal B-cell lymphomas, after gastrointestinal.

18.2 Classification

The aetiology and clinical features of the cutaneous lymphomas has been thoroughly reviewed recently.[1,3–5]

1 Primary cutaneous T-cell lymphomas

- Mycosis fungoides
- Sézary syndrome
- CD30+ve T-cell lymphoproliferative disorders
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Unspecified

2 Primary cutaneous B-cell lymphomas

- Cutaneous follicle centre lymphoma
- Diffuse large B-cell lymphoma
- Marginal zone lymphoma

The majority of cases can be diagnosed on haematoxylin and eosin (H&E) sections with appropriate immunophenotyping, most commonly by immunohistochemistry, and in some cases by flow cytometry.[6] Furthermore, review by a pathologist colleague experienced in these disorders is strongly recommended. The need for clinicopathological correlation cannot be overemphasised. Molecular analysis examining for the presence of a clonal T-cell receptor (TCR) gene rearrangement by polymerase chain reaction (PCR) on fresh and formalin-fixed tissue is useful, particularly in difficult cases[7,8] (see Section 7.2).

The classification of these disorders is controversial.[9] The two most widely used classifications have been the World Health Organization (WHO)[10] and the European Organisation for Research and Treatment of Cancer (EORTC)[11] (see Table 18.1). It is recommended that pathologists classify these conditions according the WHO classification, which aligns the cutaneous lymphomas with systemic lymphomas.[9] (See Section 18.11).

18.3 Staging system

Cutaneous T-cell lymphomas can be classified into four stages (see Table 18.1).

Table 18.1 Classification of cutaneous T-cell lymphomas

Stage I	Disease confined to the skin with limited patches/plaques (stage Ia), disseminated patches/plaques (stage Ib), or skin tumours (stage Ic)
Stage II	Lymph nodes enlarged but uninvolved histologically
Stage III	Lymph node involvement documented by histology
Stage IV	Visceral dissemination

Source: Van Doorn et al. [12]

This simple clinical staging system can be converted into the TNM classification[13] (Table 18.2), which can be applied to all the cutaneous lymphomas. However, most of the data correlating stage with prognosis relate to the most common form, MF, which is typically a chronic, slowly progressive disease of 10–20 years duration (see Section 18.4.1).

Table 18.2 TNM classification for mycosis fungoides/Sézary syndrome

T_1	Limited patch/plaque (< 10% of skin surface)
T_2	Generalised patch/plaque (> 10% of skin surface)
T_3	Tumours
T_4	Generalised erythroderma
M_0	No visceral metastases
M_1	Visceral metastases
B_0	Atypical circulating cells not present (< 5%)
B_1	Atypical circulating cells present (> 5%)
N_0	No clinically abnormal peripheral lymph nodes
N_1	Clinically abnormal peripheral lymph nodes
NP_0	Biopsy performed, not CTCL
NP_1	Biopsy performed, CTCL
LN0	Uninvolved
LN1	Reactive node
LN2	Dermatopathic node, small clusters of convoluted cells (< 6 cells per cluster)
LN3*	Dermatopathic node, large clusters of convoluted cells (> 6 cells per cluster)
LN4*	Lymph node effacement

Table based on Bunn and Lamberg[13]
T = tumour; N = node; B = blood; L = lymph; M = metastasis
*Pathologically involved lymph nodes.

There is no specific staging system for PCBCL. Indeed, if the disease has systemic (nodal, marrow or visceral) involvement, it is frequently reclassified as a systemic lymphoma with secondary skin involvement.[13] Nonetheless, if the disease is felt to arise primarily from the skin, it should still be staged, like other lymphomas, according to the standard Ann Arbor criteria, with isolated lesions considered as stage I and multi-focal lesions as stage IV.

Table 18.3 Stage classification for mycosis fungoides/Sézary syndrome

	Staging classification
IA	T_1, N_0NP_0, M_0
IB	T_2, N_0NP_0, M_0
IIA	$T_{1,2}$, N_1NP_0, M_0
IIB	T_3, N_0NP_0, M_0
III	T_4, N_0NP_0, M_0
IVA	$T_{1–4}$, $N_{0,1}NP_1$, M_0
IVB	$T_{1–4}$, $N_{0,1}NP_{0,1}$, M_1

18.4 Primary cutaneous T-cell lymphomas

18.4.1 Mycosis fungoides

Summary of clinicopathological features of mycosis fungoides and Sézary syndrome

Clinical	Adults, M>F. Protracted history of cutaneous patches, plaques and ultimately nodules, mainly trunk but may become extensive, with later extracutaneous nodal +/- hepatosplenic, other organ and blood involvement. Cutaneous variants include Pagetoid reticulosis, follicular mucinosis and granulomatous slack skin. Patients with Sézary syndrome manifest erythroderma, lymphadenopathy and circulating lymphoma cells (>1000/mm^3 of blood). Course of MF is stage-dependent; excellent if limited cutaneous disease. Sézary syndrome has aggressive behaviour.
Morphology	Epidermotropic infiltrate of small- to medium-sized lymphocytes with cerebriform nuclei, Pautrier microabscesses, accompanying inflammatory infiltrate in early stages.
Immunophenotype	TCRαβ+, CD3+, CD45RO+, CD2+, CD5+, CD4+, CD8-, CD7-, cutaneous lymphocyte antigen+. Rarely CD8+ or TCRγδ+.
Genetics	Clonally rearranged TCR genes. Complex but no-recurring chromosomal abnormalities in advanced disease.

The management of MF needs to be individualised, giving particular consideration to the stage of the disease, symptoms, age and performance status of the patient. Due to the complexity in the diagnosis and management of the disease, it is strongly recommended that patients be managed in highly-specialised centres with a multidisciplinary approach that involves a dermatologist, haematologist/medical oncologist and radiation oncologist, and a close liaison with a pathologist experienced in examining skin lymphomas. Consensus United Kingdom guidelines for CTCL have also been produced recently.[14]

The interval between onset of symptoms and the establishment of a histological diagnosis frequently takes many years and often requires repeated biopsies.[2] Indeed, for patients in whom MF is suspected, and there are a limited number of patch-stage lesions, this approach is very reasonable. It avoids embarking on numerous investigations in a disease that is indolent and where outcome is not altered by aggressive early intervention.

18.4.2 Prognosis

The most important factor in planning management and determining prognosis is the stage of the disease. Indeed, the vast majority of patients with early-stage disease (stage IA, IB, IIA) do not progress to more advanced-stage disease.[2,15] Patients presenting with isolated patch or plaque disease

(stages I and IIA) have a median survival of more than twelve years. Moreover, patients with stage IA disease do not appear to have a decreased survival when compared with an age-, sex-, and race-matched population.[15] Patients with advanced-stage disease (stages IIB, III and IVA) with tumours, erythroderma, and lymph node or blood involvement, but no visceral involvement, have a median survival of five years from time of presentation. Patients with visceral involvement (stage IVB) have a median survival of only 2.5 years or less.[5,11,15,16]

Although most patients with early-stage disease (patches or plaques confined to the skin) having an indolent course, progression to cutaneous tumours, nodal or visceral disease can occur. Cutaneous tumours can develop either as increasing depth of the small atypical lymphocytes of MF, or as a result of large-cell transformation. Large-cell transformation is defined as large cells (≥4 times the size of a small lymphocyte) in more than 25% of the infiltrate, or if these cells formed microscopic nodules.[17,18] There is a variable incidence of 8–39% reported and it is associated with a very poor prognosis.[17–19] The risk of transformation relates to the presence of stage IIB-IV (31% versus 14%), tumour-stage disease, elevated β2 microglobulin and elevated lactate dehydrogenase (LDH).

18.4.3 Staging investigations

For patients with patches and/or plaques with no palpable lymphadenopathy (i.e. clinically early-stage I–IIA disease), extensive staging investigations are not required and usually restricted to physical examination and full blood examination (Sézary cells are very rarely detected). Occasional patients will present with loco-regional lymphadenopathy, which may reflect dermatopathic changes in the node rather than true nodal involvement with MF. A recommended approach in these cases is to stage the patient with computed tomography and bone marrow examination (including flow cytometry and molecular analysis for T-cell receptor gene-rearrangement). If small loco-regional nodes do not resolve following local skin therapy, lymph node biopsy is performed. Conversely, if large nodes (>3–4 cm) are detected, a representative node biopsy should be performed before initiating therapy, given the major prognostic impact of such a finding and the required alteration in the therapy applied to include systemic sites. The hesitancy in performing node biopsies relates to the high incidence of skin colonisation with pathogenic organisms in patients with CTCL, which increases the risk of infection following surgery.

18.4.4 Prognostic markers

There are currently no definitive prognostic factors beyond clinical stage for MF. Although the absence of CD7, high LDH, large-cell size, periodic acid-Schiff (PAS) inclusions and the number of circulating Sézary cells (SC) have been implicated as adverse prognostic markers, these features are usually associated with advanced-stage disease, leaving the problem of determining which patients with early-stage disease are destined to do poorly.

18.4.5 Treating early-stage (IA–IIA) mycosis fungoides

Overview

As the vast majority of patients present with early-stage disease, the treatment guidelines focus on this group of patients. Very few randomised trials have been performed in this disease and the guidelines are therefore based largely on level III evidence. Indeed, there has been only one randomised trial comparing aggressive systemic chemotherapy combined with total skin electron beam (TSEB) to skin-directed therapy involving emollients, topical chemotherapy, phototherapy and superficial radiation. This landmark study, which demonstrated no advantage in early aggressive therapy, has underpinned the approach to the management of CTCL[16] (level II evidence). As the use of early application of systemic therapy does not affect survival, non-aggressive approach to therapy is warranted, with treatment aimed at improving symptoms and cosmesis while limiting toxicity. Given that multiple skin sites are often involved, the initial treatment choices are usually topical or intralesional corticosteroids, or phototherapy with psoralen plus ultraviolet-A radiation (PUVA), or ultraviolet-B (UVB). Ultraviolet B is only effective in patients with patch disease. PUVA is usually

required for patch/plaque disease, but it too becomes less effective as the lesions thicken. For even thicker plaques, particularly if localised, radiotherapy is effective. There is the very occasional patient who presents with truly localised MF (single lesion); whether this is curable is unknown and our approach is to treat such patients with local radiotherapy with 'curative' intent.

'Second-line' therapy for early-stage disease is often topical chemotherapy using mechlorethamine (nitrogen mustard — NM) or carmustine (BCNU). Retinoids can be effective for disease refractory to topical therapies and are usually considered before the use of chemotherapy. Very large tumours may require orthovoltage/megavoltage radiotherapy. Total skin electron beam therapy is usually reserved for patients with extensive skin involvement that has failed previous therapy. Local experience is that TSEB is most successful in patients with relatively indolent disease, as early relapses (months) are common in patients with rapidly progressive disease.

Topical corticosteroids

Early-stage CTCL, especially patch-stage MF, can be treated with topical corticosteroids. Class I (potent) topical corticosteroids such as betamethasone dipropionate 0.05% or mometasone furoate 0.1% are the most effective at obtaining objective disease regression.[20] Patients with stage T1 disease (limited patch/plaque with <10% of skin surface involved) have an approximately 60–65% complete response (CR) rate (biopsy proven), and a 30% partial response (PR) rate. Patients with T2 disease (generalised patch/plaque with >10% of skin surface involved) have a 25% CR rate and a 57% PR rate.

Phototherapies

CTCL can be treated effectively with the various forms of phototherapies, including PUVA, UVB and electron beam radiation therapy (see below). PUVA therapy can be useful in treating patch- and plaque-stage CTCL, but tumour-stage disease is less responsive. Response rates to PUVA therapy in patients with patch disease are high, with CR rates of approximately 58–83% and overall response rates of up to 95%.[21–23] Furthermore, remission is often prolonged, with a reported mean duration of 43 months.[22]

Topical chemotherapy

In early-stage disease, chemotherapy for CTCL is frequently administered topically. Active agents include NM and carmustine. However, the use of these agents can be impractical if lesions are extensive and with long-term use, they carry a risk of secondary epidermal cancer.[24,25]

Alpha interferon

Alpha interferon (IFN), a biological response modifier, can be effective using doses of 3–15 million units (MU) daily (most commonly 5 MU daily).[26,27] Although it does appear to have a synergistic effect with phototherapy[28], there is no advantage in using it in combination with retinoids.[29]

Retinoids

Retinoids belong to the family of steroid hormones that bind to the nuclear receptors (retinoic acid receptor — RAR; retinoid X receptor — RXR) and subsequently interact with various transcription factors. RAR and RXR have various isoforms (α, β and γ) that are differentially expressed in tissues. The skin contains both RAR and RXR. Non-RXR-selective retinoids such as etretinate, arotinoid, acitretin and isotretinoin (13-*cis*-retinoic acid) have been used alone or in combination with PUVA, interferon alpha, or even chemotherapy. They are reported to have response rates in the range of 5–65%.[30–40] Bexarotene is a new synthetic retinoid that selectively binds to the RXR subfamily and is formulated as either as capsule or a topically applied gel.[41–44] However, it is not commercially available in Australia.

Radiotherapy

Treatment is usually aimed at improving symptoms and cosmesis, although in truly localised disease, the intent of therapy may be curative. There is a clear gradient of both diminishing likelihood of CR and length of remission with increasing stage of disease; patients with T1 disease have a >80% CR rate with radiotherapy (either local field or total skin electron beam therapy), compared to 20–30% CR rates for T4 disease. Five-year relapse-free survival rates with radiation alone are 40–60% for T1 disease, but <10% for T4 disease.[45–51] Irrespective of stage and curability, however, radiotherapy can provide excellent palliation of troublesome symptoms of CTCL such as pruritus, scaling and ulceration.

18.4.6 Target volume

For most patients, the target volume is the epidermis and/or dermis. Most lesions may therefore be treated with very soft (low penetrance) beams — superficial x-ray therapy (50–145 kvp) for small areas, or 4–9 MeV electron beams for larger areas. Higher energy beams (orthovoltage/megavoltage) are occasionally necessary for thicker lesions.

The technique of total skin electron beam therapy (TSEB) has been developed to treat patients with extensive disease. The technique is now generally limited to patients with T3/4 disease, and to those who are no longer responding to topical therapies.

18.4.7 Dose

Although very small doses of radiation can provide effective palliation of CTCL lesions, there does appear to be a dose–response relationship for complete remission. Doses of 35–40 Gy are associated with higher CR rates than doses of <25 Gy, particularly with more advanced stages of disease.[45,52–55]

18.4.8 Fractionation

Fraction size depends on several factors. Small fields in cosmetically insignificant areas may be hypofractionated, for example, 30 Gy in ten fractions, three or five times per week. However, in cosmetically-sensitive areas where large fields are being irradiated and there is pre-existing damage to the skin, or in cases of re-treatment, doses of only 1.0–1.5 Gy per fraction may need to be used. This may result in a course of treatment taking up to ten weeks.[16,56]

Guideline — Indications for specific treatment modalities in early-stage (IA–IIA) mycosis fungoides		Level of evidence	Refs
Topical steroids	Limited patch-stage	III	16, 20, 48
PUVA/UVB	Extensive patch-stage	III	16, 21–23, 57–59
Topical chemotherapy	Limited patch/plaque stage	III	16, 24, 25
Retinoids	Extensive patch-stage (2nd-line)	III	33–39
Bexarotene	3rd line*	III	41, 42, 44
Alpha interferon +/- phototherapy	2nd or 3rd line	III	26–28, 60
Radiotherapy	Plaque- or tumour-stage	III	16, 45–47, 49–56, 61
Oral methotrexate	2nd or 3rd line	III	62–64
Systemic chemotherapy	3rd line	III	63–70
Denileukin diftitox	3rd line	III	71

*not commercially available in Australia

18.4.9 Treating advanced-stage (IIB–IV) mycosis fungoides

Overview

Treatment of advanced-stage disease (or indeed refractory early-stage disease) is more problematic. It always requires a multidisciplinary approach involving dermatologist, oncologist/haematologist and radiation oncologist. Although systemic multi-agent chemotherapy is often considered early in patients with advanced-stage disease, the randomised National Cancer Institute study demonstrated that combination chemoradiotherapy offered no survival benefit over 'conservative' topical therapy.[16] Consequently, topical therapy should be utilised first where practicable, and systemic therapy considered in refractory or rapidly progressive disease. The type of systemic therapy depends largely on age, performance status of patients and extent and tempo of the disease. For indolent but progressive disease, IFN can be effective. The single- or multi-agent chemotherapy regimens described below are selected depending on disease characteristics and side-effect profile. The value of photopheresis is limited to patients with circulating malignant cells or clonal population detected by molecular analysis[72] (see Sézary syndrome below). The biological regulators denileukin diftitox (DAB_{389}IL-2) and interleukin (IL)-12 tend to be used for advanced multi-relapsed disease, but are not commercially available in Australia. There is limited information about the efficacy of autologous or allogeneic transplantation for MF.[5]

Systemic chemotherapy

In slowly progressive disease that has systemic manifestations or has proven refractory to topical therapy and/or retinoids, single-agent therapies such as low-dose oral methotrexate (15–25 mg/m^2/week)[62], chlorambucil, cyclophosphamide or etoposide may be employed with very low risk of side effects. For more aggressive disease, multi-agent chemotherapy is usually considered. There is no recognised superior multi-agent chemotherapy regimen for MF and no proven advantage of utilising anthracyclines as initial therapy. Regimens often include one or more of

cyclophosphamide, vincristine, vinblastine, prednisolone, methotrexate or mechlorethamine.[5,63,64,73] Other effective agents include liposomal doxorubicin[67,74] and nucleoside analogues/pathway inhibitors such as 2-chlorodeoxyadenosine, deoxycoformycin, fludarabine or gemcitabine.[65,66,68] Response rates are in the range of 30%, with reported median response durations varying from months to years depending on patient selection criteria. Nonetheless, patients invariably relapsed, with no evidence in literature of regimens with curative potential. Of note, combination chemotherapy increases the risk of infection in a group of patients frequently colonised with potentially pathogenic bacteria.[5] High-dose chemotherapy with autologous transplantation achieves high response rates, but durable remissions are very rare. There is emerging evidence that a graft versus lymphoma effect exists in CTCL, and the use of allogeneic transplantation requires further investigation.

Biological response modifiers

Newer therapies have been explored using biological regulators including the recombinant targeted fusion protein that combines the receptor binding sequence of IL-2 with the cytotoxic A-chain and translocation B chain of diphtheria toxin (denileukin diftitox; ONTAK®; DAB_{389}IL-2).[71] Interleukin-12[75] and alemtuzumab (Campath-1H), the humanised monoclonal antibody targeted against CD52w (a pan-lymphocyte antigen)[76,77], have demonstrated efficacy in CTCL. However, the side-effect profile with all these biological agents is substantial, at times. Cyclosporine in not recommended.[78]

Guideline — Indications for specific treatment modalities in advanced-stage (IIB–IV) mycosis fungoides		Level of evidence	Refs
Topical steroids	Symptomatic control	III	16, 20, 48
Radiotherapy	Symptomatic control	III	45–47, 49–56, 61
Oral methotrexate	2nd or 3rd line	III	62–64
Systemic chemotherapy	2nd or 3rd line	III	63–70
Alpha interferon +/- phototherapy	2nd or 3rd line	III	26, 27, 60
Alemtuzumab	2nd or 3rd line	III	76, 77
Bexarotene	3rd line*	III	43
Extracorporeal photopheresis**	1st, 2nd or 3rd line	III	72, 79–88
Denileukin diftitox	3rd line*	III	71

* not commercially available in Australia; **patients with circulating clonal cells only (i.e. Sézary syndrome)

18.5 Sézary syndrome

The most common definition of Sézary syndrome (SS) is one of pruritic exfoliative or infiltrated erythroderma (with histological features of CTCL) accompanied by circulating Sézary cells (SC). Although there is no consensus about the number of SC required to define the syndrome, most commonly, a SC count >$1x10^9$/L or >5% of peripheral blood leukocytes is accepted.[89–91] As SS is considered the leukaemic variant of MF, an elevated SC count should be considered an essential component of the diagnosis.

In general terms, the treatment is similar to that of advanced-stage MF.

One treatment that is more effective in SS compared to other CTCL is extracorporeal photopheresis (ECP). The first trial reported that 83% of patients with erythroderma responded to photopheresis.[92] Further and large phase II studies have reported the therapeutic benefit of ECP in CTCL, though the response data have been variable, ranging from 30% to 80% depending on study entry criteria, patient selection, and intervals between diagnosis and treatment.[72,79–88,93,94] As ECP has been used in CTCL patients refractory to all other therapies, no phase III (randomised) trials have been performed.

18.6 Primary cutaneous CD30 positive T-cell lymphoproliferative disorders

In the WHO classification, lymphomatoid papulosis (LyP) (types A and B), primary cutaneous anaplastic large-cell lymphoma of T-cell type (ALCL), and borderline lesions are considered subtypes of primary cutaneous CD30(+) T-cell lymphoproliferative disorders.[10] (See Table 18.4)

Table 18.4 WHO Classification: mature T-cell neoplasms, cutaneous types: variants and subtypes

Primary cutaneous CD30-positive T-cell lymphoproliferative disorders • Primary cutaneous anaplastic large-cell lymphoma (C-ALCL) • Lymphomatoid papulosis (LyP) (types A and B) • Borderline lesions: LyP type C and C-ALCL, LyP-like histology

Source: Jaffe et al.[10]

Summary of clinicopathological features of C-ALCL

Clinical	Clinical and morphologic overlap with lymphomatoid papulosis. Adults/elderly, median age 60 years, M>F. Single or localised cutaneous nodules; multicentric in ~20%. Extracutaneous dissemination in 10%, especially multicentric cases, mainly to lymph nodes. Partial/complete spontaneous regression in 25%, but relapses frequent. ~90% five-year survival.
Morphology	Dermal +/- subcutaneous involvement. Cytology as for systemic ALCL, usually with greater pleomorphism and Reed-Sternberg-like cells.
Immunophenotype	CD3+ (rarely null cell), CD4+, CD30+ and cytotoxic protein positive most cases; ALK protein negative, EMA — usually.
Genetics	Clonally rearranged TCR genes in most. Lack t(2;5) translocation.

Primary cutaneous anaplastic large-cell lymphoma (C-ALCL): This terminology is used by the WHO classification. The EORTC prefers the term ‘large-cell CTCL, CD30+’ and separate out ‘large-cell CTCL, CD30(-)’ disease because of the more aggressive clinical behaviour of the latter[9] (see below). Patients who present with cutaneous large-cell CTCL should be classified according to the WHO classification: if they are CD30(+) they fall under ‘primary cutaneous ALCL, CD30(+)’; if CD30(-) they fall under ‘peripheral T-cell lymphoma, unspecified**’.** In both cases, the morphological characteristics of the cells should be described by the pathologist (i.e. anaplastic, immunoblastic or plemorphic), and CD30 expression (or lack of) emphasised.

Typically, primary cutaneous CD30(+) CTCL presents with solitary nodules that frequently ulcerate and may spontaneously regress (particularly after biopsy). The prognosis of CD30(+) cutaneous lesions is extremely good. This is in sharp contrast to the CD30 (-) cutaneous lesions and systemic CD30 (+) lymphoma. Indeed, systemic ALCL is a very different condition arising from the lymph nodes and requiring management similar to other systemic lymphomas.[95] Although relapses occur in approximately 40% of patients with CD30 (+) CTCL, systemic dissemination occurs in only 10%,

with 5–10 year survival rates exceeding 95%.[96] Consequently, therapy should be relatively non-aggressive.

Prior to therapy, patients should be fully staged to determine regional-node involvement and exclude systemic ALCL. It is unknown whether localised disease is curable, but one approach to localised disease (which is the most common presentation) is to use local radiotherapy. Whether this is more effective than surgery alone remains unknown. However, it is well tolerated and has negligible long-term risks. Chemotherapy is virtually never required for localised disease, but is recommended if regional nodes are involved.[96] Systemic ALCL can have secondary cutaneous involvement (15% in one series) and should be managed as for the systemic disease. Patients with CD30 (+) ALCL developing from pre-existing MF often have a poor prognosis.[97]

Guideline—Indications for specific treatment modalities in C-ALCL		Level of evidence	Refs
Surgery and radiotherapy	If limited disease	III	95–97
Oral methotrexate	More extensive disease	IV	
Systemic chemotherapy	Very rarely needed	IV	

Lymphomatoid papulosis: Lymphomatoid papulosis is characterised by recurrent self-healing papules or nodules. Three histologic subtypes of LyP have been described.[11] Despite its histologically malignant appearance, LyP has a clinically benign course with continuing self-healing lesions. Observation only is usually required (to determine if spontaneous resolution occurs). However, if lesions are problematic, PUVA, topical corticosteroids, nitrogen mustard, IFN or oral methotrexate can be considered. Oral tetracyclines have been used, but given that LyP can undergo spontaneous resolution, the benefit of such treatment is unclear.[98] Approximately 15–30% of patients will develop lymphoma, most commonly MF or Hodgkin lymphoma, so continuing clinical review is required.[99,100]

Guideline — Indications for specific treatment modalities in LyP		Level of evidence	Refs
Observation	If limited	III	95, 98–100
Topical steroids	If localised	IV	
Phototherapy	If extensive	III	
Oral methotrexate	2nd or 3rd line	III	
Alpha interferon +/- phototherapy	2nd or 3rd line	III	
Systemic chemotherapy	Rarely needed	III	

18.7 Large-cell cutaneous T-CD30 negative (EORTC classification)

Although in the category of 'peripheral T-cell lymphoma, unspecified' in the WHO classification, this is a separate group in the EORTC classification, and warrants discussion. These cases may present with localised or generalised nodules or tumours. They have an aggressive clinical course. The histological appearance of CD30 (-) ALCL may be identical to that of MF, undergoing transformation into large-cell lymphoma. The treatment of these tumours should be more aggressive. Once full staging is performed, it should be managed as for aggressive lymphoma (i.e. like diffuse large-cell) such that patients receive combination anthracycline-based chemotherapy followed by involved-field

radiotherapy where appropriate. In general terms, radiotherapy alone would be considered inadequate. Because of the poor outcome in these patients, novel treatment strategies should be explored.

Guideline — Indications for specific treatment modalities in CD30 negative large-cell (EORTC), peripheral T-cell lymphoma unspecified (WHO)		Level of evidence	Refs
Systemic chemotherapy	Routine	IV	101–104
Radiotherapy	Additional to chemotherapy if localised	IV	

18.8 Subcutaneous panniculitis-like T-cell lymphoma

Summary of clinicopathological features

Clinical	Wide age range and no male/female predilection. Indurated subcutaneous nodules/plaques extremities or trunk, no adenopathy. Systemic symptoms variable. Haemophagocytic syndrome may occur. Aggressive course in most (median survival ~27 months), particularly the TCRγδ+ type, but may be chemo/radio-responsive. Late dissemination to nodes and other organs.
Morphology	Diffuse subcutaneous infiltration by pleomorphic small- to medium-sized lymphocytes with rimming around individual fat cells; reactive foamy or phagocytic histiocytes common; apoptosis and karrhyorrhexis typical; angio-invasion may be present.
Phenotype	Mature activated cytotoxic phenotype (TIA-1+, granzyme B+, perforin+); most are TCRαβ+, CD3+, CD8+, CD56-; minority are TCRγδ+, CD4-, CD8-, CD56+.
Genetics	Clonal TCR gene rearrangements; EBER-; no typical cytogenetic changes.

The lesions in this condition preferentially infiltrate the subcutaneous tissue.[9,10] Patients present with multiple subcutaneous nodules and plaques, mostly on the extremities and trunk, and usually in the absence of lymphadenopathy and visceral involvement. Constitutional symptoms of fever and weight loss occur occasionally and are not infrequently related to an associated haemophagocytic syndrome.[10,105] The natural history is aggressive, although nodal and systemic dissemination is rare. The outlook is generally poor, even with aggressive chemotherapy. Relapse is frequent.[105]

Guideline — Indications for specific treatment modalities in subcutaneous panniculitis-like lymphoma		Level of evidence	Refs
Systemic chemotherapy	Routine	IV	10, 105
Radiotherapy	Additional to chemotherapy if localised	IV	

18.9 Primary cutaneous B-cell lymphomas

18.9.1 Cutaneous follicle centre lymphoma

This is the most common of the PCBCL (40%).[9,106] The WHO classification uses the term ‘follicle center (FC) lymphoma’ in preference to the ‘follicle center cell (FCC) lymphoma’ of the EORTC.[10] Lesions tend to be solitary or grouped nodules, or plaques, often localised to the scalp, forehead or back. Systemic dissemination is rare.

These are indolent lymphomas. In general terms, radiotherapy (RT) is a very important component of treatment and should encompass all lesions, if possible. Although some authors have recommended doxorubicin-based chemotherapy, the studies are small and the outcome appears similar to that expected with RT alone.[107] Surgery alone is not recommended. The overall survival is excellent (97% five-year survival), but because relapses occur frequently (30–60%), continuing follow up is required.[4,108] Recently, rituximab has been successfully used in cutaneous FC, FCC and DLBCL.[109,110]

Guideline — Indications for specific treatment modalities in cutaneous follicle centre lymphoma		Level of evidence	Refs
Surgery and radiotherapy	If limited	III	4, 108, 111–114
Systemic chemotherapy	Rarely needed	IV	
Rituximab	If extensive and relapsed or poor tolerance to chemotherapy	III	109, 110

18.9.2 Diffuse large B-cell lymphoma

The WHO classifies all lesions with a diffuse infiltrate of large B-cells into this category. In contrast, there are few patients categorised as such in the EORTC classification, with most lesions being categorised as FCC lymphoma (see Section 18.9.1). The clinical relevance of this is the very reasonable concern that with the increased use of the WHO classification, good prognosis lesions classified as FCC lymphoma by the EORTC will be now be labelled as PCLBCL and subsequently treated too aggressively.[115] Therefore it is critical to the management of this disease to stratify patients into good and poor prognosis.

The EORTC has recognised a specific clinical entity — primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) — as an aggressive disease confined to the legs of the elderly. It has been a topic of much debate as to whether PCLBCL-leg should be regarded as a distinct entity on the basis of site.[11,116] Consequently, two interrelated European studies have investigated the prognostic factors for PCLBCL. The most important adverse factors appear to be *bcl-2* expression followed by multiple skin lesions, age >70 years, location on the leg, and round cell morphology.[117]

Currently, all data with long-term follow up are based on studies utilising the EORTC classification, dividing patients broadly into PCLBCL-leg and FCC lymphoma with large-cell histology. The latter group have a much more indolent course and are less likely to require chemotherapy. A recent large 566-patient study has confirmed the robustness of the EORTC classification.[118]

We recommend aggressive treatment in only those patients with large-cell histology with adverse prognostic features. In the absence of comparative studies of chemoradiotherapy versus radiotherapy alone, the balance of evidence would suggest that poor prognosis patients should be managed as for *systemic* DLBCL where feasible, namely anthracycline-based chemotherapy with RT for localised lesions. However, patients with adverse prognostic features are typically elderly and consequently chemotherapy is often not feasible and RT alone is recommended. Unfortunately, the vast majority of patients relapse or have systemic progression.[113,107] The use of additional rituximab warrants further investigation.[109] Patients with a good prognosis should be treated as for FC lymphoma, predominantly with RT.

Guideline — Indications for specific treatment modalities in cutaneous diffuse large B-cell lymphoma (with poor prognostic features)*		Level of evidence	Refs
Systemic chemotherapy +/- rituximab	Routine	III	107, 109, 113, 119–121
Radiotherapy	Additional to chemotherapy if localised	III	

*Radiotherapy alone should be considered for patients who are classified as FCC by the EORTC classification, and for selected patients with few adverse prognostic features (adverse features are: *bcl-2* expression, multiple skin lesions, age >70 years, location on the leg, round cell morphology — see text for details)

18.10 Cutaneous extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type

Primary cutaneous marginal zone lymphoma (MZL) is rare, although in one series of non-nodal/non-gastrointestinal MALT lymphomas, the incidence was 12.5%.[122] There is also controversy in the literature as to the appropriate nomenclature for MZL. The WHO classification would include many cases of what the EORTC group has called immunocytoma and FCC lymphoma.[123,124]

Management includes complete staging with marrow and CT scan, particularly in patients with multiple disease sites. In other non-nodal/non-gastric MZL, localised RT is extremely effective and consequently, it is generally recommended to use localised RT in cutaneous MZL. However, for small localised lesions, the advantage of RT over surgical resection alone is unknown. The outcome of treatment is extremely good, and although relapses can occur in 50%+ of patients, the five-year survival is 98–100%.[113,118,125]

Guideline — Indications for specific treatment modalities in cutaneous marginal zone lymphoma		Level of evidence	Refs
Surgery and radiotherapy	If limited	III	113, 120, 121, 125
Systemic chemotherapy	Rarely needed	III	

18.11 Addendum

Willemze et al.[126] have recently published the WHO–EORTC classification for cutaneous lymphomas. The key modifications are:

- The PCTCL, unspecified group incorporates provisional entities of primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma, cutaneous gamma/delta T-cell lymphoma, and primary cutaneous CD4+ small/medium-sized pleotropic T-cell lymphoma.
- The entity SPLTCL is now restricted to those of alpha/beta cell origin (indolent behaviour).
- CD4+/CD56+ hematodermic neoplasm (blastic NK cell lymphoma) is recognised as a separate entity.
- Lesions previously classified by the EORTC as primary cutaneous follicle centre cell (FCC) lymphoma will now be classified as follicle centre (FC) lymphoma, using the same morphological criteria used by the EORTC for FCC lymphoma. This means that fewer cases of FC lymphoma will be classified as large B-cell lymphoma as per the ‘prior’ WHO classification.
- primary cutaneous large B-cell lymphoma is divided into ‘leg-type’ and ‘other’.

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CHAPTER 19 PRIMARY CEREBRAL LYMPHOMA

19.1 Introduction

Primary cerebral lymphoma (PCL) is defined as a lymphoma confined to the central nervous system without evidence of systemic disease. It is an uncommon entity, but appears to be increasing in frequency in immuno-competent individuals.[1] No large randomised trials exist to dictate appropriate management and treatment of this condition. Recommendations are based on level III evidence. Objective responses to treatment are common and may be of long duration, but the disease frequently recurs, even many years after initial diagnosis and treatment.

The management of PCL requires referral to a specialised centre with multidisciplinary care.

19.2 Staging

There is no defined staging process. As a minimum, patients require a CT or MRI scan of the brain. Additional investigations may include: ocular examination, CSF examination and systemic staging including bone marrow biopsy and CT scan of chest and abdomen.[2] HIV testing is indicated in at risk groups.

19.3 General comments on treatment

No randomised studies have examined the most appropriate form of therapy for PCL and there is no standard therapy. However, most major centres use either chemotherapy alone or chemotherapy in combination with radiotherapy.

19.4 Surgery

All patients require a tissue diagnosis, but aggressive surgical resection does not result in a survival benefit and is not indicated.[3]

Guideline — Primary cerebral lymphoma — biopsy	Level of evidence	Refs
Patients with suspected primary cerebral lymphoma require biopsy only rather than resection.	III	3

19.5 Radiotherapy

Whole brain irradiation results in improved survival.[1] Dose escalation or non-standard fractionation provides no additional survival benefit.[4] Radiotherapy may be used as salvage treatment in patients who have previously been treated with chemotherapy.

19.6 Chemotherapy

Chemotherapy appears to provide significant improvements in survival above those achieved by irradiation alone. High response rates can be achieved with durable complete responses, but require agents that effectively cross the blood–brain barrier. Many strategies are effective in producing objective responses, including: single-agent high-dose methotrexate, chemotherapy with blood brain barrier disruption, combination intravenous and intrathecal therapy, and combination chemotherapy and radiotherapy.[1,5–10]

Guideline — Primary cerebral lymphoma — chemotherapy	Level of evidence	Refs
Patients with primary cerebral lymphoma may be treated with chemotherapy alone or chemotherapy in combination with radiotherapy.	III	1, 5–10

19.7 Toxicity

Both radiotherapy and chemotherapy are associated with cognitive deficits, particularly when intravenous and/or intrathecal Methotrexate is given following radiotherapy.[8] Single-agent high-dose methotrexate is well tolerated in elderly patients.[7]

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CHAPTER 20 PALLIATIVE CARE

20.1 Introduction

Palliation is appropriate whenever a decision is made based upon the patient's wishes and the clinical evidence that further intensive or curative treatment is not indicated. Recently an Australian author claimed 'that haematology is a neglected area in terms of sensitive care of the dying'.[1,2] Certainly, a recent major text dealing exclusively with lymphoma does not broach the subject as an 'issue' per se.[3]

There are specific reasons, perhaps, why haematologists who care for patients with lymphoma and similar diseases have not utilised the services of palliative care teams, both at a domiciliary and inpatient level, to the same extent as medical oncologists dealing with solid tumours. Simple measures described in this chapter will often significantly improve the quality of life in patients who clearly have terminal disease. These include treatments such as single-agent chemotherapy, corticosteroids and radiation therapy, which are of significant palliative value.

The aim of this chapter is to review issues specific to the palliation of lymphomas. The reader is referred to the Australian Palliative Care Clinical Pathway for guidelines on general palliative care.[4] These cover symptoms such as pain, dyspnoea, cough, excessive secretions, and fatigue, as well as cultural and psychosocial issues, and the management of complications of treatment. There is good evidence that specialist palliative care teams improve the control of pain and other symptoms as well as increasing the wellbeing of patients and their carers.[4,5] The palliative care team should be involved early in the management of patients, especially those with complex problems.

Advanced and incurable lymphoma may be asymptomatic and run a prolonged course requiring minimal or no treatment (see Chapter 12 — Low-grade lymphoma), or it may be aggressive and rapidly growing. Advanced lymphoma may manifest with large masses that are unsightly or cause obstruction. Obstruction occurs most commonly to the biliary tract and the superior vena cava. Because lymphomas are very sensitive to chemotherapy and radiotherapy, a wide range of therapeutic options remain open to deal with lymphomatous masses and their effects. As the aim of management is to improve wellbeing, anti-lymphoma treatment should be used only when the side-effect profile of the intervention is minimal.

20.2 Corticosteroids

Corticosteroids are lympholytic and may also reduce oedema associated with a mass. Corticosteroids are useful because they reduce the size of lymphomatous masses and may also stimulate appetite. Long-term use is associated with a large number of side effects that can be difficult to manage, such as diabetes and proximal myopathy. Therefore, where possible, steroids should be used in short courses.

20.3 Single-agent chemotherapy

A large number of chemotherapy agents are active against lymphoma and have low toxicity when used as single agents in a palliative sense. These include etoposide, mitoxantrone, and vinblastine. However, the likelihood of a response diminishes rapidly with repeated use or a long history of previous treatment. Therapy should be continued only if there is stable disease, or a response, and the patient's general fitness is sufficient to tolerate side effects.

20.4 Biotherapeutics

Apart from the obvious use of blood transfusions and blood component therapy for symptomatic relief, the use of monoclonal antibodies in a 'palliative mode' has been recognised. Rituximab (MabThera), a chimeric human mouse anti-CD20 monoclonal antibody lysing CD20 positive cells, can be used to achieve palliative responses in often heavily pre-treated patients (see Chapter12).

20.5 Radiotherapy

Radiotherapy, even in very low doses, is extremely effective in reducing massive local disease and alleviating problems from pressure. Durable responses have been documented with doses as low as 2x2 Gy. Girinsky reported on the use of this regimen in a series of 48 patients with low-grade lymphoma who all had advanced stages and previous treatment with at least two courses of chemotherapy. There was an 80% response rate, and 57% complete response rate. Freedom from relapse at two years was 56%.[6] Higher doses up to 30 Gy are indicated for intermediate or high-grade lymphomas.

Guideline — Palliative treatments in lymphoma	Level of evidence	Refs
Principles of palliation established in solid tumour malignancies apply in the management of patients with lymphoma.	III, IV	1, 2, 4, 5
Active treatments such as single-agent chemotherapy, corticosteroids, monoclonal antibodies and radiotherapy may be of significant value in terminally ill patients with lymphoma.	III, IV	3, 6

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CHAPTER 21 COMPLICATIONS OF TREATMENT

21.1 Introduction

The use of radiotherapy and or chemotherapy can result in a wide range of acute and chronic side effects. These are generic concerns for cancer treatment in general. Side effects include bone marrow suppression, and cardiac and lung damage. A full discussion is beyond the scope of this document. These guidelines deal with complications that are of greater significance in younger patients with lymphoma, including infertility, secondary malignancy and psychosocial effects of treatment.

21.2 Infertility

There are no randomised studies comparing the incidence of infertility after various chemotherapy regimens for lymphoma. The data presented here are based on descriptive series and in some cases, personal communications from respected authorities.

21.2.1 After conventional-dose chemotherapy

Hodgkin lymphoma

Sperm counts may be low to start with in men with extensive disease prior to treatment.[1] Old-style regimens such as MOPP (or, to a lesser extent, MOPP-ABVD) commonly caused infertility.[2] However, the commonly used current regimen, ABVD, may cause temporary oligospermia or irregular menses for several months[3,4], but rarely, if ever, permanent infertility in either men or women (Joseph Connors: personal communication: no cases of infertility in 200 women treated with 2–6 cycles of ABVD). The effect on fertility of more aggressive regimens such as BEACOPP is not known, although any regimen containing procarbazine is likely to cause infertility in men. Pelvic irradiation is rarely administered for Hodgkin lymphoma (HL) in the modern era. If performed in young women, it is usually done with oophoropexy (surgical movement of the ovaries to the midline behind the uterus, or high up at the pelvic brim, away from the field of radiotherapy) and ovarian shielding. Men can have testicular shielding, which reduces the dose to below that which causes infertility.

Low-grade lymphoma

A variety of treatments including low-dose alkylating agents (e.g. chlorambucil, cyclophosphamide), fludarabine and monoclonal antibody therapy are commonly used. Alkylating agents can cause gonadal failure and infertility. The incidence depends on age, particularly in women (higher age = higher infertility) and the cumulative dose.[5] Azoospermia is universal at total chlorambucil doses above 400 mg, but sperm counts may recover in some patients after a period off chemotherapy.[6] Irreversible germinal aplasia following cyclophosphamide is uncommon until at least 6–10 g has been administered.[7] Conventional doses of cyclophosphamide, vincristine and prednisolone (CVP) are unlikely to cause permanent infertility.[8]

There is little data on the effect of fludarabine on fertility. One report on a 47-year-old man documented a significant reduction in sperm count during treatment.[9] There are no data on fludarabine in combination with other chemotherapy drugs. There is no reason to believe that naked antibody therapy with anti-CD20 monoclonals (rituximab) and anti-CD52 monoclonals (Campath-1H) should influence gonadal function, but no record of this been formally evaluated has been sighted. The impact of radio-labelled anti-CD20 antibodies such as iodine-131 tositumomab (Bexxar: Ashwin Kashyap: personal communication) and yttrium-90 ibritunomab tiaxetan (Zevalin) has also not been evaluated.

Intermediate-grade lymphoma

Surprisingly, there is little formal data in large numbers of patients of the fertility effects of conventional CHOP (6–8 courses at three week intervals), the most widely used regimen in this

context. CHOP is associated with temporary effects on fertility in both sexes (6–18 months of oligospermia is not unusual in men), which generally recovers thereafter (Joseph Connors: personal communication). Infertility is uncommon at conventional cumulative doses of cyclophosphamide (4.5–6 g/m^2) with CHOP-like chemotherapy and in the absence of pelvic radiotherapy.[10] The paucity of published data cannot exclude the possibility, however, that a small percentage of men may be persistently azoospermic and that women who recover ovarian function may be at risk of premature menopause.[11] The effects of more intensive approaches, including giving CHOP each two weeks instead of the traditional three weeks, or with the addition of VP16, is unknown (Michael Pfreundschuh: personal communication).

Other regimens used in the past, but less frequently today, include MACOP-B or VACOP-B. These have little impact on future fertility.[12] Hyper CVAD/araC-MTX is now being used for advanced mantle cell lymphoma, a disease predominantly of older males. No fertility studies have been done in this patient population (Jorge Romaguera; personal communication). An intensive regimen used by the French (LNH-80) involving 6 g/m^2 cyclophosphamide and multiple other chemotherapy agents resulted in infertility in only 15% of males evaluated after long-term follow up.[13]

High-grade lymphoma

Many of these are treated with acute leukaemia-based regimens. The limited published data suggest that any effect on fertility is likely to be temporary.[14] CODOX-M/IVAC is an aggressive regimen for Burkitt's lymphoma; anecdotally, men have regained fertility after this protocol (Ben Mead: personal communication).

General comments

In men who have received chemotherapy but recovered fertility, the quality of sperm is not affected.[15] Other studies have shown no evidence of a higher incidence of congenital anomalies in children born to men or women who have had prior chemotherapy.[16] A recent review evaluated pregnancy outcome among sexually active male survivors of childhood cancer, comparing the results with their brothers who had not had cancer.[17] The male:female ratio of the offspring of the two groups was 1.0:1.03 versus 1.24:1.0 respectively (p = 0.016), raising the possibility of a relative deficit of male infants among the offspring of the partners of male survivors. The proportion of pregnancies of partners of male cancer survivors that ended with a live-born infant was lower if the male had been treated with dactinomycin or procarbazine doses >5 mg/m^2. Other chemotherapy did not effect the rates of live birth and of stillbirth.

Key point

The implications of chemotherapy on fertility should be discussed with all patients for whom this is relevant.

Guidelines — Chemotherapy	Level of evidence	Refs
For patients receiving conventional chemotherapy for lymphoma (ABVD for Hodgkin lymphoma, CHOP q21 for lymphoma), sperm cryopreservation in men or oocyte retrieval (in women) is not recommended routinely.	IV	3, 4, 10

This advice should be individualised, however, in patients:

- requiring pelvic or testicular radiotherapy
- with poor-risk disease, who may need early intensified therapy and stem cell transplantation

- receiving newer regimens such as fludarabine-based protocols and CHOPq14 or CHOP-VP16. In these circumstances, the possibility of infertility should be discussed where relevant, and referral to an appropriate specialist considered.

The impact of delaying chemotherapy on the management of the disease needs to be taken into account.

21.2.2 After high-dose chemotherapy / transplantation

A number of factors influence the likelihood of recovering fertility and gonadal function after transplantation. These include gender, age, prior treatment, nature and intensity of conditioning, and possibly after allografting, the extent of chronic graft versus host disease (GVHD). Some general observations are as follows:

Recovery of fertility after high-dose cyclophosphamide alone, as used in conditioning for aplastic anaemia, usually occurs in men and women towards the end of the first year post-transplant, although recovery is age-dependent in women and such treatment may induce an earlier onset of menopause.[18]

- High-dose busulphan-cyclophosphamide causes permanent ovarian failure in the vast majority of women, but in men, over half will recover some degree of spermatogenesis.[19,20] The risk of azoospermia may correlate with the extent of chronic GVHD. Sperm counts tend to recover in the second year post-transplant and may progressively increase over the next three years.

- Recovery of fertility occurs in 10–20% of patients in adults after cyclophosphamide — total body irradiation (TBI) — although the incidence is dependent on age (especially in women) and TBI dose.[19] Recovery after TBI may take four to seven years. There are few data on high-dose alkylator combinations such as busulphan-melphalan. The incidence is not well documented after BEAM, but there are anecdotal reports of recovery of fertility in both sexes.[20] There are no published data after use of fludarabine-containing reduced-intensity conditioning regiments.

- In general, pregnancies after transplants usually have a successful outcome, although there appears to be a higher risk of complications such as preterm delivery and low birthweight babies in female recipients who receive TBI[21], possibly because of effects on the endometrium and myometrium.

21.2.3 Preservation or restoration of fertility after sterilising chemotherapy

Males

Pre-chemotherapy

(i) Prevention of gonadal damage: there are data suggesting that testosterone may reduce the risk of azoospermia from long-term treatment with cyclophosphamide.[22] Conversely, completely withdrawing testosterone from the testis using gonadotrophin releasing hormone (GnRH) agonists before (or even after) chemoradiotherapy protects and/or restores sperm counts in a rodent model.[23] Both these approaches are experimental and should only be used in the context of clinical trials.

(ii) Sperm retrieval: the usual practice is to offer semen cryopreservation prior to high-dose treatment, preferably after a period without any exposure to chemotherapy.[24] This can be collected by masturbation or by testicular biopsy if an ejaculated specimen is not possible pre-treatment. Semen cryopreservation should be offered to oligospermic patients as non-assisted fertilisation, for example, intracytoplasmic sperm injection (ICSI) means that very few sperm are necessary for successful fertilisation.[25] Experimental strategies include cryopreservation of testicular tissue or isolated germ cells (reviewed in Bone Marrow Transplant).[26]

Post-chemotherapy

(i) Fertility: men with low sperm counts post-treatment may be fertile; 30% with idiopathic infertility and sperm counts between 1–5x10^6/ml (normal >20x10^6/ml) may be expected to father children within two to three years. One approach in persistently azoospermic patients post-chemotherapy, if sperm collection has not been performed beforehand, is a testicular biopsy; occasionally sperm are present, which may then be collected, stored and subsequently used for ICSI.

(ii) Hypogonadism: after high-dose chemotherapy, roughly 10% of men, particularly those over 45–50 years, have low testosterone levels and symptoms of hypogonadism such as fatigue, poor muscle strength and low libido.[27] Recent reports suggest adrenal androgen deficiency may not be uncommon.[28] Erectile dysfunction is not uncommon and is often related to cavernosal arterial insufficiency as demonstrated by colour-flow Doppler.[28] Testosterone replacement and sildenafil may be effective.[29]

Females

Pre-chemotherapy

(i) Prevention of gonadal damage: There is no proven treatment that prevents infertility in women receiving high-dose chemotherapy. There is one report of the oral contraceptive pill protecting ovarian function in women receiving chemotherapy for Hodgkin's lymphoma. More recent research has focused on the use of GnRH agonists in this context.[26,30] These are being assessed in continuing clinical trials, as are GnRH antagonists (Kate Stern: personal communication). The theory is to suppress ovarian function through decreased secretion of pituitary gonadotrophins. While there are promising animal data, evidence suggesting that radio-chemotherapy directly destroys primordial follicles (which are not cycling) independent of gonadotrophin status raises doubts about the usefulness of these approaches in humans receiving sterilising chemotherapy.[11]

(ii) Oocyte retrieval[26]: options include:

- oocyte retrieval after superovulation, in vitro fertilisation and embryo cryopreservation pre-transplant, then subsequent embryo transfer of thawed embryos post-transplant when wishing to conceive[31]

  This is not possible in children. Implantation of a viable embryo currently is associated with a 15–20% chance of pregnancy.

- oocyte retrieval pre-transplant, cryopreservation, subsequent thawing and fertilisation by sperm followed by embryo transfer

  This is less successful than embryo cryopreservation, in part because of lower survival of oocytes after freezing and thawing. It may carry risks such as chromosomal loss and spindle anomalies.[11]

- ovary cryopreservation and either subsequent reimplantation of the intact ovarian tissue post-transplant *or* subsequent in vitro maturation of oocytes followed by fertilisation and embryo transfer

  Some centres offer freezing of small slices of ovarian tissue retrieved laparoscopically prior to transplant. One advantage of this procedure is that, unlike oocyte referral, it can be arranged at short notice without undue delay in initiating chemotherapy. It has not yet been proven in adult humans that fertility can be restored by these approaches, although preliminary studies are encouraging.[32,33] Tumour contamination is a concern. There are limited data regarding the incidence of overt or occult ovarian involvement by lymphoma. Involvement by HL is probably very rare[11], but old data suggest that involvement by non-Hodgkin lymphoma at autopsy (presumably in patients with disseminated lymphoma) is not infrequent.[34] Moreover, using a mouse lymphoma model, investigators have shown that transmission of lymphoma to graft

recipients can be mediated by cryopreserved ovarian tissue samples taken from donors with lymphoma.[35]

Post-chemotherapy

(i) Fertility: in the absence of patient oocytes, in vitro fertilisation using donated ova and partner sperm.[36]

(ii) Hypogonadism: in addition to symptoms such as hot flushes and vaginal dryness, oestrogen insufficiency may contribute to loss of bone mineral density, which frequently occurs post-transplant, particularly in the first six months.[37] Women of post-menopausal age usually require short- to medium-term hormone replacement therapy (HRT); younger women who may potentially recover fertility usually receive the oral contraceptive pill till age forty, and then HRT until age fifty, the average age of spontaneous menopause. HRT may have a beneficial effect on bone density.[38] Topically administered vaginal oestrogen cream is often used to provide adequate local oestrogenisation. Some patients have low testosterone levels and persistent problems with loss of energy and libido, despite adequate oral oestrogen replacement. They may benefit from androgen replacement therapy in the form of transdermal testosterone cream.[39]

21.2.4 Sexual activity and pregnancy early after chemotherapy

There are few data in the literature to assist in recommendations in this area. A murine study found cyclophosphamide in the seminal fluid of treated males, longer retention of cytotoxic in the seminal fluid than plasma, and an adverse effect on implantation.[40] There are no data to our knowledge of cytotoxic levels in vaginal secretions.

Chemotherapy-induced sex chromosomal and autosomal aneuploidy in human sperm declines to pre-treatment levels in 90 days.[41] Based on approximately three-months period for a complete cycle of spermatogenesis, the use of contraception where relevant is recommended for six months after chemotherapy, to limit the risk of transmitting these defects.

Key points

In patients receiving high-dose chemotherapy prior to transplantation, the following are recommended:

(a) *Pre-transplant*: referral to a fertility specialist. In women, the possibility of chemotherapy-induced premature menopause, and the acute and long-term effects of this, should be explained. Use of a continuous contraceptive pill during therapy is not unreasonable in pre-menopausal women, but is not proven. If available, enrolment in a trial evaluating GnRH agonists or antagonists should be considered.

(b) *Post-transplant*:

Women

(i) if ovarian failure occurs, HRT should be considered, if appropriate

(ii) regular surveillance of gonadal function off HRT to detect spontaneous recovery of fertility may be indicated in selected patients

(iii) regular gynaecological review (by a gynaecologist with particular interest and expertise in post-transplant issues such as oestrogen deficiency, infection, and, in allograft recipients, vaginal graft versus host disease, is strongly recommended), cervical cytology, and, in those receiving HRT, mammography

(iv) bone mineral density scans in women not on HRT, particularly if there are other risk factors for osteoporosis

(v) testosterone levels should be checked in patients with symptoms suggestive of androgen deficiency

Men

(i) regular surveillance of gonadal function post transplant

(ii) enquire about libido and erectile dysfunction. Consider

(a) testosterone replacement if low testosterone levels and symptomatic, and

(b) sildenafil if erectile dysfunction and no contra-indication.

Guidelines — Advice to patients	Level of evidence	Refs
During cytotoxic therapy, sexual intercourse can continue, but reliable contraception should be used. Condoms should used be used within 48 hours of chemotherapy if the male is treated, to avoid seminal transmission of cytotoxics, particularly if the female partner is pregnant.	IV	41
Sperm banking should be offered to males who are receiving potentially sterilising chemotherapy and who may wish to have children in the future.	IV	24, 25
Women receiving chemotherapy in which fertility and/or premature menopause are relevant should discuss the potential impact of their treatment on these issues with their oncologist and, in some cases, with a fertility expert.	IV	11, 31–33
Conception of a child by men (and possibly by women) should be delayed for at least three months until after the completion of cytotoxic therapy affecting the gonads.	IV	41

21.3 Secondary malignancy following treatment

21.3.1 Introduction

While advances in the treatment of HL and lymphoma have resulted in many long-term survivors, it is clear that survival does not come without risk.

Second malignancy is the leading cause of death in survivors of HL[42], and is considered to be the most serious consequence of therapy. Long-term follow up demonstrates an increased risk of myelodysplasia and leukaemia in chemotherapy-treated patients, and of solid tumours in those whose treatment included radiation.[43] The influence of chemotherapy in the occurrence of solid tumours is less clear.[44]

The risk of developing leukaemia and lymphoma has been demonstrated to be greater during the first decade following treatment, then reducing and reaching a plateau midway through the second decade.[45] In contrast, the risk of developing a solid tumour continues to increase with time. The highest risk is in those patients surviving longer than fifteen years. Solid tumours as a second malignancy have been documented out to twenty years and beyond following treatment.[45,46]

Assessment of the risk of second malignancies is confounded by the long latency, especially for solid tumours, and the relative rarity of such events. Most analyses are performed comparing incidence in large survivor databases with incidence in 'normal' populations to produce ratios of observed to expected (O/E) incidence. These analyses span a number of decades over which treatment practices may have altered significantly. Heterogeneity, both with regard to type of disease and treatment, should be considered when interpreting results.

The risk of second cancers appears to be higher in patients treated for HL[47] than in lymphoma and other malignancies (Table 21.1). This suggests that disease related factors might play a role in the development of secondary malignancy in HL.

Table 21.1 Risk of all second cancers by first primary diagnosis irrespective of treatment

First primary cancer	Relative risk
Hodgkin lymphoma	2–4
Non-Hodgkin's lymphoma	1.2–1.4
Chronic lymphocytic leukaemia	–1.3
Ovarian	1.2
Cervical	–1.4
Testicular	–5.0
Colorectal	1.0
Breast	1.3

Source: Holland, Blast & Morton[47]

21.3.2 Second haematological malignancies

After treatment for Hodgkin lymphoma

Acute non-lymphoblastic leukaemia (ANLL) accounts for most cases of secondary acute leukaemia. Observed rates of secondary leukaemia show significant acceleration in the risk of ANLL following treatment, but the absolute increase in risk is small and diminishes dramatically by ten years. Radiotherapy appears to play only a minor role in accelerating the risk of secondary leukaemia.[48] Regimens that contain mustine[49] and chlorambucil[50] have been associated with higher rates of ANLL than ABVD.[48] Newer regimens such as ABVD are associated with a lower risk of leukemia[48], with a fifteen-year actuarial risk of 0.7%, which is similar to the rates observed with radiation alone.[51] The use of escalated-dose BEACOPP has been associated with a potential increase in the five-year actuarial risk of secondary AML/MDS compared with COPP-ABVD (0.4% versus 2.5% p=0.03).[52]

In a large cohort of 1984 patients treated over a twenty-year period with a variety of regimens, including MOPP, ABVD and MOPP/ABV, the risk of lymphoma was increased[53], with a relative risk of 21.5. Some late cases occurring beyond ten years were noted.

After treatment for non Hodgkin's lymphoma

A review of >29,000[54] patients treated from 1973 to 1987 showed an overall increase in the risk of second cancers, with the O/E ratio reaching 1.77 at ten years. The risk of leukaemia following treatment for lymphoma of various histologic types has been shown to be increased[55]. Mustine derivatives have the greatest risk, and cyclophosphamide is associated with a non-statistically significant increase in leukaemia risk. In this cohort, radiotherapy did not increase the risk of leukaemia.

Another cohort study[56] examined >6000 subjects with lymphoma who survived two years after diagnosis. At two years, there was an increase in the risk of leukaemia, with an (O/E) ratio of 4.83. Among fifteen-year survivors there was an increased risk (O/E ratio 1.37) for second solid tumours (of all types), and a significantly increased risk of HL (O/E ratio of 25).

21.3.3 Second solid tumours

Radiotherapy

Radiotherapy has consistently been associated with an increase in the risk of solid tumours. The contribution of chemotherapy is more variable.[53] Relative risk ratios for solid malignancies are much lower than for leukaemia, but the absolute number of cases is higher, with solid tumours accounting for more than 50% of secondary malignancies in most reported studies, and up to 90% in one series.[53] Patients treated at a younger age appear to be at higher risk[53], with relative risks of all second cancers shown to be increased 14-fold in children treated before the age of ten[43,43], particularly those treated with high-dose extended field radiotherapy.[43,57,58]

Breast and thyroid cancers are the most common solid second malignancies in the irradiated population, followed by bone and connective tissue, skin, GIT, and brain, tumors.[43,59] Elevated risk persists for more than twenty years, with an increase in risk for female breast, thyroid and bone at ten years, and elevated risks of cervical and digestive tract tumours becoming apparent in the second decade of follow up[43,43].

Breast cancer

The influence of age at irradiation on risk is particularly evident in breast cancer, the most common second malignancy in female survivors of HL, who received mantle irradiation. Those aged less than fifteen at time of irradiation have the greatest risk; with an O/E ratio of up to 39 reported in women between the ages of ten and nineteen at the time of breast irradiation[43,60,61]. Women aged thirty or more at the time of irradiation had no increased relative risk[61,61]. Clinical and pathologic features consistently reported in studies of breast cancer occurring after treatment of HL includes: the median latency period between treatment and diagnosis of fifteen years, with 95% occurring after ten years following radiation; histopathologic characteristics similar to primary breast cancers; and medial and bilateral cancers observed more frequently than in the non-irradiated population.[60,62,63]

Thyroid cancer

An increased risk of thyroid cancer after exposure to radiation, either directly or from scatter irradiation, has been reported after irradiation for HL, lymphoma and several other paediatric tumours.[43,44,53,59,64,65] While the thyroid gland in children has been shown to be particularly sensitive to the carcinogenic effects of radiation, Japanese reports have also indicated an increased risk in irradiated adults[64,64].

Thyroid cancers caused by radiation begin to appear five to ten years after exposure. The greatest relative risk occurs after fifteen to twenty years. However, increased risk has been shown to be present at fifty years, and is likely to persist for life[46,46].

The most common type of radiation-induced thyroid cancer is papillary carcinoma. Tumour behaviour does not appear to differ from spontaneously occurring tumours at the equivalent age[46].[46]

The use of screening in these patients remains controversial. However, ultrasound has been shown to be a useful non-invasive tool in screening for thyroid abnormalities[66].[66]

The role of chemotherapy

Whilst the relationship of second solid tumours related to chemotherapy is less certain, the additive role of chemotherapy to radiation has been suggested in several studies. A specific review of secondary bladder cancer as a second malignancy[67] demonstrated a dose–response relationship with cyclophosphamide and bladder cancer (Table 21.2). Radiotherapy did not contribute to the increased risk of bladder cancer in this study

Table 21.2 Relative risk of bladder cancer with cyclophosphamide dose escalation

Dose of cyclophosphamide	Relative risk of bladder cancer
<20 g	2.4
20–49 g	6
>50 g	14.5

Conclusion

There is ample evidence demonstrating the risk of second cancers developing after treatment for HL and lymphoma. With long-term follow up, about 10% of patients develop a second malignancy. The most commonly seen haematological malignancy is ANLL, and the most common solid tumours are breast and thyroid cancer. Changing chemotherapy and radiation schedules may result in a change in the frequency of second malignancies with contemporary treatment. More intensive therapy, both chemotherapy and radiotherapy, may be associated with greater risk. Some agents appear to carry specific risk, for example, mustine. Patient variables such as age at diagnosis and gender, as well as disease variables, for example, HL, also influence the risk. The effects of current treatment protocols on the risk of secondary neoplasia are most common before ten years for subsequent haematological malignancies, whereas solid tumours may not become evident for more than ten years.

Guidelines — Advice to patients	Level of evidence	Refs
Patients should be informed about the risks of second malignancy at the time of treatment as well as at completion of therapy.	IV	42–46
Patients should be informed about the effects of smoking, diet, sun exposure and lifestyle habits that may increase their risk of developing second malignancy at specific sites, such as lung, skin, breast, digestive tract and cervix.	IV	55
Lifelong surveillance for secondary cancers is appropriate. A management plan should be organised for surveillance relevant to each individual patient, with the patient, their family and the general practitioner.	IV	42–46

Key points

- More intensive chemotherapy and radiotherapy may both be associated with a greater risk of second malignancy.
- All patients should have at least annual full blood examination for the first decade after treatment.
- In women younger than thirty treated with mantle radiation, routine annual mammography from seven to eight years after treatment is recommended in addition to regular self-examination and six-monthly physician examination. Abnormalities should be further investigated with ultrasound and biopsy.[49,53,68-70]
- The safety of hormone replacement therapy in postmenopausal women who have received mantle radiation is uncertain. There is some evidence that oestrogen deficiency may reduce risk of secondary breast cancer.[53, 68,70]
- The role of screening tests for second thyroid cancer for patients treated with radiation therapy to the head, neck and chest, is uncertain. Ultra-sound and physical examination can be used at appropriate intervals, for example, one year post-completion of therapy, then three-yearly to ten years, followed by annual thyroid ultrasound from ten years after treatment. Given the greater incidence of this complication following radiotherapy in childhood, it may be more important to screen this population.

21.4 Psychosocial effects of treatment of lymphoma

Quality of life in long-term survivors may be affected by physical acute and chronic medical complications from chemotherapy and radiotherapy. In addition, there is a range of potential psychosocial problems that may result from the impact of the diagnosis of a life-threatening illness, the rigours of treatment, and the attendant social disruption. There are few studies adequately addressing these issues. Most studies include patients with a variety of diagnoses, including solid tumours, and many only study the early period after treatment, and not long-term adjustment. Older studies may have less relevance due to improvements in management. Some comprehensive studies involving controls have been performed in patients with HL and childhood cancers, but none specifically study patients with lymphoma. Studies of the ability of survivors to obtain insurance and employment have been performed in the United States and Europe, but may not be directly comparable to the opportunities and standards currently existing in Australia.

21.4.1 Health-related quality of life

The quality of life of long-term survivors of lymphoma has not been well studied. Hospital-based studies of adults with HL compared with matched controls have found that energy levels had not returned to patients' satisfaction in 37% of cases[71].[71] Similarly, more physical impairment and chronic fatigue has been reported[72]. In addition, significantly greater restriction in performing strenuous activities and lower overall health for as long as ten to eighteen years after treatment has been observed[73].[73] Although not systematically studied, physical limitations that have an impact on global quality of life, such as fatigue and dyspnoea, may not be seen with the same frequency in patients with lymphoma, compared with HL, in whom sterility and early menopause has been more common and where gonadal failure may contribute to symptomatology. Health-related quality of life in patients at one-year post autologous stem cell transplantation was little different from those having combination chemotherapy for lymphoma[74].[74] A higher level of fatigue reported in the autografted group of patients has been postulated to relate to gonadal failure[75].[75] The impact on quality of life of

long-term treatment-related complications, such as osteoporosis, has not been studied, nor has the effect of CNS prophylaxis or treatment in adults with lymphoma.

21.4.2 Psychological complications

Early psychological effects

Anxiety and depression was assessed prospectively in patients with lymphoma and shown to be most prevalent at the time of diagnosis, but likely to recur[76].[76] There are no studies specifically addressing the immediate impact of treatment-related side-effects on psychological wellbeing and quality of life in lymphoma. This study[76] also concluded that alopecia, mucositis and change of taste contributed to psychiatric morbidity. There are no studies that address whether the severity of immediate side-effects of treatment has any effect on long-term psychological health.

Psychological distress and adaptation

A study comparing adolescent and adult patients with HL at a median of two years after treatment with controls found subtle, non-impairing psychological distress. Although most measures of psychological dysfunction did not differ significantly from controls, a significant number of patients reported increased irritability[77].[77] These authors report denial as a principal coping mechanism, but some patients had symptoms of a post-traumatic stress syndrome. Similar to these findings, a more recent study did not find an increase in late psychological distress in adult patients with HL compared to controls[72].[72] In contrast, one study found that long-term psychological adaptation does not occur to the same degree in adult survivors of HL[78], with psychological distress being elevated by one standard deviation above that of healthy subjects.

Two studies, although containing small numbers of adult patients with lymphoma, suggest that survivors are typically accepting and adapt to the changes in their lives.[79,80] These studies are the only reports of the frequency of mental health disturbance as a long-term complication in survivors of lymphoma.

One study, which assesses the psychologic and neuropsychologic function of patients after autologous bone marrow transplantation, showed that patients with haematological conditions including HL and lymphoma showed more distress than patients with breast cancer, but became less distressed over time[81].[81]

Depression

Depression correlated with symptoms of fatigue in survivors of HL in one study.[71] A large survey of survivors of paediatric lymphoma showed a significantly increased risk of reporting symptoms of depression, with intensive chemotherapy adding to the risk[82].[82] However, suicidal ideation in survivors of paediatric and adult HL does not appear to differ significantly from controls[77].[77] One study in adults, in which 50% of the patients had lymphoma, suggests an increase in depression and fear of relapse for an average of four months after diagnosis[76].[76] Although anxiety and depression was seen more at diagnosis, new episodes occurred throughout the year post-diagnosis, but patients were only followed for twelve months.

Memory and cognitive disturbance

Cognitive disturbance was reported in the majority of adult survivors, but only objectively found by neuropsychological testing in a subset in patients with both HL and lymphoma[80], and in a group with HL alone[72] compared to controls ($p = 0.15$). Survivors with lymphoma complained of memory disturbance (not confirmed by formal testing), which may be a reflection of increased anxiety and depression.[76,80] Verbal memory and psychomotor functioning was found to be significantly reduced in patients with breast cancer or lymphoma receiving systemic chemotherapy, compared with local therapy only[80].[80] Higher-order cognitive functioning generally worsened over time.

21.4.3 Social complications

Interpersonal relationships

A study comparing age- and sex-matched healthy controls found that adult survivors of HL had reduced social functioning (interference with family life and friendships; p = 0.048), with no statistical difference in emotional status[72].[72] There are no similar studies in lymphoma.

A large cohort of patients who had survived childhood cancer, including 85 patients with lymphoma, were studied[83].[83] When adjusted for effects of income, education, age at follow up and vital status with controls, there was no decrease in the incidence of marriage, live-in relationships or rate of divorce. In contrast, a study in HL patients[84] suggested a higher divorce rate for men than compared to the general population. The timing of divorce in relation to therapy was not reported.

Sexual function

In an uncontrolled study of patients with HL, over a third of patients complained of sexual problems[78].[78] Decreased sexual interest and activity and a feeling of reduced physical attractiveness has been reported in patients with HL, in whom infertility historically has been of greater incidence.[77,71] Most modern regimens are not sterilising and effects on sexual functioning are unlikely to be as significant. A 20% overall incidence of loss of libido at one year after diagnosis was seen in a study of 57 patients with lymphoma[**76**].[76]

Education, employment and social status

The psychosocial effects of childhood and adolescent HL, at least five years after completion of treatment, have been studied. Although subjects had missed a mean of six months of school and 40% reported unpleasant school experiences, their educational levels exceeded those of a matched population. There was no increase in alcohol or drug abuse[84].[84] In this study and another study of survivors of childhood HL[77], almost all subjects said that they had benefited in some way from the experience of having a malignancy. However, most expressed concerns about discrimination in employment and in obtaining life or health insurance.

In contrast, studies of adult survivors of HL suggest that they experience job discrimination and have lower employment rates than the general population, resulting in a negative socioeconomic effect from their diagnosis and treatment.[71,78,84] In addition, they have a low incidence of obtaining life insurance policies and have difficulty obtaining finance.[72,73] There are no studies addressing financial discrimination of patients surviving lymphoma. An early prospective English study of patients with lymphoma showed a high proportion of healthy patients who did not return to employment, with 18% not working for more than twelve months or retiring early[76].[76] Retirement was more frequent in females and older patients.

21.4.4 Summary

There is a paucity of prospective, systematic and contemporary studies evaluating the psychological impact of the diagnosis and treatment of lymphoma.[85,86] The limited data available suggest that clinicians should be mindful of the possibility of psychological disturbance in the short and long term and, with the assistance of a multidisciplinary team, support patients who are experiencing social, financial or employment difficulties. Most studies suggest depression and anxiety occur early, with most patients learning to adapt. Paediatric patients may be more vulnerable to late depression. Hypogonadism may contribute to psychological symptoms. Interpersonal difficulties may be most acute during treatment, but sexual difficulties may be related to hypogonadism, and self image related to infertility. Memory and cognitive disturbance may occur from treatment and could affect social interaction and work performance. Although there are no studies to evaluate its benefit, early intervention with the provision of counselling and support to both patient and partners would seem prudent. Continuing support, with assistance with work, family, and financial and life goals, may benefit those experiencing discrimination or suffering from uncertainty about their future health.

Patients may require intervention to cope with increased anxiety at the time of clinical reviews and dealing with fear of relapse. Anxiety and depression may require referral to appropriate health care professionals.[87]

Guidelines — Physician alerts after treatment for lymphoma	Level of evidence	Refs
Multidisciplinary care enhances psychosocial and sexual functioning, with fertility counselling and management of hypogonadism.	IV	76, 85, 86
Clinicians should be alert to symptoms of depression even in the longer term, particularly in the paediatric population.	III-2 IV	71, 82, 76, 82
Memory and cognitive disturbance may occur after systemic chemotherapy and may be worsened by anxiety, particularly at the time of clinic attendance. Patient interviews may need to be enhanced with written material and diagrams.	IV	72, 80
At the patient's request, clinicians may need to communicate with the education facility and/or workplace (with regard to patient privacy) to counter discrimination in employment or study.	IV	71, 77, 78, 84
Chronic fatigue and prolonged restriction of strenuous physical activity may follow treatment for lymphoma.	IV	71–73

21.5 Blood donor / organ donor

21.5.1 Blood donor

As lymphoma is a blood-borne disease, lymphoma patients should never donate blood.

21.5.2 Organ donor

For the same reason, lymphoma patients are never suitable as organ or tissue donors. The one exception appears to be corneas, although this should be at the discretion of the state licensing authority.

Key points

- Patients should understand that they should not donate blood or organs.
- Keep the patient's treatment team and other doctors informed.

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CHAPTER 22 COMMUNICATION WITH THE PATIENT

22.1 Introduction

Treating lymphoma patients is not just about treatment of the disease; it is also about helping the individuals deal with issues related to their illness. In these guidelines, we will present evidence to support the importance of good doctor–patient communication and of doctors being socially and culturally competent in dealing with patients. Communication with patients includes the ability to converse and provide best evidence-based and culturally appropriate information on issues that are important to their wellbeing. Frequently asked questions that relate to diet, exercise and psychological therapies are discussed in Chapter 23 and to complementary and alternative health practices in Chapter 24.

22.2 Communication with the patient

22.2.1 The initial consultation

Patients and their carers often seek information about their cancer at the time of diagnosis, but studies have shown that only part of the initial consultation is remembered.[1] Therefore, the provision of information should not end with the initial consultation.

It is not necessary to make all treatment decisions at the initial consultation.

A qualified and appropriate interpreter is important for patients who do not have English as their first language or whose understanding of English is limited in any way. The interpreter should be a professional and not a family member.

Breaking bad news in language the patient understands should be the responsibility of the clinician in charge and it should not be delayed unduly.

Figure 22.1 How much should the patient be told?

The NHMRC recommends the following approach[2], adapted from The Cancer Council NSW[3]:

- allow enough uninterrupted time in the initial meeting
- assess the individual's understanding
- provide information simply and honestly
- encourage individuals to express feelings, to be frank and honest in giving information about their health
- encourage patients to make their own decisions
- give advice but not coerce
- respond to individual's feelings with empathy
- give a broad time-frame for the prognosis
- discuss treatment options
- avoid the notion that nothing can be done
- give bad news in a quiet, private place
- provide information about support services
- arrange a time to review the situation
- document the information provided.
- that lymphoma is not a contagious disease.

There is evidence to suggest that most cancer patients wish to be fully informed of all available information, and they usually want a close relative or friend present at the initial interview.[4] Subsequent discussions about the meaning of the diagnosis, and what actions could be taken, are as important as the disclosure of the initial diagnosis, if not more important.[5] Cancer patients' understanding, recall and/or satisfaction with the consultation increase when techniques such as audiotapes or personalised letters are used.[6–8] Vagueness and obscurity make a difficult situation worse.[9] Decision aids, including information on the disease, improves knowledge, reduces decisional conflict and stimulates patients to be more active in their decision making without increasing their anxiety or affecting overall levels of satisfaction with the decision making process.[10] However, the effect of decision aids on patient outcomes (such as quality of life, persistence with choice) remains uncertain.[10]

Guideline — Patient information	Level of evidence	Refs
Patients and their carers often seek information about their cancer at the time of diagnosis, but studies have shown that only part of the initial consultation is remembered. Therefore, the provision of information should not end with the initial consultation.	II	1
Information for patients with lymphoma should include: • the meaning of lymphoma, suspected risk factors and the extent of disease • proposed approach to investigation and treatment, including information on expected benefits, the process involved, common side effects, whether the intervention is standard or experimental and who will undertake the intervention • the likely consequence of choosing a particular treatment, or no treatment • the time involved • the costs involved • the effect of cancer and its therapy on interpersonal, physical and sexual relationships • typical emotional reactions • entitlements to benefits and services, such as subsidies for travel or prostheses • access to cancer information services.	IV	3, 4

Providing an accurate and detailed record of the information given to the patient may facilitate continuity of care from within the treatment team and from the patient's general practitioner.

Surveys of referring doctors show that the letters to them from the consultant should cover diagnosis, clinical findings, future tests/test results, treatment recommendations, likely side effects and prognosis.[2]

Patients have a right to obtain a second opinion at any time. Having a second opinion may help them clarify questions, decide which doctor they prefer to manage their condition, and decide which course of treatment to follow. It can also reinforce that advice already given was accurate, and increase their confidence.

22.2.2 Preparing patients for potentially threatening procedures and treatment

People diagnosed with lymphoma may undergo a number of potentially stressful medical procedures and interventions, such as surgery, biopsies, chemotherapy and radiotherapy. Providing patients with lymphoma with information on the procedure they are about to undergo significantly reduces their emotional distress and anticipatory side effects, and improves their psychological and physical recovery.[11–14]

Various formats for providing information about procedures have been shown to decrease anxiety and psychological distress. They include discussions with a clinician or allied health professional[15], booklets[16], or videotape information.[17]

Sensory information describes what a person is likely to experience before, during and after a procedure, including their feelings in response to pre-operative medication and pain. Such information

has produced significant reductions in anxiety in patients undergoing medical procedures.[12] The best results appear to be achieved by providing both sensory and procedural information.[13]

Guidelines — Preparing patients for treatment	Level of evidence	Refs
Providing patients with lymphoma with information about the procedure they are about to undergo significantly reduces their emotional distress and anticipatory side effects, and improves their psychological and physical recovery.	I II	11–14
Various formats for providing information about procedures have been shown to decrease anxiety and psychological distress. They include discussions with a clinician or allied health professional, booklets, and videotape information.	II	15, 16 17
Sensory information significantly reduces anxiety in patients undergoing medical procedures. The best results appear to be achieved by providing both sensory and procedural information.	I	11, 12

22.2.3 Counselling and support

In a meta-analysis of 45 randomised controlled trials of adults with cancer, those receiving psychological therapies had, on average, a significant improvement of 12% in emotional adjustment, 10% in social functioning, 14% in treatment and disease-related symptoms, and 14% in overall improvement in their quality of life, compared to those not receiving psychological therapies.[18]

For some patients, access to volunteer peer support and self-help groups, including electronic online support groups[19], may be helpful. Non-randomised research suggests that peer support and self-help groups decrease feelings of social isolation, depression and anxiety.[20]

Younger people diagnosed with lymphoma may benefit from meeting others in a similar situation through specific support groups for their age groups. Educational pamphlets are available from regional cancer councils and are particularly informative for individuals with lymphoma and their carers.

A number of people may be involved in providing counselling and support in either a formal or informal manner. They can include family, friends, doctors, nurses, other health care professionals, and a cancer support service.

Guidelines — Patient support	Level of evidence	Refs
Support needs for individuals with lymphoma and their families may include:		
• counselling	I	12
• exploring feelings with a member of the treatment team	III	19
• access to a cancer support service and/or support group education	III	20, 21
• assistance with practical needs (e.g. child-minding, transport).	III	19

22.2.4 Recognition of cultural factors in patient management

Studies have shown the incidence of lymphomas and the approaches to dealing with cancers and treatment outcomes differ among different cultural groups. It is therefore important to apply this knowledge when managing patients with lymphomas.

Metabolic genetic polymorphisms may affect responses and tolerance to chemotherapy and radiotherapy, and increase susceptibility to drug-induced adverse reactions, for example, agranulocytosis.[21,22] Orientals have reduced NAD(P)H:quinone oxidoreductase activity which catalyses two-electron reduction quinone compounds. This affects a patient's response to quinone-based cancer therapy because there is a decreased production of cytotoxic metabolites and a susceptibility to toxicities. There is a need to determine population frequencies polymorphisms. Genetic polymorphisms probably contribute to ethnic-specific effects on cancer susceptibility.

Cultural explanations for cause of cancer

Different ethic groups may handle cancer in different ways. Some believe that the cause of lymphoma is related to actions they have taken. For example, Vietnamese believe breast/cervix cancer is caused by poor hygiene and that it could be contagious.[23]

People's understanding of the symptoms of cancer can be influenced by their cultural upbringing, for example, somatisation among Asians with cancer versus 'psychologisation' among Caucasians.[24] The discovery of cancer may mean God's punishment. Some people may feel uncomfortable in touching someone with cancer, or would rather not know if they had incurable cancer. Vietnamese people, for example, believe that cancer cannot be prevented.[23]

Quality of life; attitudes to treatment

In a study of outpatients affected by leukaemia, it was found that, compared with American patients, Portuguese patients reported better physical functioning, less bodily pain, more vitality, better social functioning and better general quality of life as measured by the Functional Living Index — Cancer (FLIC) total score.[25]

Significant differences have been found between the attitudes and practices of Hispanic and Anglo families of children in both conventional and alternative treatment for cancer.[26,27] The influence of culture on anxiety has also been examined in Hispanic and Anglo children with cancer undergoing invasive procedures. It was found that Hispanic parents reported significantly higher levels of anxiety than Anglo parents.[28] A recent study of first generation Greek migrants in Australia also found their attitudes to cancer management at variance with generally considered good clinical practice.[29]

Key point

There is a need to develop culturally competent methods to assess the needs of patients with lymphoma. In the design of questionnaires and surveys, objective comparison of psychosocial adjustment to cancer in different cultures requires instruments that are valid and reliable in each culture.[10] There is a place for qualitative methods, which allow the collection of greater depth information, identification of processes and relations among behaviours, and framing of variables and hypotheses for quantitative research.

Health professional issues

It is necessary to:

- conduct studies to evaluate the attitudes of medical, nursing and other staff in caring for patients of different cultural backgrounds

- provide training in the following to improve a health professional's cultural competence in dealing with patients with lymphoma:
  - 'breaking bad news', and to whom
  - whether patients should know certain information
  - how much a patient would like family members involved
  - care beyond medical management
  - after death
  - how to express grief and to remember the deceased
- provide culturally competent communication and counselling, telephone help line and community support
- assess cultural competence of printed cancer education materials, and other information
- mobilise religious groups, churches and other culturally specific groups
- collaborate with other non-cancer related and culturally competent health promotions.

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CHAPTER 23 NUTRITION, EXERCISE AND PSYCHOTHERAPIES

23.1 Introduction

This chapter addresses the questions patients frequently ask about diet, exercise, and psychological support. Questions about complimentary and alternative health practices are discussed in Chapter 24.

23.2 Nutrition

23.2.1 Nutrition and dietary recommendations

Nutrition is an important aspect of patient care. Its goals are to support nutritional status, body composition, functional status, and quality of life.[1] Maintenance of body composition and adequate nutritional status can help people with cancer look and feel better, and can maintain or improve both performance and daily functional status.[2] It may also help them tolerate therapy.[3] The type of nutritional intervention will depend on the basis of the nutritional risk or deficit. Studies have stressed the importance of incorporating nutritional evaluation, counselling, intervention (as needed) and follow up in the routine care of the oncology patient.[4]

Dietary guidelines for lymphoma patients are basically the same as those for the general population, that is, a healthy balanced diet. The following recommendations were developed by the Commonwealth Department of Health and Family Services from recent research in nutrition[5]:

> To obtain a balanced and varied diet, it is important to eat food from the five food groups each day. The main food groups are as follows:
>
> 1 Bread, cereals, rice, pasta, noodles
>
> 2 Vegetables, legumes
>
> 3 Fruit
>
> 4 Milk, cheese, yoghurt
>
> 5 Meat, fish, poultry, eggs, nuts, legumes.
>
> In addition to eating a variety of foods, it is recommended to:
>
> 1 Drink eight glasses of water every day for adults. All fluids, except for alcohol, contribute to this requirement.
>
> 2 Eat a diet low in fat and in particular, low in saturated fat.
>
> 3 Eat only a moderate amount of sugars and foods containing added sugars.
>
> 4 Choose low salt foods and use salt sparingly.
>
> 5 Maintain a healthy body weight by balancing physical activity and food intake.

The actual amount of protein and kilojoules each patient needs will vary, depending on the person's current nutritional status, particular nutritional deficits and individual factors. The aim is to build up strength, improve tolerance to treatment and aid in recovery. Calculating individualised kilojoule and protein requirements for a patient with lymphoma (and/or family or caregiver) will allow them to

meet specific and realistic goals. A dietician can offer guidance in determining the appropriate macronutrient and micronutrient needs for individuals.

Guidelines — Nutrition and dietary recommendations	Level of evidence	Refs
Studies have stressed the importance of incorporating nutritional evaluation, counselling, intervention (as needed) and follow up in the routine care of the oncology patient.	IV	4
Dietary guidelines for lymphoma patients are essentially the same as those for the general population, that is, a healthy balanced diet. Recommendations have been developed by the Commonwealth Department of Health and Family Services from recent research in nutrition.	IV	5
A dietician can offer guidance in determining the appropriate macronutrient and micronutrient needs for individuals.	IV	4

Energy and dietary fat

There is little evidence to suggest an etiological link between dietary factors and lymphoma, but the area warrants additional investigation. Studies have not shown an association between lymphoma risk and energy[6] or dietary fat intakes.[7–9]

Guideline — Energy and fat intake	Level of evidence	Refs
Adults should be advised to keep within healthy weight range and their fat intake to <25% of their energy intake.	IV	5

Meat

There is no significant association between animal protein intake and lymphoma as evidenced by both cohort and case control studies.[6,8,10] Several studies showed a positive association between red meat and lymphoma risk.[6] Other studies did not confirm this association.[8,9,11]

High-temperature cooking (such as barbecuing) of red meat can produce carcinogenic oxidised heterocyclic amines. However, no statistically significant increase in risk of lymphoma was found with consuming barbecued or broiled meat.[7]

Dairy products

Some case control and cohort studies have shown a link between milk consumption and lymphoma.[7,8,12,13] The data were not consistent, with others reporting no association between milk and dairy product consumption and an increased risk of lymphoma.[6,9]

Only pasteurised diary products should be consumed.

Fibre

Fibre is a heterogenous group of plant non-starch polysaccharides and non-carbohydrates that is resistant to digestion in the upper digestive tract. The majority of case-control and cohort studies have shown that the consumption of fruit and vegetables is inversely related to the risk of lymphoma.[6–9,11,14] To date, the results of antioxidant trials using beta-carotene have not shown that it is responsible for tumour suppression. Thus vegetable consumption should not be replaced by taking selected

vitamins/antioxidants, as the active ingredient(s) are unknown. Two case control studies have looked at cereal fibres.[7,8] Both showed a frequent use of wholegrain foods was inversely related to lymphoma.

Guideline — Fibre requirements	Level of evidence	Refs
Eat five or more serves per day of a variety of vegetables and fruits, all year round.	III	6, 11, 14
It is recommended that adults consume a minimum of 30 g of fibre daily, in keeping with the general healthy diet guidelines.	IV	7, 8

Alcohol

The majority of case control and cohort studies show no association between alcohol and the risk of lymphoma in men and women.[7,8,15,16] Several case control studies[17–19] showed an inverse association between lymphoma risk and a higher alcohol intake for all types of alcoholic beverages, varying from >3.4 g to >5 drinks/day.

Key point

The Australian dietary guidelines recommend two standard drinks for women and four standard drinks for men per day, with two alcohol-free days per week.

Tea and coffee

Three of four studies that looked at the association between tea and coffee and the risk of lymphoma showed no association between risk of lymphoma and a regular intake of coffee and/or caffeinated and decaffeinated tea.[9,19] Some animal studies have shown that green tea may delay disease progression of lymphoma[20], but more studies are needed to confirm these results. No conclusions can be drawn.

Key point

Drink no more than 2–4 cups of coffee/tea per day.

Nitrate

Nitrate is endogenously reduced to nitrite. Nitrosation reactions give rise to N-nitroso compounds, which are highly carcinogenic. There has been some speculation on the level of nitrates in drinking water and the risk of cancer. All cohort studies and case-control studies to date have found no association with nitrate levels in drinking water and lymphoma risk.[21,22]

Guideline — Nitrate and lymphoma risk	Level of evidence	Refs
No cohort or case-control study to date has found any association with nitrate levels in drinking water and lymphoma risk	III	21, 22

Multi vitamins and antioxidants

The popularity of multivitamin supplementation and mega doses of vitamins has increased over the past decade. Published trials of vitamin supplementation for cancer prevention and treatment have not been particularly promising.[5,14] There is no evidence to suggest that standard-dose vitamin

supplementation is harmful, even when taken in addition to a fully balanced diet. However, as well as the financial burden that can accompany vitamin supplementation, there are certain instances where vitamins may be counterproductive, for example, high folate diet and methotrexate therapy, antioxidants and radiotherapy — loss of O_2 free radicals.

Several laboratory studies have shown possible beneficial effects with beta-carotene, Vitamin E, Vitamin A and Vitamin C in immunoregulation with lymphoma. Most clinical studies, however, found no association between the intake of specific dietary carotenoids[12], Vitamins A, C, E and multivitamins and lymphoma risk, even with long-term use.[13,23,24] Two studies found that Vitamin C and beta-carotene were inversely related to risk of lymphoma.[8,11] More research is indicated in humans, however, before recommendations can be made.

Guideline — Antioxidant vitamin supplementation	Level of evidence	Refs
Antioxidant vitamin supplementation is not advised at present to protect against lymphoma.	III	12, 13, 23, 24

23.2.2 Influence of psychosocial stress on diet and nutrition

Food is more than a commodity that sustains health and promotes growth. It is a means of communication, a source of pleasure, and a major focus of social activity.[2] The best way to increase a patient's consumption of food is to determine individual food preferences and to provide the patient with as many of the highly preferred foods as possible. This requires flexibility and imagination.

Many psychological and social factors affect food choices and promote a reduced food intake. These include:

- The stress of coping with the cancer diagnosis and loss of control can have a major affect on nutritional intake.
- Learned food aversions may contribute to a decreased oral intake.
- Anorexia may be aggravated by changes in the palatability of many common foods.
- Food likes and dislikes are highly individual.
- Social factors such as living alone, or inability to cook or prepare meals, can contribute to a poor oral intake.
- Fatigue and weakness may impair the ability to carry out daily activities.
- Normal routines change during treatment and can affect intake.

All these factors can significantly affect the patient's quality of life, social interaction, and outlook.[2,14]

23.2.3 Alternative diets and dietary modification

There are no special foods or diets that have been scientifically proven to cure cancer. More than 40 different cancer diets have been claimed to prevent or treat cancer.[25–27] Several of these diets are an extension of conventional medicine; others are more in the realm of alternative approaches. Usually, the diets suggest avoiding meat, many are strictly vegetarian (e.g. Gerson diet, macrobiotic diet), and compelling evidence is largely absent. Many unproven dietary treatments recommend restrictive diets, for example, omitting food groups. This can compromise the intake of essential nutrients, cause

unwanted weight loss and tiredness, and decrease the immune function. As a result, life expectancy and quality of life may suffer.

The following are points to consider before dietary changes are made:

- Collect enough information before making a decision
- The diet should not conflict with the above healthy eating guidelines
- Ability to maintain a healthy weight
- The changes should not interfere with medical treatment
- Are the doses of vitamins and minerals toxic to the body?
- Take into account the cost, time and effort to prepare diet
- Does the diet claim to have realistic or unrealistic results?

23.2.4 Effects of chemoradiotherapy

Patients with lymphoma most commonly experience nutritional problems induced by chemotherapy. It is important to note that side effects of treatment vary from patient to patient. Not all patients have side effects during treatment, and most go away when treatment ends.

To support the nutritional status of the patient undergoing cancer therapy, adequate symptom management is first-line nutritional intervention. Nutritional problems can be induced by each type of anti-cancer therapy, such as procarbazine, vincristine and prednisolone.[28] The frequency and severity of these side effects depend on the class of drug, the dose, the drug combination, individual susceptibility, and whether the chemotherapy is part of a combined modality program. Symptoms that last longer than two weeks are especially significant. Glutamate has been shown to ameliorate vincristine neuropathy without reducing its antitumor effect.[29] Chemotherapy toxicity adversely affects nutritional intake, digestion, or absorption through one or several mechanisms, for example, it has an adverse impact on the gut and central nervous systems.[2,30]

Myelosuppression can lead to an increased susceptibility to infection, or a neutropenic reaction that increases the metabolic demands of the patient. The patient's metabolic needs may increase 25% with a temperature of 39°C.

Protein deprivation has also been shown to increase risk of infection and enhance myelotoxicity caused by chemotherapy.[31,32]

The role of diet in the development of infection and food-borne illnesses in patients with neutropenia is unclear. There is controversy in the literature about the need for low bacterial diets.[33] In patients with a weakened immune system, is important to ensure good food hygiene and proper food handling.

Lymphoma patients receiving radiation therapy may experience oesophagitis, nausea, vomiting, diarrhoea and enteritis. In addition, radiotherapy is often associated with fatigue, which may result in decreased appetite and motivation to eat.[2]

Guidelines — Effects of chemoradiotherapy	Level of evidence	Refs
Chemotherapy toxicity adversely affects nutritional intake, digestion, or absorption through one or several mechanisms, including the gut and central nervous systems.	III	2, 30
The patient's metabolic needs may increase 25% with a temperature of 39°C.	III	2, 30
Protein deprivation has also been shown to increase risk of infection and enhance myelotoxicity caused by chemotherapy.	III	31, 32
In patients with a weakened immune system, ensure good food hygiene and proper food handling.	IV	33

23.2.5 Effects of bone marrow transplantation

Nutrition support is an integral part of the supportive care of bone marrow transplant (BMT) patients. Poor transplant outcome has been associated with both underweight[34] and overweight[35] patients who are having stem cell transplants.

The effect of autologous and allogeneic BMT on nutritional status may be substantially different.[36] The use of peripheral stem cells and growth factors has greatly reduced the duration of profound neutropenia and related side effects, such as neutropenic mucositis, in autologous BMT patients. These patients usually return to premorbid nutritional status more rapidly than those undergoing allogeneic BMT. Pre-transplant conditioning using high-dose chemoradiotherapy leads to gut damage and loss of body mass. Neutropenia leads to an increase in infections that alter metabolic needs. Allogeneic BMT patients experience more profound and severe clinical conditions in the post-BMT period, including graft versus host disease (GVHD) and opportunistic infections. This may result in decreased oral intake, malabsorption of nutrients, and loss of nutrients from the gut, especially amino acids.

Negative nitrogen balance is due to intestinal losses, catabolic effects on skeletal muscle from the underlying disease and/or conditioning treatments and possible complications such as sepsis and GVHD.[37] Protein requirements are generally satisfied by the provision of 1.4–1.5 g/kg body weight/day.[36]

BMT patients have increased energy needs because of the stress-induced catabolic state from the cryoreductive therapy and associated complications.[37] Energy requirements may reach 130–150% of predicted basal energy expenditure. Recommendations for energy requirements are 30–35 kcal/kg body weight per day.[36]

Carbohydrate metabolism may be affected, especially from the administration of steroids or cyclosporine, or septic complications. Long-term cyclosporine or corticosteroid therapy for chronic GVHD can cause severe magnesium wasting, hyperlipidaemia extreme muscle wasting, glucose intolerance, hyperlipidemia, hyperphagia, osteoporosis and growth failure.

Vitamin status may be altered in allogeneic BMT patients as a result of poor intake and malabsorption.[38] The use of cyclophosphamide and radiation has been reported to increase the need for antioxidant vitamins such as beta-carotene. Trace element deficiency may occur with malabsorption and increased needs for bone marrow reconstitution. Zinc deficiency was shown to correlate with mortality after BMT.[36]

Veno-occlusive disease of the liver can cause sodium and water retention, ascites, liver failure and hepatic encephalopathy. A low sodium diet and fluid restriction is often needed. Occasionally, a low protein diet is also warranted.

Acute and chronic GVHD can affect the whole GI track, liver, leading to reduced food intake, malabsorption and liver failure. Generalised severe GVHD also causes hypermetabolism. Appropriate nutritional management of these problems includes a hyperalimentation during the severe stage of the disease, followed by a low-fibre or low-residue, low-lactose, low-fat and bland diet.

Guidelines — Bone marrow transplantation	Level of evidence	Refs
Poor transplant outcome has been associated with both underweight and overweight patients who are having stem cell transplants.	III	34, 35
Allogeneic bone marrow transplant (BMT) patients experience more profound and severe clinical conditions in the post-BMT period, including graft versus host disease (GVHD) and opportunistic infections. This may result in decreased oral intake, malabsorption of nutrients, and loss of nutrients — especially amino acids — from the gut.	III	36
Protein requirements are generally satisfied by the provision of 1.4–1.5 g/kg body weight per day.	IV	36
Zinc deficiency was shown to correlate with mortality after BMT.	III	36
Appropriate nutritional management of these problems includes a hyperalimentation during the severe stage of the disease; followed by low-fibre or low-residue, low -lactose, low-fat and bland diet.	IV	36

23.2.6 Nutritional support in bone marrow transplantation

Traditionally, total parenteral nutrition (TPN) has been the nutrition support method for bone marrow and stem cell transplant patients when oral intake becomes inadequate.[39]

There has been renewed interest in enteral nutrition for transplant patients because it is physiologically safer and less expensive than TPN. Several prospective trials looking at early post-transplant enteral feeding in adults have not found significant benefits.[40–42] However, TPN was found to be associated with more severe complications and was more expensive when compared to enteral nutrition. Another study showed positive results by using enteral nutrition as a transition step from TPN to oral diet.[43]

Glutamine is necessary for cell proliferation and enhances inflammatory cell function. It is thought that under physiologic stresses, glutamine synthesis is insufficient to meet the body's needs. In animals, glutamine supplementation was found to support immune function, reduce infectious complications, and improve tolerance of anti-tumour therapy and support gut function without affecting tumour growth.[44,45]

Some randomised double-blinded controlled trials showed patients had an improved nitrogen balance, a diminished incidence of mouth pain[46] and clinical infection, lower rates of microbial colonisation, and a shorter length of stay.[47,48] Conversely, several randomised, double-blind controlled trials found oral and parental glutamine seemed to be of limited benefit.[48]

In conclusion, further studies are required to assess whether nutrition support can improve outcome by manipulation of nutrients, route of delivery, or timing of therapy.

Guideline — Nutritional support in bone marrow transplantation	Level of evidence	Refs
A study showed positive results by using enteral nutrition as a transition step from total parenteral nutrition (TPN) to oral diet.	III	42

23.3 Exercise

23.3.1 Effect of exercise on psychological and physical health

Only a small number of lymphoma patients have been included in exercise studies to date. Two small studies that included lymphoma patients have shown aerobic exercise reduced fatigue, psychological distress[49], and the loss of physical performance[50] in patients undergoing high-dose chemotherapy and stem cell transplantation.

In one study, the exercise program involved biking on an ergometer in the supine position for 30 minutes every day during hospitalisation.[49] In the other study, patients walked on a treadmill five days a week, starting shortly after completing treatment. The duration of exercise was five sessions of three minutes in the first week, working up to a single 30-minute session by the sixth week.[50]

Fatigue is common among cancer patients, and has a detrimental effect on quality of life. Exercise is currently the most promising intervention for reducing fatigue in cancer patients[51]. It may also improve psychological wellbeing.

Improvements in psychological health of cancer survivors were shown in two studies of women treated for breast cancer[52,53]. Fatigue, depression and anxiety were improved by exercising for 30 minutes a day, for 4–5 days per week.

Cancer-induced muscle wasting can occur despite adequate nutritional intake. Resistance exercise has been shown to attenuate muscle wasting in a variety of conditions such as breast cancer[54], prolonged bed rest, HIV infections, and aging.[55] In a randomised study of patients undergoing bone marrow transplant for leukaemia, fifteen repetitive resistance exercises performed up to five times per week may improve muscle mass, compared to sedentary controls.[56]

Interestingly, a randomised study of patients with a variety of cancers who underwent high-dose chemotherapy and stem cell transplantation showed a reduction in the duration of neutropenia, thrombocytopenia and hospitalisation with an aerobic exercise program.[57]

23.3.2 Prevention of co-morbidity

Exercise can also reduce co-morbidity in cancer patients because it reduces the risk of other diseases, particularly coronary heart disease, stroke, hypertension, diabetes, colon cancer and osteoporosis.[58] Both population and non-population-based studies have shown greater physical fitness is linked to longer survival.[59] Furthermore, exercise tests can be used as a predictor of survival.[60] Recent data suggest an increased level of fitness in less active subjects can improve their survival.[50]

Regular exercise can also improve mental health, prevent injury from falls in older people and help to manage arthritis. The Commonwealth Department of Health and Ageing recommends 30 minutes of moderate-intensity physical activity on most, or all days, of the week, to gain these benefits.[55]

Guideline — Exercise to prevent co-morbidity	Level of evidence	Refs
Recent data suggest an increased level of fitness in less active subjects can improve their survival.	II	50

23.3.3 Precautions

Patients should be screened for cardiopulmonary risk factors, as well as for standard disease and treatment-related toxicities, before an exercise regimen is recommended.[51] Contact sport, excessive exercise and repetitive strain should be avoided, particularly during and immediately after therapy, and in patients on high-dose or prolonged steroids, or with bone involvement.

Guideline — Exercise on psychological and physical health	Level of evidence	Refs
Regular aerobic and resistance exercises are recommended to patients.	II–III	49, 50, 56, 57

23.4 The role of psychotherapy in patient treatment

There is overwhelming evidence that some form of psychotherapy benefits patients with cancers. There are at least ten randomised studies on assessing the impact of psychotherapy on cancer patients.[61–72] Two main modalities of psychotherapy — cognitive-behaviour type and expressive-supportive group therapy — have been used in these studies. They conclusively show that such treatment improves the quality of life of the patients, but there is no conclusive evidence that this type of therapy influences patient survival. Two of these studies[64,67] involving patients with haematological malignancies, including lymphoma, showed that psychosocial intervention and compliance to treatment have a beneficial effect on patient outcome.

It is not uncommon that patients who are receiving chemotherapy or radiation treatment experience both physical and psychosocial stresses. A number of randomised trials also demonstrate the benefit of psychosocial interventions in reducing nausea and emotional distress for patients undergoing chemotherapy.[73] The interventions include: relaxation with guided imagery, behavioural treatment (systemic desensitisation), and biofeedback. Interestingly, a recent study shows that self-administered stress management during chemotherapy is more cost effective than professionally administered intervention.[74]

The concept that the mind can alter health is an extremely attractive one, as it bestows power of controlling personal destiny. Various types of mind-over-matter techniques, including psychosocial therapy, meditation, biofeedback and yoga, have been shown to reduce anxiety and to control certain physiological functions. However, as the idea that one can alter the course of cancer through mental power is not substantiated, the enthusiastic pursuit of this therapeutic goal could lead to the detrimental consequence of guilt and inadequacy in the patient.[75]

Guideline — Psychotherapy	Level of evidence	Refs
Some form of psychotherapy should be offered to patients with certain cancers because it has a positive affect on quality of life, and possibly in the overall treatment of lymphoma.	II	61–72

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CHAPTER 24 ALTERNATIVE AND COMPLEMENTARY THERAPIES

24.1 Introduction

Patients with lymphoma, in a similar way to patients with other cancers, frequently seek therapies not suggested by the treating physician. The patient's wish to seek complementary or alternative medicine (CAM) is often a manifestation of his or her desire to participate in the management of their disease. A health care professional who appreciates this patient need shows understanding, and this can enhance open communication with the patient. These therapies, in most instances, represent unproven clinical methods of treatment, and are frequently referred to as CAM. No clear definition for alternative therapies has been established[1], mainly because such therapies encompass a vast number of practices and systems of health care. In the literature, some complementary medicine practitioners attempt to distinguish between 'alternative' and 'complementary' cancer therapies.

Alternative therapy includes any unproven treatment that is promoted as a cancer cure in place of mainstream cancer care.[2,3] Recent reviews have found no evidence to support that any alternative therapy can cure cancer.[4-6] Promotion of alternative therapy thus raises certain ethical issues, such as guiding patients away from effective treatment, creating false hope, and financial exploitation.[2]

Complementary therapy is defined by those who practise in this field as treatment that complements mainstream medicine for enhancing quality of life. Some complementary therapies operate in the allopathic framework or conventional medicine; others derive from distinctly different origins and reflect concepts of health and disease that vary greatly from those of Western medicine.[7]

Several surveys involving cancer patients suggested that the most popular reason for seeking alternative or complementary therapies was to improve quality of life and to have better control of their destiny.[8] Interestingly, some studies indicate that patients seeking alternative therapies actually have a poorer quality of life.[9,10,11]

24.2 Recent trends and sociodemographic factors

By the end of the twentieth century, surveys showed that CAM treatments were used by 25–50% of the general population in industrialised nations[6,12-14], and up to 85% in the developed world.[15] In some countries, the number of visits to CAM providers was greater than the number of visits to primary care physicians.[12] This trend appears to be increasing.[16]

There are no published data on the use of CAM therapy in lymphoma patients specifically. However, large surveys of cancer patients often included a substantial proportion of patients grouped under the heading of 'haematological cancer'.[17] Patients with lymphoma or cancer of the brain/central nervous system may be more likely to seek alternative therapies.[8,18] The key predictors of alternative therapy use in Australian cancer patients appear to be younger age and marital status (positive association), and level of satisfaction with conventional treatment (negative association).[17] Other characteristics consistently reported by international and local surveys include higher income and education.[16,17,19-21] Patients frequently try multiple alternative therapies — more than 75% trying two or more.[17] In Australia, estimates of the annual national costs of CAM medicine preparations and practitioner visits exceed A$900 million.[18]

Referral is generally by family or friends, indicating that even at the end of the twentieth century, word of mouth remained the usual method of finding alternative therapy practitioners.[20] With the advent of computer technology, patients have easy access to hundreds of Internet web sites, which may change the referral pattern.

A high proportion of patients using alternative methods of treatment do not discuss this with their treating physician.[12,17] The most commonly cited reason for a patient to not disclose their alternative therapy use is that the physician did not ask.[22]

Evidence indicates CAM use is not without risks. Adverse effects ranged from 0.2% to 31%, including death.[15,22,23] Adverse effects associated with herbal remedies could be due to factors such as the properties of the herbs or contamination, misidentification, adulteration, and inappropriate advertising of products, because adherence to stringent good manufacturing practice is not required.

24.3 Evidence for CAM therapies

There is no published literature on alternative cancer therapies relating specifically to lymphoma. A review of some of the common alternative and complementary medicines is outlined below:

24.3.1 Herbal and related products

Yearly sale of herbal products is a multi-million dollar industry world-wide. Many herbal products consist of multiple compounds, and it is often difficult to define the principal active constituent(s). As these remedies are not subjected to government regulations as conventional drugs, few have been formally tested for efficacy and safety. Indeed, in some cases, the benefit and side effects may be due to more than one compound. Thus the conventional pharmacological wisdom of isolation and synthesis of (single) active ingredients is often not a viable option. Modern pharmaceutical drugs are derived from isolation of active ingredients from plants.

A few of the current herbal products consist of only a single herb. Some of these have been submitted to clinical tests. Below is an overview of herbs relating to cancer patients for which there is sufficient trial data, as well as systematic reviews or meta-analysis.[23,24]

Guideline — Herbal and related products in common use			Level of evidence	Refs
Common name	Indication	Evidence for effectiveness		
Aloe vera	Various	Poor	IV	23
Cannabis	Nausea/vomiting	Good	II*	24
Ginger	Nausea/vomiting	Encouraging	III	23
Ginseng	Various	Poor	IV	23, 25
Kava	Anxiety	Good	II	23, 25
Mistletoe	Cancer	Poor	IV	23
Shark Cartilage	Cancer	Poor	III	23
St John's Wort	Mild/moderate depression	Good	II	23, 25
Valerian	Insomnia	Encouraging	III	23

* Efficacy has only been compared to moderately effective anti-emetics.

Is there any evidence for the claim that 'natural' products are safe?

Although it is widely perceived that 'natural' products are safe, there is evidence that they can harm and that some are toxic.[11,15] The exact incidence of harm is unknown, as adverse event reports of these products are not required. In addition, the absence of guidelines and standardisation of processing, manufacturing and storage of herbal products can result in highly contaminated or toxic products.[23]

There are many reported drug interactions[6,25,26], for example:

- ginko, ginger, garlic, feverfew can interfere with anticoagulation
- ginseng can increase blood pressure (problematic, particularly in thrombocytopaenic patients)
- St John's Wort interferes with Cp450 hepatic metabolism
- Cats Claw (Uña de Gato) may reduce erythrocytes in patients receiving chemotherapy
- coenzyme Q10 increases levels of potentially toxic metabolites in patients receiving chemotherapy.

Some herbal products sensitise the skin to radiotherapy. Some interact with anaesthetics and blood pressure fluctuations. Herbs such as garlic, feverfew, ginger and ginkgo have anti-coagulant action. The risk of interaction between drugs and herbal compounds is highest for patients with renal and hepatic dysfunctions. Several Australian and overseas studies have shown the side-effects ranged from <1% to as high as 31%. Deaths have also been reported.[11,15]

24.3.2 Acupuncture

Acupuncture is one of several elements of traditional Chinese medicine.[27] This can be done by stimulation of the acupuncture points by a needle, pressure, electric current, or laser. There is a mass of literature on acupuncture. Despite several hundred clinical controlled trials, the results are often contradictory, due to study designs, sample size and other methodological challenges. Risks associated with acupuncture are rare. They include infection (problematic in pancytopaenic patients) and pneumothorax. Pain and minor bleeding at the site of insertion is a common but transient side effect.

There is good evidence for the use of acupuncture to treat nausea and vomiting (chemotherapy-induced and post-operative), as well as back pain, dental pain, and migraine.[27] However, more vigorous study comparing acupuncture with standard anti-emetics and analgesics are needed.

24.3.3 Homeopathy

Homeopathy is based on two highly controversial principles: the law of similars (i.e. like cures like), and the notion that highly 'potentised' (diluted) remedies can be effective. Controversy exists as to whether these remedies contain a single molecule of the original substance. A meta-analysis of all randomised placebo-controlled trials concluded that the clinical effects of homeopathy are not entirely due to placebo.[28] The question of whether such remedies have a place in lymphoma treatment remains unanswered.

24.3.4 Manual healing methods

There is a variety of healing approaches that involve some kind of body contact or manipulation. These include: massage, reflexology, chiropractic therapy, and aromatherapy. Small trials have been conducted that show no or doubtful benefits in alleviating cancer-related symptoms.[3,4]

24.3.5 Hypnotherapy

Several clinical trials have been conducted to assess hypnotherapy in emesis induced by cancer treatment and cancer-associated pain. A review of this topic concluded that the data are encouraging but inconclusive.[29]

24.3.6 Meditation

Meditation is a general term describing treatments in which a person empties his or her mind of extraneous thoughts. The physiological effects of meditation are those of deep relaxation. There is evidence from controlled clinical trials suggesting that meditation-induced relaxation can be used clinically to control cardiovascular risk factors and chronic pain and anxiety. This could be of benefit to cancer patients.[25] Potential adverse effects of meditation include tension, anxiety, depression and confusion. Patients with psychotic or borderline personality disorders should avoid meditation.[25]

24.3.7 Relaxation

The range of relaxation techniques makes it hard to assess efficacy of this type of therapy. However, several RCTs show some form of relaxation reduces stress and pain and improves QOL of cancer patients.[3,30] Studies are needed to identify which relaxation therapy is the effective one and how it compares with conventional treatment.

24.3.8 Spiritual healing

Spiritual healing has been defined as the direct interaction between one individual (the healer) and a patient, with the intention of improving the patient's condition or curing the illness.[31] Treatment can occur through personal contact or at a (sometimes large) distance. Variations include therapeutic touch, Reiki, faith healing, intercessory prayer. In therapeutic touch, for example, the effect is thought to result from the channelling of energy from the healer to the patient. 'Healers' suppose to sweep away energy blockage with their hands. The ability of therapeutic touch practitioners to detect energy field was disproved in a recent study.[32]

Key points:

There is no evidence that CAM practices can cure lymphoma. Natural does not always equate to harmless.

Alternative medications should be questioned when suspected drug reactions occur and included in notification reports.

Guideline — Evaluation of complementary and alternative medicine (CAM) practices and armamentarium	Level of evidence	Refs
Some herbal products sensitise the skin to radiotherapy. Some interact with anaesthetics and blood pressure fluctuations. Herbs such as garlic, feverfew, ginger and ginkgo have anti-coagulant action. The risk of interaction between drugs and herbal compounds is highest for patients with renal and hepatic dysfunctions.	IV	23
There is good evidence for the use of acupuncture to treat nausea and vomiting (both chemotherapy induced and post-operative).	II	27

24.4 Discussing CAM with the patient

Doctor–patient communication must include direct questioning and documentation, because patients may not consider natural products to be drugs.

A good knowledge of CAM allows the clinician to have frank discussions with the patient. This does not mean endorsement. It provides the opportunity to establish a good understand of the patient's needs beyond the treatment of the lymphoma, that is, caring for the patient and not just treating the disease.

Once aware of any alternative therapies, physicians can alert patients about products that are contraindicated during chemotherapy, surgery and radiotherapy, as well as the financial burden of CAM.

Physicians should show respect for the patient's beliefs and values, ensure that the patient remains involved in health care decisions, and bear in mind that patients use these therapies for a variety of reasons.

Patients need answers to questions about clinics, web sites and practitioners claiming cancer cures.

The physician must gain the patient's confidence so that the patient does not feel inhibited about discussing alternative treatments. Straightforward scientific-based information, or lack thereof, may be all the patient is seeking.

If the physician is unaware of a particular treatment, the Poisons Information Centre may be able to provide the information needed.

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CHAPTER 25 COST EFFECTIVENESS

25.1 Economic burden of lymphoma in Australia

In Australia, lymphoma is a common cancer with serious health consequences. It includes more than 20 lymphoproliferative diseases classified into two main groups, non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). In 2000, the annual incidence of all lymphomas was 18.3 per 100,000 males and 13.5 per 100,000 females, making it the sixth most common cancer for men and women.[1] For both men and women, lymphoma (all) is the sixth most common cancer, and in children aged 0–14, it is the third most common cancer.[1] Treatments for lymphoma include radiotherapy, chemotherapy, transplantation and antibody therapy.

The estimated burden of disease attributable to lymphoma in Australia is outlined in Table 25.1. Years of Life Lost (YLL) due to lymphoma are considerably higher than Years Lost due to Disability (YLD). This reflects the fact that the 'burden of cancer' is dominated by mortality rather than lengthy periods of disability'.[2]

Table 25.1 Burden of disease attributable to lymphoma in Australia, 1996

	Total		Males		Females	
	Number	Per cent	Number	Per cent	Number	Per cent
Deaths	1 595	1.2	810	1.2	785	1.3
YLL	19 535	1.4	9 848	1.3	9 687	1.6
YLD	3 915	0.3	2 116	0.3	1 799	0.3
DALY*	23 451	0.9	11 964	0.9	11 487	1.0

Source: Australian Institute of Health and Welfare[2]
* disability adjusted life years

The Australian Institute of Health and Welfare have estimated the costs of lymphoma at a macro level. In 1993–94, cancer was estimated to account for 6% of health care system costs in Australia, with lymphoma accounting for 5.5% of the cost of cancer care. It ranked sixth in terms of the most 'expensive' cancers in Australia, with total health care expenditure on lymphoma estimated at $105.7 million in 1993–94.[31] Lymphoma ranks as the fourth and fifth most costly cancer for males and females respectively aged 0–24, and the third most costly cancer for males aged 24–44.[3] Total treatment costs per case of lymphoma were estimated at A$18,519 in 1993–94, which ranks sixth in terms of the most costly cancer to treat.[3] However, there is relatively little micro-level information available in Australia about treatment patterns and resource use for lymphoma, particularly in terms of resource use by stage at diagnosis.

25.2 Economic evaluation

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences. Cost-effectiveness evaluation (CEA) is the form of economic evaluation in which the consequences of interventions, procedures or programs are measured in the most appropriate natural units, such as life-years gained, complications avoided, or cases correctly diagnosed. While many CEAs consider a single measure of output, others present an array of output or outcome measures alongside cost, allowing the decision maker to form his or her own view of the relative importance of each measure.

[1] This estimate includes hospital, medical, pharmaceuticals, nursing home and allied health services, public health programs, research, other institutional and non-institutional and administration expenditure (Mathers et al. 1999[3]).

In a cost-utility analysis (CUA), the consequences of an intervention, procedure or program are adjusted by health state preference scores or utility weights. This means that the quality of the life years gained can be assessed, which is particularly useful for interventions that extend life at the expense of side effects (such as some chemotherapy for cancer), or produce reductions in morbidity rather than mortality (such as some treatments for chronic conditions such as arthritis).

Whatever form of economic evaluation is used, an intervention, procedure or program can be considered efficient relative to the alternatives if it can be shown to produce a given level of benefit for the minimum cost.

25.3 Role of economic evidence in the development of guidelines

The NHMRC has identified two main areas where economic evidence is important in the development of clinical practice guidelines:

- determination of which treatment alternatives are the most cost effective
- determination of whether a proposed clinical practice guideline is cost effective.

In the development of these guidelines, the emphasis has been in the first instance on identifying those interventions for which there is evidence of effectiveness, before addressing questions of cost effectiveness. There is limited evidence available within Australia to assess the costs and cost effectiveness of alternatives for management of lymphoma. However, there is a range of international literature that provides information about the relative cost effectiveness of alternatives, and this information can be used to inform the development of these guidelines.

The approach taken in reviewing the economic evidence involved:

- identifying those areas where economic evidence is likely to be important
- identifying those areas where economic evaluation evidence is available
- reviewing and summarising the economic evaluation literature.

However, it is important to note that international economic evaluation literature is limited in its relevance to Australia because of differences in cost structures and reimbursement arrangements, and because the comparator in international studies may not reflect current practice in Australia.

A search was conducted using the databases Pre-Medline, Medline and Embase, covering the period 1994–April 2004. Economic evaluation literature that pre-dates 1994 was considered to be of limited relevance because of changes in technology, cost structures and management practices. The key words included *lymphoma*, *economic evaluation*, *cost-effectiveness analysis*, *cost benefit analysis*, *cost analysis* and *cost*. Articles were included if they were judged to be economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences. Articles were classified into eight main areas:

- diagnosis
- follow up
- treatment of Hodgkin's lymphoma
- treatment of low-grade non-Hodgkin's lymphoma
- treatment of aggressive and high-grade non-Hodgkin's lymphoma

- treatment of childhood lymphoma
- treatment of immunodeficiency-associated lymphoma
- treatment of non-Hodgkin's lymphoma (where type of lymphoma was not specified, or several types of lymphoma were combined in the study sample).

These groupings reflected the main areas in which economic evaluations of interventions have been undertaken.

It should be noted that of the 45 articles included in these guidelines, the majority investigated the effect of an intervention on some type of clinical outcome such as haematological engraftment, treating complications, or output, for example, length of stay (LOS). Only 13 articles investigated the effect of an intervention on outcomes such as mortality, survival, quality of life on utility (QALY), or lifeyears saved (LYS).

These 13 articles were reviewed using the criteria recommended in *How to compare the costs and benefits: evaluation of the economic evidence (NHMRC).*[4]

Table 25.2 NHMRC's criteria: Assessing evidence using shadow prices

	Ranking of evidence on effects	
Ranking of evidence on costs	High	Low
Strong	Recommend if: < $70,000 per life year Do not recommend if > $100,000 per life year	Recommend if < $30,000 per life year Do not recommend if >$70,000 per life year
Weak	Recommend if < $30,000 per life year Do not recommend if > $70,000 per life year	Recommend if < $30,000 per life year Do not recommend if >$30,000 per life year

Source: *How to compare the costs and benefits: evaluation of the economic evidence* (NHMRC)[4] Table 6.1 pg 67.

The NHMRC provides comprehensive guidelines for evaluating the economic evidence for clinical practice guidelines. The evidence on both effectiveness and costs can be compared, providing a range of possibilities shown in the Table above. The threshold cost per life year should vary with the quality of evidence. The *lower* the ranking of the evidence, the more likely the decision will be to not recommend an option where the cost per life year falls between $30,000 and $100,000.

Table 25.2 shows that 'if highly ranked evidence is available on effects and there is strong evidence on costs, then options that cost less than $70,000 per life year saved are recommended and those that cost $100,000 are rejected. Those that cost between $70,000 and $100,000 should be considered.'

'If effectiveness evidence is ranked as low and the cost evidence as weak, options that cost more than $30,000 per life year saved are rejected.'

'If neither of the above cases applies [that is, where one of the criteria (costs or effects) is weak and the other is strong], then options of less than $30,000 are recommended and those greater than $70,000 are rejected. Those that are between $30,000 and $70,000 should be considered.'[4]

Health care alternatives require further consideration if they fall between $70,000-$100,000 per life year saved and rank highly for effects and costs, or if they fall between $30,000-$70,000 per life year saved and rank highly on one but not the other. Issues that enhance the attractiveness of a health care

option and move the threshold towards a higher price include equity implications, prevention of adverse flow on effects to other sectors, rare diseases with no other health options, improvement of survival and quality of life and severe and preventable conditions.[4]

This methodology has not been applied in the development of these Guidelines. Rather, the economic information has been summarised and presented, but not graded. Hence they have not been assessed applying NHMRC's criteria and shadow prices framework.

However, assessment of overseas economic evaluations and even some Australian economic evaluations in these terms should be treated with caution. Whether these costs and outcomes would be realised if the intervention were adopted in the Australian context depends upon a number of factors, but particularly on whether the comparator for the study reflects current practice in Australia. This also applies where cost-effectiveness evaluations are made in terms of clinical comparators, as is the case in the majority of studies.

Cost effectiveness results from studies are presented as reported in the relevant studies, but also, for comparative purposes, converted to 2004 Australian dollars. The conversion was undertaken using the OECD purchasing power parity estimates (<www.oecd.org/std/ppp/>) for the relevant year of the study to convert to Australian dollars, then using the Australian Bureau of Statistics Health Price Index (weighted average of eight capital cities) (ABS, 2004; Consumer Price Index Catalogue 6401.0) to convert the relevant costs to 2004 Australian dollars. Results in terms of 2004 Australian dollars are reported in parentheses following the original results. However, in comparing across studies it should be noted that the results from different studies are not directly comparable. In particular, the scope of the studies may differ in terms of the range of costs and consequences considered, the perspective of the study, and the choice of comparator. In addition, particularly for earlier studies, there may be important changes in cost structures and technology that limit comparability. The indicative cost-effectiveness estimates in 2004 Australian dollars should be treated as providing a guide to the likely cost effectiveness of the interventions in the Australian setting.

The findings of the literature review are summarised below. In a number of studies, the subject sample involved more than one patient group. Where this has occurred, the studies have been included in each of the relative sections. Detailed results from these studies have only been given in the sections where they are first discussed. In all subsequent sections the reader is referred back to the first section in which the study is reported for the relevant results.

25.3.1 Diagnosis

There have been relatively few papers assessing the cost effectiveness of different diagnostic procedures and these are primarily related to staging.

In a German study, Klose et al. 2000[5] compared FDG-PET to CT scanning and found FDG-PET to be more accurate in the primary staging of lymphomas, with an effectiveness of 100% compared to 81.88% for CT scanning. The incremental cost-effectiveness ratio (ICER), interpreted as the additional costs of a more effective strategy per additional correctly-staged patient, was €3133 (A$5496) per correctly-staged patient. Sensitivity analysis indicated the potential for more cost saving with optimal utilisation of PET facilities. The authors concluded that the use of FDG-PET might result in cost savings because of better planning of further diagnostic procedures and of treatment. However, more research is needed to assess the long-term treatment and cost effects of more accurate staging.

A further study in the United States by Hoh et al. 1997[6] found that whole body PET-based staging, when used to guide further conventional diagnostic strategies, is cost effective compared to current conventional staging. It may reduce the total cost of staging work by focusing procedures only to necessary regions. Accurate staging was performed in 17 of 18 patients using whole body PET, compared to 15 of 18 with conventional methods. PET correctly increased the stage in 17% of

patients. The total cost of PET was US$37,850 (A$67,915) compared to US$68,192 (A$122,358) for conventional staging.

In Japan, Kosuda et al. 2003[7] conducted a study investigating the diagnostic impact of combined ^{201}T1 and ^{67}Ga brain SPECT on the management of patients suspected of having central nervous system (CNS) lymphomas. They found that it was useful for differentiating CNS lymphomas or germinomas from other cerebral tumours, and that it could potentially determine whether patients have stereotactic biopsy or craniomotomy. Expected cost savings in the 1–50% range of pretest probability of CNS lymphoma or germinoma would be from minus US$842 (A$1342) to plus US$2047 (A$3263) per patient, indicating it would be cost effective only in patients highly suspected of having CNS lymphoma or germinoma.

The studies are limited in that they rely on estimates of sensitivity and specificity of PET based on small sample sizes rather than randomised controlled trials. Results should be used as an indication of the costs and cost effectiveness of the alternative interventions only.

25.3.2 Follow up

Only one study evaluating follow-up strategies was identified and involved a basic costing comparison conducted in the United States. Edelman et al. 1997[8] compared the costs of utilising a literature-supported suggested follow-up regimen, developed by the authors, with current typical follow up for patients with HD and NHL. The total cost of follow up was obtained by first multiplying the number of patients at risk each year by the cost of follow up for that year. The cost was then calculated from the sum of all years (five) of follow up. The number of patients at risk in the first year of follow up was obtained by multiplying the number of patients with the disease by the percentage anticipated to achieve complete remission. For subsequent years, the relapsed patients in the preceding years were subtracted.

They found that for both patient groups, the cost of the literature-supported strategy — US$900,000 (A$1.7M)/1000 HD pts and US$500,000 (A$900,000)/1000 NHL pts — was lower than for current typical follow up — US$1.4M (A$2.6M)/1000 HD pts and US$1.8M (A$3.4M)/1000 NHL pts. However, a number of assumptions were made in this study. First, follow-up testing would only be obtained during periods of maximal risk of recurrence. Second, the rate of recurrence would be constant over the study period. Third, there would be no further surveillance testing after the study period. Fourth, all stage I and II HD patients would receive radiation therapy as part of their treatment and require routine thyroid testing. Further, as no sensitivity analysis was conducted, the results should be viewed with caution.

25.3.3 Treatment of Hodgkin's disease

A number of studies have evaluated costs and outcomes and cost effectiveness of various treatment alternatives. In the main, these studies have been conducted using specific patient groups and will be discussed accordingly.

Relapsed, refractory, resistant, progressive or poor/slow responding patients

Several studies investigating costs and outcomes have been undertaken since 1994, although there is considerable variation in terms of treatments evaluated, evaluation type, and the trial and other data used to evaluate effectiveness. The majority of studies were cost and outcome studies, with only one cost-effectiveness evaluation. The results are summarised in Table 25.3.

In general, these studies indicate that blood stem cell transplantation may result in better clinical and quality of life outcomes at lower costs than bone marrow transplantation. Some chemotherapy regimens also appear to result in better clinical outcomes and cost savings. The only cost-effectiveness study conducted indicated that the cost effectiveness of high-dose chemotherapy (HDC) is below the A$30,000 per-life-year-gained threshold. The use of granulocyte colony-stimulating

factor (G-CSF) in addition to either transplantation or chemotherapy appears to be clinically effective and cost saving.

As these studies evaluate different treatment approaches and are predominately cost and outcome evaluations, it is not possible at this stage to recommend any one treatment over another on the basis of cost effectiveness. At best, the studies provide an initial indication of possible cost savings for certain treatment options.

Table 25.3 Results of studies investigating costs and outcomes of alternative treatments for relapsed, refractory, resistant, progressive, or poor/slow responding patients

Study	Country	Study question	Conclusion
Vellenga et al. 2001[9]	The Netherlands	Comparison of PSCT versus ABMT transplantation for relapsed/poorly responding patients	PSCT results in significantly better clinical outcomes (faster engraftment, fewer transfusions), less supportive care requirements, and better reported QoL. PSCT is more cost effective than ABMT, with total transplantation costs of US$13,954 (A$22,724) versus US$17,668 (A$28,772).
Van Agthoven et al. 2001[10]	The Netherlands	Comparison of PBPCT versus ABMT transplantation for chemo-refractory or relapsed patients	PBSCT is associated with better QoL and lower costs. The average total treatment costs were €22,560 (A$38,721) versus €28,428 (A$48,792), a relative cost advantage of 21%.
Tarella et al. 1998[11]	Italy	Comparison of PBPCT transplant + G-CSF versus PBPCT alone for relapsed patients	PBPCT + G-CSF significantly accelerated haematological recovery, significantly reduced incidence and severity of fever and infectious complications, and significantly reduced post-transplant hospital days. Average treatment cost for PBPCT + G-CSF was US$3627 (A$5906) lower than for PBPCT alone — US$18,241 (A$29,705) versus US$21,868 (A$35,611).
Smith et al. 1997[12]	USA	Comparison of PBPCT transplant + filgrastim versus ABMT transplant for relapsed patients	PBPCT + filgrastim is safe and more effective than ABMT and represents significant cost savings. It resulted in similar short-term survival, significantly better haematological recovery, LOS and lower total costs — US$45,792 (A$85,502) versus US$59,314 (A$110,750). Sensitivity analysis confirmed the robustness of the results.
Mazza et al. 1999[13]	Italy	Comparison of HDC + PBPCT transplant in non ICU setting versus ICU setting	HDC + PBPCT in a non ICU setting resulted in an overall response rate of 71%, and treatment-free rate (3–27mth) of 56%. At a mean cost of US$18,092.60 (A$29,463), the procedure is affordable without strict ICU-setting precautions.
Bennett et al. 1995[14]	USA	Assessment of cost of care and outcomes for HDC + ABMT or PBSCT over time for relapsed or refractory patients	Survival rates improved and cost of care decreased over time. The most significant factor for survival was the experience of the transplant team. Costs decreased at a rate of 10% per annum.

Beard, Lorigan and Sampson 2000 [15]	UK	Comparison of HDC versus Std chemotherapy for relapsed patients	HDC is clinically and cost effective. Additional life years gained were 1.1 (trial data) and 5.5 (20yr projection). Cost/LYG were £12,636 (A$31,159) (trial data) and £2527 (A$6231) (20yr projection). Sensitivity analysis shows that cost effectiveness remains under £25,000 (A$61,648)/LYG even when the marginal cost of HDC is increased to £20,000 (A$49,318).
Dranitsaris and Sutcliffe 1995[16]	Canada	Comparison of miniBEAM chemotherapy + G-CSF versus miniBEAM alone for patients with progressive disease	G-CSF reduced LOS and hospital, antibiotic and management costs. Total costs were CAN$4682.08 (A$8124.86) versus CAN$4753.54 (A$8248.86), a saving of approx CAN$1580 (A$2742) for hospitalisation and CAN$70 (A$121) when the cost of G-CSF is included.

Patients in remission

Only one paper was identified that specifically evaluated the cost effectiveness of treatments for patients in remission. Faucher et al. 1994[17], in a French cost-effectiveness analysis, compared transplantation methods with or without G-CSF. They found that PBPCT plus G-CSF had significantly better clinical outcomes (shorter engraftment rate and better haematological recovery), shorter LOS (15 versus 20 versus 20 days), and lower cost — US$197.7 (A$450.4) versus US$255.2 (A$581.3) versus US$245.1 (A$558.3) — than ABMT plus G-CSF or ABMT alone.

Cost effectiveness, evaluated in terms of haematological recovery, was in favour of PBPCT plus G-CSF. The cost-effectiveness ratios (CERs) for granulocyte and platelet recovery were US$9360 (A$21,232) and US$14,830 (A$33,783) for PBPCT plus G-CSF, versus US$11,450 (A$26,083) and US$21,550 (A$49,092) for ABMT +G-CSF, versus US$13,350 (A$30,412) and US$22,220 (A$50,618) for ABMT alone. The results of sensitivity analysis did not affect the findings.

This study provides some evidence that PBPCT plus G-CSF may be cost effective, but additional evidence from further research is needed before a definitive recommendation can be made.

Patient status not specified/varied

Three cost and outcome studies compared different transplantation methods with or without G-CSF. The results are summarised in Table 25.3. As the transplantation methods (and/or the use of G-CSF or IL-3) compared were different for each of the studies, it is not possible to recommend one method over another and the results should be used as an indication only.

Table 25.4 Results of studies investigating costs and outcomes of alternative treatments/interventions for patients where studies do not specify status or where patients of varied status are included in the study sample

Study	Study country	Study questions	Conclusion
Souetre, Quing and Penelaud 1996[18]	France	Comparison of ABMT transplant +G-CSF versus ABMT alone	Use of G-CSF is associated with improved therapeutic efficacy (reduced length/severity of infection, neutropenia, mucosity) LOS, and a moderate reduction in direct medical costs. Av. total cost/patient was US$43,341 (A$92,602) versus US$44,656 (A$95,412), a saving of US$1315 (A$2810). Sensitivity analysis indicates the evaluation is robust.
Luce et al. 1994[19]	USA	Comparison of ABMT transplant +GM-CSF versus ABMT alone	Use of GM-CSF resulted in lower costs — US$70,300 (A$150,303) versus US$82,500 (A$176,270) — a saving of US$12,200 (A$26,067), mainly due to difference in initial hospitalisation (21% lower than for no GM-CSF). (Note: This study was retrospective and no efficacy data were included.)
Uyl-de-Groot, Huijgens and Rutten 1996[20]	The Netherlands	Comparison of transplant methods with or without G-CSF (review) PBPCT versus ABMT PBPCT versus ABMT PBPCT versus ABMT + G-CSF	PBPCT resulted in improved efficacy and reduced hospital costs. Treatment costs were 15–30% lower than for ABMT — US$19,770–$21,809 (A$45,037–49,682) (PBPCT) versus US$23,290–30,592 (A$53,055–69,690) (ABMT) versus US$24,140–32,443 (A$54,992–73,906) (ABMT + G-CSF). Sensitivity analysis indicates the dominance of PBPCT is robust.
Schulman et al. 1998[21]	USA	Comparison of ABMT transplant + CM-CSF +IL-3 versus ABMT transplant + CM-CSF	For patients undergoing bone marrow transplant, Il-3 + CM-CSF resulted in no significant clinical or survival benefit (survival probability of 78% versus 76%) compared to CM-CSF alone. There was no significant effect on costs — US$89,651 (A$167,395) versus US$79,892 (A$149,173) — or quality-adjusted life-months (QALM) (6.26 mths versus 6.57mths) during the 13-month study period.

25.3.4 Treatment of low-grade non-Hodgkin's lymphoma

A number of studies have been undertaken evaluating costs and outcomes, and cost effectiveness of various chemotherapy treatments and the management of complications resulting from treatment. A further study investigated the effect of setting on treatment cost.

Chemotherapy

A few studies were found that evaluated costs and outcomes of different chemotherapy regimens or agents. Only one of these was a cost-effectiveness study. The others only compared costs and clinical outcomes.

Wirt et al. 2001[22], in a combined French and United States study, used a Markov model to compare the cost effectiveness of CHVP+interferon alfa-2b with CHVP alone. They found that the addition of low-dose interferon is cost effective, with a marginal cost effectiveness of US$16,900 (A$28,961)/QALY (simple model), and US$17,049 (A$29,217)/QALY (two-stage model). Sensitivity analysis showed that the results were robust, and the marginal cost effectiveness to be best expressed in the range of US$12,000–$17,000 (A$20,564–$29,133)/QALY.

A United Kingdom study by Sweetenham et al. 1999[23] compared the cost and clinical outcomes of CHOP, fludarabine and rituximab, and found rituximab to have similar efficacy but fewer adverse events (AE) and lower total cost than the other interventions. The total AE-related treatment costs per patient were £5049 (A$12,450) (CHOP), £2953 (A$7282) (fludarabine) and £109 (A$269) (rituximab). The total treatment costs per patient were £7210 (A$17,779) (CHOP), £10,022 (A$24,713) (fludarabine) and £6080 (A$14,993) (rituximab), with sensitivity analysis ranges of £5892–6267 (A$14,529–15,454) (rituximab), £5975–8445 (A$14,734–20,825) (CHOP) and £8917–1126 (A$21,989–7436) (fludarabine).

A review by Wake et al. 2002[24] concluded that rituximab appears to be clinically effective, with lower overall treatment cost due to fewer adverse events. However, they concluded that the extent to which beneficial effects are outweighed by adverse events is impossible to quantify, and that the absence of direct comparative data makes it difficult to assess whether the ratio of benefits to disbenefits with rituximab is better, worse or the same as currently used alternatives.

In Germany and Switzerland, Herold and Hieke 2002[25] compared the costs of toxicity for CHOP, COP/CVP and fludarabine in Canada, Germany and Italy. In Canada, all three regimens were compared; in Germany, CHOP and COP/CVP were compared; and in Italy, CHOP was compared with fludarabine. Results indicated that toxicity costs were substantial for all regimens and are likely to be substantial cost drivers. In Canada, CHOP-associated AE costs — €5.036 (A$7.824) — were higher than for COP/CVP — €3.252 (A$5.052) — and fludarabine — €1.273 (A$1.978). In Germany, CHOP-associated AE costs — €2.515 (A$3.907) — were comparable to COP/CVP — €2.658 (A$4.130). In Italy, CHOP-associated AE costs — €2.179 (A$3.385) — were considerably less than for fludarabine — €4.908 (A$7.625). Neutropenia and fever/infection were the most common and most expensive AEs to treat. The costs for chemotherapy-associated neutropenia and fever/infection for each of the regimens were as follows: in Canada, CHOP — €3.873 (A$6.017) — was higher than COP/CVP — €1.452 ($2.256) — and fludarabine — €1.149 (A$1.785); in Germany, CHOP — €0.9420 (A$1.463) — was lower than COP/CVP — €1.429 (A$2.220); and in Italy CHOP — €1.625 (A$2.525) — and fludarabine — €1.655 (A$2.571) — were comparable. Sensitivity analysis indicated that the results were robust.

Although these studies indicate that some regimes or agents appear to be relatively more cost effective or cost saving, at this stage there is insufficient evidence to recommend one regime or agent over others on the basis of cost effectiveness. It should also be noted that extrapolating these results to the Australian context is not appropriate, as relative cost effectiveness is driven largely by the costs of the different chemotherapy regimes and modes of delivery, which can vary internationally.

Setting

Mazza et al. 1999[13], in an Italian study, investigated the effect on costs and outcomes when patients receiving HDC plus PBPC transplantation were treated in a non-ICU instead of the usual ICU setting. For information on the results of this study, see Section 25.3.3.

Managing complications in advanced-stage patients

One Canadian study by Bobey and Woodman 1998[26] used predictive modelling to assess the potential cost effectiveness of combination chemotherapy plus G-CSF compared to combination chemotherapy alone. The results showed that with combination chemotherapy, 19% of advanced-stage patients experienced febrile neutropenic events, and 43% required chemotherapy dose modifications. The

authors also found that 36% of patients could be identified as high risk for neutropenic complications and that administration of G-CSF for high-risk patients resulted in an estimated incremental cost per life-year-saved of CAN$3300 (A$4446). While these results suggest potential cost effectiveness, recommendations cannot be based on the findings of only one study. The findings should be taken as indicative of potential cost savings, with further research required.

25.3.5 Treatment of aggressive and high-grade non-Hodgkin's lymphoma

A number of studies have been undertaken evaluating costs, costs and outcomes and cost effectiveness of various treatment alternatives. In the main, these studies have been conducted using specific patient groups. They will be discussed accordingly.

Newly diagnosed patients

One Dutch study was identified that investigated the costs of treatment. This was a costing comparison by Van Agthoven et al. 2002[27], who compared the cost of CHOP-like chemotherapy according to trial protocols[2] with standard local practice (SLP). The results indicated that the costs for the trial protocols are comparable to those for SLP. Total costs (for diagnosis, treatment and follow up) were Prot1-yng — €16,901 (A$29,008); Prot2-yng — €19,136 (A$32,844); SLP-yng — €16,064 (A$27,572); Prot-eld — €20,296 (A$34,835); SLP-eld — €16,587 (A$28,469). This study provides basic information. It does not allow for definite conclusions, but may suggest cost savings with trial regimens. It is not known whether the findings can be extrapolated into the Australian context.

Relapsed, refractory, resistant, progressive or poor/slow responding patients

A number of studies evaluating cost effectiveness and costs and outcomes have been undertaken since 1994. These are, however, varied in relation to the treatments evaluated, evaluation type and the trial and other data used to evaluate effectiveness. Only two of the studies were cost-effectiveness evaluations. The majority were cost and outcome studies. The results are summarised in Table 25.5.

The findings from the studies generally indicate that blood stem cell transplantation may result in better clinical and quality of life outcomes at lower cost than bone marrow transplantation, and that some chemotherapy regimens appear to be more clinically effective at lower cost. The cost-effectiveness studies indicate that both HDC and HDC plus ABMT have a cost-effectiveness ratio below the A$30,000 per life-year-gained threshold.

However, because of the variation in the treatments evaluated, the approaches used, and the difficulty in extrapolating results to the Australian context due to international variation in treatment delivery mode, at this stage it is difficult to recommend potential cost effectiveness of any one treatment over another. At best, the studies provide an initial indication of possible cost savings for particular treatment options.

[2] The trial protocols consisted of Prot1-yng (8x CHOP q 3wk or 6 x CHOP q2wk plus G-CSF), Prot2-yng (8 x (q 3 wk, CHVmP on day 1m BV on day 15) for patients under 65 years of age and Prot-eld (6 or 8 x CHOP q 3wk +G-CSF) for patients over 65 years of age. The Standard local practice treatments consisted of (6 or 8 x CHOP q 3wk).

Table 25.5 Results of studies investigating costs and outcomes of alternative treatments for relapsed, refractory, resistant, poor/slow responding patients or poor mobilisers

Study	Study country	Study questions	Conclusion
Vellenga et al 2001.[9]	The Netherlands	PSCT versus ABMT for relapsed/poorly responding patients	See Section 25.3.3.
Van Agthoven et al. 2001[10]	The Netherlands	PBPCT versus ABMT for chemo-refractory or relapsed patients	See Section 25.3.3.
Beard, Lorigan and Sampson	UK	HDC versus Std chemotherapy for relapsed patients	See Section 25.3.3.
Messori et al. 1997[28]	Italy	Comparison of HDC + ABMT transplant versus Std salvage chemotherapy for relapsed patients	Cost effectiveness of ABMT is very favourable, with an ICER of US$9229 (A$16,660)/discounted LYG — 95% CI of US$5390–24,012 (A$9671–$43,085), and US$4623 (A$8295)/undiscounted LYG — 95% CI of US$4297–19,138 (A$7710–34,340). Sensitivity analysis confirmed upper limits always below cut off line of US$50,000 (A$89,716) (Note: Study sample comprised highly selected pts and effectiveness data were obtained from different studies.)
Uyl-de-Groot, et al[29]	The Netherlands	Comparison of CHOP chemotherapy + ABMT transplant versus CHOP alone for slow responders to CHOP	Despite no significant difference in complete remission, overall disease-free survival or long-term QoL, cumulative costs for ABMT are significantly higher. Av. treatment cost of ABMT is significantly more — US$34,445 (A$78,467) versus US$3118 (A$7103). Long-term costs of ABMT are US$34,580 (A$78,774) more expensive. ABMT patients experienced .14LY and .22 QALY less than CHOP patients.
Uyl-de-Groot et al. 1995[29]	The Netherlands	Comparison of chemotherapy + ABMT transplant versus chemotherapy alone for relapsed patients	Cost of chemotherapy ranges from US$3120–12,900 (A$7107–29,387). Total ABMT cost is US$40,220 (A$91,623). Average cost of introducing ABMT in to the Netherlands is US$27,410–$37,100 (A$62,441–$84,515)/patient.
Stockerl-Goldstein et al. 2000[31]	USA	Comparison of chemotherapy + transplantation for good mobilisers versus poor mobilisers	Total cost was significantly higher for poor mobilisers, but there was no significant difference in survival or relapse. Total costs for bone marrow-related care/patient were US$140,264 (A$246,852) for poor mobilisers versus US$80,833 (A$142,559) for good mobilisers.

Mazza et al. 1999[13]	Italy	HDC+PBPCT in non ICU setting versus ICU setting	See Section 25.3.3.

Patients in remission

Two studies were found that investigated the costs and outcomes of several different treatment methods. In a French study, Limat et al. 2000[32] investigated the effect of cell dose on the cost and consequences of PBSCT. They found that CD34+ cell dose >5 x 10^6 appears to be optimal clinically and economically compared to cell dose <5 x 10^6. The higher cell dose resulted in significant earlier engraftment, with a total cost saving of US$4210 (A$7409). The cost savings were principally related to reduction in hospital stay — US$3010 (A$5297) — and number of transfusions — US$815 (A$1434). Sensitivity analysis showed the analysis was robust and that infusion of cell dose >5 x 10^6 would result in cost savings of more than US$2750 (A$4840). This study provides some evidence that higher cell dose may result in cost savings, but more evidence is required.

In Belgium, Van Tiggelen et al. 1999[33] conducted an exercise comparing the effectiveness and costs of three treatment options: methotrexate plus CVB chemotherapy plus ABMT, induction chemotherapy plus LNH84, and CHOP. They concluded that CHOP — 2060 to 2745 ECU (A$4440–5916) — is less costly than induction chemotherapy plus LNH84 — 7232 ECU (A$15,587) — or chemotherapy plus ABMT — 19,262 ECU (A$41,515), yet as effective. This was, however, a basic costing study using effectiveness results from previous studies and applying expected costs to the treatments considered. The results need to be viewed with caution.

Patients with a poor prognosis

Only one study evaluating treatment methods was identified. A cost and outcomes study conducted by Lee et al. 1998[34] in the United Kingdom compared PBPC transplantation plus G-CSF (following high-dose chemotherapy) with PBPC transplantation alone. The results indicate that the use of G-CSF leads to more rapid haematological recovery and is associated with more predictable and shorter hospital stays. Despite the additional cost of G-CSF, there was no increase in overall health care expenditure but a trend towards reduced expenditure. The mean expenditure per inpatient stay was £6500 (£5465–8101) (A$16,967 — $14,265–$21,146) for the PBPC plus G-CSF group compared to £8316 (£5953–15,801) (A$21,707 — $15,539–41,245) for the PBPC alone, a mean saving of £1816 (A$4740) per patient. This study provides some evidence of cost saving, but more evidence is required.

Managing complications in advanced-stage patients

For information on studies in this area see Section 25.3.4.

Patient status not specified

Two studies evaluating treatment methods were found. A French cost and outcome study by Limat et al. 2000[35] investigated the effect of cell dose on the cost and consequences of PBSCT. They compared CD34+ cell dose >5 x 10^6 with CD34+ cell dose ≤5 x 10^6, and found that CD34+ cell dose >5 x 10^6 leads to increased hematopoietic engraftment with consequent cost savings. There was a large reduction in procedure costs — US$2740 (A$4279) or 11% — directly related to hospitalisation — US$680 (A$1062) — and the number of platelets transfused — US$1340 (A$2043). Sensitivity analysis indicated that the results are robust.

In a United Kingdom study, Hackshaw, Sweetenham and Knight 2004[36] compared chemotherapy plus G-CSF with chemotherapy alone. They undertook a meta-analysis of six randomised and one non-randomised trial to determine the effectiveness of the treatments, and conducted a simple cost-effectiveness analysis. Results showed that the inclusion of G-CSF was associated with a significant reduction in the incidence of severe neutropenia (44%) and in patients with clinically relevant infections, but there was no evidence of an effect on remission rates or survival. The cost-

effectiveness model indicated that a relatively large proportion of patients need to be hospitalised several times in the absence of G-CSF for routine G-CSF to become cost effective. For instance, if 15% of patients were each hospitalised twice during their course of treatment, G-CSF would have to be purchased at a cost 85% lower than the list price; if 45% of patients were each hospitalised five times during treatment, no reduction in the purchase price is required for the cost to the health service to be less than the cost of using it. They concluded that given the current cost of G-CSF, it would only be cost effective among patients for whom high rates of hospital stay due to neutropenia or infection are expected. However, extrapolating these findings to the Australian context may not be appropriate.

Older patients

Only one cost and outcomes study was identified that evaluated treatments in this population. An Italian study by Zagonel et al. 1994[37] compared chemotherapy plus G-CSF with chemotherapy alone. They found that overall response rates, percentage of complete remissions, and incidence of chemotherapy-related side effects (neutropenia and related infections) were comparable. There was, however, significantly less chemotherapy delay, duration of delay, and infection-related hospital days, with consequent lower costs in the G-CSF group — 8440.97 ECU (A$26,215.34) versus 13,300.98 ECU (A$41,309). The authors concluded that G-CSF for older patients, at high risk of prolonged hospitalisation due to neutropenia and/or fever, appears safe and cost effective. However, the sample size in this study was very small and there was limited information on pricing, so the results need to be viewed with caution.

25.3.6 Treatment of childhood lymphoma

Economic analyses of treatments for childhood lymphoma have concentrated on interventions aimed at treating or preventing complications resulting from treatment. The majority of the studies have been cost and outcome studies, with only one cost-effectiveness study identified. The results are summarised in Table 25.6.

In general, the studies suggest that the use of G-CSF does not appear to be cost saving, although G-CSF administration, based on individual timing of blood count, that is, blood counts measured at times individual to each patient and depending on their neutrophil count and the duration of previous cycles of G-CSF, may have an effect. Ceftriaxone plus amikacin may be cost saving and rasburicase appears to be cost effective for prevention and treatment.

It is not possible to recommend any one treatment over another as the studies evaluate different treatment approaches and are predominately cost and outcome studies. At best, the studies provide an initial indication of possible cost savings for certain treatment options.

Table 25.6 Results of studies investigating costs and outcomes of interventions/treatments aimed at treating or preventing treatment complications

Study	Study country	Study questions	Conclusion
Rubino et al. 1998[38]	France	Comparison of chemotherapy + G-CSF versus chemotherapy alone for prevention/ treatment of febrile neutropenia	No significant difference in clinical endpoints. Treatment cost with G-CSF — US$29,675 (A$53,247) — was lower than the cost without G-CSF — US$30,774 (A$55,218). Sensitivity analysis showed no difference in results.
Bennett et al. 2000[39]	USA	Comparison of chemotherapy + G-CSF versus chemotherapy alone for prevention/ treatment of neutropenia	Despite better clinical outcomes, there was no significant difference in overall resource use and costs — US$34,190 (A$55,677) with G-CSF versus US$28,653 (A$46,660) without). Sensitivity analysis confirmed the findings.
Ammann et al. 2002[40]	Switzerland	Comparison of G-CSF using individual timing of blood count versus standard twice weekly treatment	Individual timing resulted in a clinically relevant and significant reduction in the number of G-CSF injections and blood counts, with consequent less pain and lower costs (reduction of US$152 (A$260)/cycle).
Annemans et al. 2003[41]	Belgium, UK, Spain, The Netherlands	Comparison of rasburicase versus no rasburicase for prevention and treatment of hyperuricaemia and tumour lysis syndrome	Rasburicase is highly cost effective for the prevention of hyperuricaemia and tumour lysis syndrome in all countries — ICER €425–1710 (A$982–2780)/LYS. Treatment is cost saving (authors stated that results not shown because for cost saving strategy, figures are not informative). Sensitivity analysis shows the results are robust.
Pession, Prete and Paolucia 1997[42]	Italy	Comparison of ceftriaxone + amikacin versus ceftazidime for treatment of febrile granulocytopenic children	Ceftriaxone + amikacin is as effective, but is associated with a more favourable cost-benefit ratio. Extrapolated from a previous study, the savings for single treatment (1 and 6 day) are US$11 and $65.60 (A$20 and $117.70). Applied to the study sample of 183 pts, the cost reduction for antibiotics and injection material would be US$12,009 (A$21,548).
Castagnola et al. 1999[43]	Italy	Comparison of ceftriaxone + amikacin versus ceftazidime for treatment of febrile granulocytopenic children	Ceftriaxone + amikacin is effective in 72% patients and is associated with cost savings. Extrapolated from a previous study, the savings for single treatment (1 and 6 day) are US$11 and $65.60 (A$20 and ($117.70).

25.3.7 Treatment of immunodeficiency-associated lymphoma

Only one relatively old study was found that investigated the costs and outcomes of treatments in this area. Tirelli and Vacher 1994[44], in a small, one-centre, United States study, evaluated the economic and clinical benefits of the prophylactic use of G-CSF following chemotherapy. They found that the use of G-CSF was associated with a significant reduction of treatment-related myelosuppression

(mean duration of nadir was 8.4 days compared to 10.8 days for the control group), resulting in shorter hospitalisation and a decrease in the overall cost of treatment, although not significant. The total cost of treatment with G-CSF was US$2282 (A$4578) compared to US$3232 (A$6480) for patients treated with chemotherapy alone. However, as this is a relatively old study, conducted with a sample of consecutive patients at a single institution, the results should be viewed with caution and should only be considered as an indication of possible cost saving.

25.3.8 Treatment of non-Hodgkins's lymphoma (where type of lymphoma has not been specified or several types of lymphoma were combined in the study sample)

A number of studies have been undertaken evaluating costs and outcomes and cost effectiveness of various treatment alternatives. In the main, these studies have been conducted using specific patient groups and will be discussed accordingly.

Relapsed, refractory, resistant, progressive or poor/slow responding patients

Although several studies investigating cost and outcomes have been undertaken since 1994, there is considerable variation in terms of treatments evaluated, and the trial and other data used to evaluate cost effectiveness. All of the studies were cost and outcome studies. The results are summarised in Table 25.7.

It appears that blood stem cell transplantation may result in improved clinical outcomes at lower cost and that the use of G-CSF, either with transplantation or chemotherapy, is clinically and cost effective. Some chemotherapy regimens may also result in better clinical outcomes and cost savings.

However, as these studies are only cost and outcome studies, and all evaluate different treatments, it is not possible to recommend one treatment over another. The studies do, however, give an indication of possible cost savings.

Table 25.7 Results of studies investigating costs and outcomes of alternative treatments for relapsed, refractory, resistant or poor/slow responding patients

Study	Study country	Study question	Conclusion
Uyl-de-Groot et al. 1999[45]	The Netherlands	Comparison of PBPCT transplant + filgrastim versus ABMT transplant	It appears that PBPCT + filgrastim is more cost effective than ABMT. PBPCT + filgrastim resulted in significantly accelerated granulocyte recovery and lower cost — US$16,890 (A$31,537) versus US$20,713 (A$38,675), an implied cost reduction of 18%.
Tarella et al. 1998[11]	Italy	PBPCT + G-CSF versus PBPCT (relapsed)	See Section 25.3.3.
Smith et al. 1997[12]	USA	PBPCT+ filgrastrim versus ABMT (relapsed)	See Section 2.3.3.
Jerjis et al. 1999[46]	The Netherlands	Comparison of APSCT versus ABMT transplantation	APSCT results in improved haematological recovery, less supportive care needs (less fever, transfusions, and medications) and significant cost savings — 34,178 NLG (A$61,650) versus 43,469 NLG (A$78,410).
Bennett et al. 1995[14]	USA	Assessment of cost of care and outcomes for HDC + ABMT or PBSCT over time for relapsed or refractory patients	Survival rates improved and cost of care decreased over time. Most significant factor for survival was the experience of the transplant team. Costs decreased at a rate of 8% per annum.
Dranitsaris and Sutcliffe 1995[16]	Canada	miniBEAM+ G-CSF versus miniBEAM (progressive)	See Section 2.3.3.
Souetre and Quing 1994[47]	France	Comparison of lenograstim versus none for treating complications	Lenograstim is associated with a reduction of total direct medical costs as a result of reduced morbidity and shorter LOS for reasons other than chemotherapy. Total cost was FF115,534 versus FF122,831 (A$255,064 versus $271,175), a reduction of FF7297 (A$16,110). Sensitivity analysis varying per diem room costs support the findings of cost savings — cost savings of FF3667–16,377 (A$8096–36,156).

Patients in remission

For information on studies in this area see Section 25.3.3.

First-line therapy

A French cost and outcome study by Woronnoff-Lemsi et al. 1997[48] compared PBPCT with ABMT transplantation and found that PBPCT resulted in significantly better engraftment, fewer days of intravenous antibiotics, fewer transfusions, and shorter LOS. Overall costs for PBPCT — US$35,381 (A$70,939) — were less than for ABMT — US$41,759 (A$83,726) —a saving of US$6378

(A$12,788). Sensitivity analysis indicated that the results are robust. This study provides some evidence of cost saving, but more evidence is required.

Patient status not specified/varied status

Several studies evaluating different treatments have been identified, although there is considerable variation in terms of treatments evaluated and evaluation type. These include one cost-effectiveness study and one cost-benefit analysis, with the remainder being cost and outcome studies. The results are summarised in Table 25.8. As the treatments evaluated were all different, it is not possible to recommend one method over another. The results should be used as an indication of the effect of interventions on costs and outcomes only.

Table 25.8 Results of studies investigating costs and outcomes of alternative treatments/interventions for patients where studies do not specify status or where patients of varied status are included in the study sample

Study	Study country	Study questions	Conclusion
Souetre, Quing and Penelaud 1996[18]	France	ABMT+ G-CSF versus ABMT	See Section 25.3.3.
Luce et al. 1994[19]	USA	ABMT + GM-CSF versus ABMT alone	See Section 25.3.3.
Uyl-de-Groot, Huijgens and Rutten 1996[20]	The Netherlands	Review — PBPCT versus ABMT, PBPCT versus ABMT+G-CSF	See Section 25.3.3.
Schulman et al. 1998[21]	USA	ABMT + CM-CSF + IL-3 versus ABMT + CM-CSF	See Section 25.3.3.
Dranitsaris, Altmayer and Quirt 1997[49]	Canada	Comparison of chemotherapy + G-CSF versus chemotherapy alone	Administration of G-CSF dosage 5 *ug*/kg/day for 11 doses following CHOP resulted in an overall net cost of CAN$1257 (A$1920), which is close to cost neutrality. Sensitivity analysis shows a dose reduction to 2 *ug*/kg/day would result in a net benefit of CAN$6564 (A$10,025), which is a societal cost saving. Cost-benefit analysis resulted in an institutional cost saving (neutropenic events avoided) of CAN$5007 (A$7647), and a societal cost saving (lost production avoided) of CAN$8016 (A$12,243).
Elting et al. 2003[50]	USA	TCP versus control cycle	Incremental cost attributed to thrombocytopenia is US$1037 (A$1825). However, only 40% of cycles were considered high/very high cost. Interventions targeted at this subset would significantly reduce the cost of thrombocytopenia.

Study	Study country	Study questions	Conclusion
Annemans et al. 2003[41]	Belgium, UK, Spain, The Netherlands	Comparison of rasburicase versus no rasburicase for prevention and treatment of hyperuricaemia and tumour lysis syndrome	Rasburicase is cost effective for the prevention of hyperuricaemia and tumour lysis syndrome in all countries — ICER = €30650–41383 (A$67,273–70,858/LYS). For treatment, it is highly cost effective — ICER = -€9776–2059 (-A$22,600–3347). Sensitivity analysis indicates that for prevention, it is sensitive to the risk of hyperuricaemia and tumour lysis.

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CHAPTER 26 LATE BREAKING DEVELOPMENTS: IMPACT OF ANTI-CD20 MONOCLONAL ANTIBODIES ON LYMPHOMA THERAPY

26.1 Introduction — rituximab

Subsequent to the completion of drafts for the guidelines earlier in 2004, several important studies in both low-grade and aggressive lymphomas have been published, either in full or at the American Society of Haematology (ASH) meeting in December 2004. These revolve in particular around the use of the chimeric human-mouse anti-CD20 monoclonal antibody (rituximab, MabThera). This is a human immunoglobulin antibody with variable regions isolated from a murine anti-CD20 monoclonal antibody. Its use is described in Chapters 12 and 13. It has been studied extensively in vitro and is able to lyse CD-20 positive cells by complement activation or antibody-dependent cell-mediated cytotoxicity. It has other mechanisms of action, which include induction of apoptosis, block of the G1S transition, and an impairment of differentiation. CD-20 is expressed on normal B-cell lymphocytes and in most malignant B-cell lymphomas. It appears essential for the regulation of cell cycle and differentiation.[1]

Currently in Australia it is available under the PBS Authority system, where the approved indication is relapsed or refractory low-grade B-cell lymphomas, relapsed or refractory follicular B-cell lymphomas, or untreated CD-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with chemotherapy in patients over 60 years of age. The new information that has emerged through the course of 2004 and into 2005 will widen the indications for the use of rituximab in the treatment of lymphomas.

26.2 Low-grade lymphomas — new indications for rituximab

The German Low-grade Lymphoma Study Group (GLSG) has shown that the addition of rituximab to a combination of fludarabine, cyclophosphamide, and mitozantrone (FCM) significantly increases the response rate and prolongs survival when compared with chemotherapy alone in patients with relapsed and refractory follicular and mantle cell lymphomas.[1] This was a randomised study of some 147 patients. The response rate for R-FCM overall was 79%, including 33% complete remissions as compared with 58% for chemotherapy alone, with 13% complete remissions. The R-FCM arm was significantly superior in terms of progression-free survival and overall survival. There were no differences in clinical relevant side effects in both study arms.

However, in a separate study carried out by the same group, the addition of rituximab to CHOP chemotherapy had a long lasting impact on subsequent treatment in remission in follicular lymphoma, but not in mantle cell lymphoma.[2] The GLSG embarked on two parallel studies in follicular lymphoma and mantle cell lymphoma. One was a prospective randomised comparison of R-CHOP versus CHOP alone. This was followed by a second randomisation in remission for interferon maintenance versus myeloablative radio-chemotherapy with subsequent stem cell transplantation in patients under the age 60. All older patients received interferon maintenance. The disease-stage status of these patients is defined in the presentation abstract.

In the follicular lymphoma group ,the treatment with R-CHOP appeared to have a long-lasting beneficial effect on progression-free survival, which appears to be in the range previously achieved only by chemotherapy followed by peripheral stem cell transplantation. Similarly, a significantly higher response rate and a longer time to disease failure was observed in patients with mantle cell lymphoma. However, no difference was revealed for the progression-free survival after R-CHOP versus CHOP and subsequent therapy with interferon or peripheral blood stem cell transplantation. Therefore, in follicular lymphoma, the addition of rituximab to CHOP has a long-lasting beneficial effect, with a substantial impact on subsequent treatment in remission. In mantle cell lymphoma, the benefit of rituximab appears to be restricted to the remission induction period only.[2] Of greatest

interest, however, are the data suggesting that the addition of rituximab to chemotherapy in previously untreated patients increases event-free survival and response duration.

The Roswell Park Cancer Institute has reported a nine-year follow up of patients with low-grade or follicular non-Hodgkin's lymphoma (including patients with no prior treatment), treated with rituximab plus CHOP chemotherapy. The overall response rate was 100%, with 87% of patients achieving a complete response. The median times to progression and disease relapse were 82.3 months and 83.5 months respectively. The authors concluded that the rituximab/CHOP combination provided a lengthy response duration in patients with relapsed or newly diagnosed indolent non-Hodgkin's lymphoma.[3]

Similarly, the first analysis of the GELA–GOELAMS FL-2000 study of untreated patients with follicular lymphoma was presented at the 2004 ASH meeting. Patients were randomised to a CHOP-like regime containing etoposide in association with interferon, versus a similar arm in which six infusions of rituximab had been added. The first analysis of all patients in this trial demonstrated a significant improvement of response to therapy in the rituximab arm. In the control arm, the event-free survival at 2.5 years was 62%, versus 78% in the rituximab arm.[4]

At ASH 2004, the East German Study Group (Haematology and Oncology) also presented results of a prospective randomised phase III study comparing rituximab plus mitozantrone, chlorambucil and prednisolone chemotherapy (RMCP) versus MCP alone in untreated advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma. Some 358 patients were randomised. The overall response rate in the RMCP arm was 85.5%, versus 65.5% in the MCP group. Event-free survival (EFS) was significantly prolonged for patients receiving RMCP versus MCP alone. The median EFS for MCP was 19 months, and at this stage the EFS for RMCP was 73%.[5]

Similarly, a United States/Canadian group study presented results of a randomised trial of CVP chemotherapy with or without maintenance rituximab in patients with advanced indolent lymphoma. Some 332 stable, responding patients were randomised after chemotherapy to either four cycles of rituximab or observation. Progression-free survival estimates at two and four years from maintenance randomisation were 74% versus 42% and 59% versus 34% for the rituximab and observation arm respectively. The estimated two-year survival from maintenance randomisation was 95% for rituximab and 91% for observation.[6]

The Swiss Group for Clinical Cancer Research (SAKK) carried out a randomised trial comparing standard schedule rituximab with a more prolonged treatment in some 200 patients with newly diagnosed or refractory relapsed follicular lymphoma.[7] All patients received standard treatment — rituximab 375 mg/M^2 weekly x 4 — or were randomised to, in addition, a single 375 mg/M^2 rituximab infusion every two months x 4. Patients with stage I–IV disease were included. In 185 evaluable patients, the overall response rate was 67% in chemotherapy naïve patients and 46% in pre-treated cases. Patients responding or with stable disease at week 12 were randomised to no further treatment or the prolonged rituximab administration. At a median follow up of 35 months, the medium event-free survival was 12 months in the no-treatment group versus 23 months in the prolonged treatment group. The difference was particularly notable in the chemotherapy naïve patients (19 versus 36 months) and as well in patients responding to induction treatment (16 versus 36 months). It was concluded that in patients with follicular lymphoma, the administration of four additional doses of rituximab at eight-week intervals significantly improved the event-free survival.

Richard Fisher presented a review entitled 'New treatment options have changed the natural history of follicular lymphoma' at the 2004 ASH meeting. He showed that trials with chemotherapy followed by monoclonal antibodies have had a significant effect on both progression-free survival and overall survival, thereby changing the natural history of follicular lymphoma.[8]

Guideline — Low-grade lymphoma — aggressive combination chemotherapy	Level of evidence	Refs
Where it is considered appropriate to treat patients with combination chemotherapy, the addition of rituximab increases both complete response rate and duration of response.	II	1–8

26.3 Large-cell lymphoma — new indications for rituximab

At ASH 2004 the GELA Group presented longer-term results of their study of R-CHOP versus CHOP in elderly patients with diffuse large-cell lymphoma. The five-year event-free survival in R-CHOP was 47% versus 29% with CHOP. The five-year overall survival was 58% versus 45%. They concluded that these long-term results continue to show a major benefit for the addition of rituximab to CHOP in the treatment of patients with large B-cell lymphoma (over the age of 60) and that this improvement increases with time.[9]

By contrast, Michael Pfreundschuh presented the results of the MinT trial, which was the first analysis of the completed MabThera international trial in young or patients (i.e. less than 60 years) with low-risk diffuse large B-cell lymphoma. They found that the addition of rituximab to a CHOP-like regime significantly improves outcome of all patients, with the identification of a very favourable subgroup with IPI = 0 and no bulky disease.[10]

Guideline — Diffuse large-cell lymphoma	Level of evidence	Refs
The outcome of patients, both over and under the age of 60, who are treated with CHOP chemotherapy, is improved by the addition of rituximab.	II	9, 10

26.4 References

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APPENDICES

APPENDIX 1 GUIDELINE DEVELOPMENT PROCESS

After the Cancer Strategies Group ranked lymphoma as a major cancer in Australia, the Australian Cancer Network (ACN) was approached to develop clinical practice guidelines for the management of lymphoma. Originally, the guidelines were designated for non-Hodgkin lymphoma, but the underlying complexity of the disease spectrum led to the redirection of the guidelines to lymphoma in its broad aspects, with the exception of multiple myeloma and chronic lymphocytic leukaemia.

Working parties were established to address the diagnostic and clinical aspects of the disease complex, but after initial meetings of each group, it was decided that both sets of guidelines would be published in one volume and that the chair of each group would sit on both working parties. The chair of the clinical group assumed overall chairing responsibilities.

The guidelines have been developed by working parties of the ACN and as far as possible, follow the National Health and Medical Research Council (NHMRC) guide to the development, implementation, and evaluation of clinical practice guidelines.[1] The document being directed towards best practice.

The Working Parties (see Appendix 2), under the chair and guidance of Professor Richard Fox and Dr David Ellis, coordinated development of the guidelines.

Lymphoma represents a protean complex of disease presentations and so may present diagnosis and treatment challenges to a wide range of medical professionals. Diagnosis, management and cost of treatment were frequently seen as moving targets during the development of the guidelines. The Working Parties were developed on a representational and skills basis from royal colleges, specialty groups, and consumer advocates.

Purpose, scope and development of guidelines

Non-Hodgkin lymphoma is an increasingly diagnosed malignancy, with a rising death rate over the decade 1990–2000.[2] Its incidence places it as the sixth most common cancer in Australia. It represents 4.1% of all cancers and 4.5% of cancer deaths.

The Working Party aimed to review the available literature and provide a template for reducing variability in treatment where appropriate, and for management to include the latest products resulting from pharmacological and biotechnological activity. The document is being presented in a form that can be readily read and used by doctors and other health professionals.

The complexity and extent of the field determined that multiple myeloma and chronic lymphocyte leukaemia would not be addressed in these guidelines.

As the general practitioner is usually the first medical contact for patients with these diseases, a special document will be developed to assist general practitioners in determining the appropriate clinical steps and referral for patients with lymphoma.

A document to assist consumers in decision-making will also be developed when the guidelines are endorsed. The Lymphoma Guidelines Working Party has had excellent input from its consumer representative.

Special study

The development of the guidelines stemmed from a meeting of a small group of interested people at the office of Professor Robert Burton (then CEO, Anti-Cancer Council of Victoria) on 30 March 2001.

The meeting concluded the development of guidelines was desirable, given lymphoma is the sixth most common cancer, it consumes high levels of resources involving a range of treatments, and the strong interest of the National Health Priority Action Council (NHPAC) Cancer Strategies Group.

The inaugural meeting of the Clinical Management Group took place in Melbourne on 25 July 2001. The Chair of the Diagnostic Working Party was present.

The terms of reference were:

- To develop evidence-based guidelines that will assist in the clinical diagnosis and management of lymphoma.
- To provide a better level of understanding through education to all involved in the care of patients with lymphoma.
- To be helpful in promoting standardisation, completeness, clarity and openness of pathological reporting.
- To improve clinical care and subsequent outcomes.
- To promulgate clear and open reporting of diagnosis.
- To ensure that the resulting guidelines are portable — that is, pocket-sized, with clinical and diagnostic in one volume — and user friendly, with complexity reduced where possible.

The guidelines were developed on the basis that they would provide a framework within which the clinician would be able to apply clinical judgement and discuss individual patient needs. Guidelines should provide a sufficiently flexible atmosphere so that consumers can be informed of the risks and benefits that may accrue from recommended interventions. It was understood that some variations would result from reasonable differences that may result from different clinical presentations and patients' perceptions, preferences and needs.

The guidelines are based on the principles that underpin the NHMRC's recommendations for the guideline development[1]:

- a focus on the improvement of patient outcomes
- a basis in the best available scientific evidence
- inclusion of statements concerning the strength of the recommendations
- the adoption of a multidisciplinary approach that involves all stakeholders, including consumers.

Process employed

The Working Party approached the development of guidelines by setting itself five essential tasks:

1 Identification of the known clinical problems and areas of uncertainty in each of the disciplines involved in lymphoma treatment.

2 Collection and review of scientific evidence, including meta-analyses, to identify the best and most appropriate practice for the various interventions in lymphoma treatment.

3 Collaboration of appropriate subgroups to review and present special issues for consideration by the full Working Group.

4 Development of a glossary of technical terms in relation to lymphoma, for incorporation in the practice guidelines.

5 A review and revision process following public consultation as required by NHMRC.

The Working Party received contributions from across Australia to help it in its task. It held regular face-to-face meetings, primarily to identify the scope of the guidelines and to review subgroup activity (see Table A1). The final editing of the document before it was submitted to NHMRC was undertaken by the Chairs of the Working Parties, with frequent electronic and telephone advice from the members.

Table A1 Schedule of Working Party meetings

Date	Present	Location	Type of meeting
30 March 2001	Profs R Burton, R Fox, A Coates, T Reeve and Dr D Ellis Apology: Dr Max Wolf	CEO's office ACCV, Melbourne	Executive meeting
25 July 2001	Lymphoma Management Group	Ansett Golden Wing Conference Room, Melbourne Airport	Working Group meeting
1 August 2001	Lymphoma Diagnosis Group	QANTAS Club Conference Rooms, Adelaide Airport	Working Group meeting
13 March 2002	Lymphoma Management Group	QANTAS CLUB Conference Room, Melbourne Airport	Working Group meeting
15 March 2002	Lymphoma Diagnosis Group	QANTAS Club Conference Rooms, Melbourne Airport	Working Group meeting
8 July 2002	Lymphoma Management Group	QANTAS CLUB Conference Room, Melbourne Airport	Working Group meeting
8 November 2002	Lymphoma Management Group	QANTAS CLUB Conference Room, Melbourne Airport	Working Group meeting
13 March 2003	Lymphoma Management Group	QANTAS CLUB Conference Room, Melbourne Airport	Working Group meeting
14 March 2003	Lymphoma Diagnosis Group	QANTAS Club Conference Rooms, Sydney Airport	Working Group meeting
2 May 2003	Profs R Fox (Chairman), K Bradstock, T Reeve and Drs D Ellis and J Seymour	TCCA Conference Room, Sydney	Executive Group meeting
7 November 2003	Lymphoma Management Group	QANTAS CLUB Conference Room, Sydney Airport	Working Group meeting
15 March 2004	Lymphoma Management and Diagnosis Groups included in 200 delegates	Stamford Sydney Airport Hotel	Consensus meeting

Since the consensus meeting in March 2004, chapter authors have updated their manuscripts and each chapter has been reviewed and edited by the Chairs at a series of meetings.

Task 1

It was established that the guidelines should focus on recommendations that would improve the diagnosis and outcomes of patients with lymphoma, and that they would have a strong clinical emphasis.

The Working Party considered it was vital to distil the best elements of clinical management. To this end, it consulted widely with clinicians and involved consumers to ensure that the guidelines would gain broad acceptance. The complexity of the disease has led to a prolonged development process.

Task 2

Evidence was obtained through various avenues, including PubMed, Medline, CancerLit, Cochrane reviews and personal databases. Search questions identified evidence, which was evaluated by the Working Party before being included in the manuscript. The reviewed literature was analysed and the resulting information incorporated in the guidelines. The Working Party fully evaluated each of the papers offered by its members in support of arguments, and agreed as to whether the paper was to be either incorporated as a reference or rejected if it did not meet the criteria applied to the clinical area in question.

In many cases, decisions had to be made on the basis of low-level published evidence, and as a result, a number of recommendations are based on level IV evidence. For those recommendations for which level I–IV evidence was lacking, conclusions were drawn from the considered opinion of clinical experts. The processes used in developing these guidelines were designed to ensure that, as far as possible, the recommendations reflect the best evidence available to those involved in the treatment of lymphoma in Australia.

The Working Party decided that it was important to give a clear indication as to the strength of the evidence for guidelines and key statements, and to provide references where appropriate.

Relevant data that lacked sufficient strength to be designated as guidelines were listed as key points, or included in discussion in the text.

Designation of levels of evidence

I Evidence obtained from a systematic review of all relevant randomised controlled trials.

II Evidence obtained from at least one properly designed randomised controlled trial.

III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.

III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

IV Evidence obtained from case series, either post-test or pre-test and post-test. In effect we listed all level III as III, regardless of category.

These levels of evidence have been adapted from the United States Preventive Services Task Force guide to clinical preventive services[3] and the NHMRC guide to the development, implementation, and evaluation of clinical practice guidelines.[1]

Task 3

During the initial development of these guidelines, the Working Party established clinical assessment subgroups. The leaders of these subgroups were members of one of the primary Working Parties and identified diagnostic or clinical problems in their respective fields (see Appendix 2). They consulted more widely before submitting manuscripts to the appropriate Working Party for consideration. This process allowed the diagnostic or clinical subgroup's contributions to be included in the relevant chapters in the guidelines.

Task 4

A glossary of terms used in the guideline document has been developed. it is expected that this will be expanded during public review.

Task 5

When the guidelines were in an advanced draft form, they were advertised as available for public comment. They were available on the ACN website and in hard copy from the ACN.

At a public meeting in Sydney on 15 March 2004, overseas and local speakers spoke about components of the guidelines.

The special matters raised at this meeting have led to further review of the guideline manuscript before its submission to public review and to a further planned review by a special overview committee.

When the process is complete, the guidelines will be submitted for evaluation to the Health Advisory Committee of NHMRC.

Target audience

The guidelines were developed to provide clinicians and treating doctors, nurses, allied health professionals and consumers with recommendations for the optimal care of people with lymphoma.

Costing issues

While the guidelines address costing matters, these are complex and the context is changing rapidly. Treatments are developing with the emergence of new knowledge, and costs of treatment are substantial. Laboratories are getting larger, and costs of diagnosis are increasing with the rapid expansion of biotechnology. It is suggested that this area be targeted for continuing research.

Implementation and dissemination

The ACN is responsible for disseminating, implementing, evaluating and updating the guidelines. The processes to evaluate and update them will be in accordance with NHMRC guidelines. The guidelines will also feature strongly in the accreditation and credentialing activity of the ACN.

On 15 March 2004, ACN and The Cancer Council Australia held a meeting in Sydney — "Improving the management of lymphoma'. The draft guidelines provided the foundation for discussion, and further amendments were made. The meeting provided a sound basis for a public review, dissemination and implementation. NHMRC endorsement of the guidelines will be sought.

- The guidelines will have been promoted at a national seminar and a state seminar on lymphoma management, and subsequently through presentations at relevant professional meetings and conferences and submissions to professional journals.[4]

- The initial print run of the guidelines will be offered to relevant professional groups. Copies will also be made available to allied health organisations, state and territory health authorities, professional colleges and associations, public policy makers, health economists and professional journals.

- The draft guidelines have been available on the internet at the ACN website. It is anticipated that the approved guidelines will be available on NHMRC and ACN websites.

- The guidelines will be advertised through the ACN quarterly newsletter, 'Wongi Yabber', which is distributed to professional colleges, ACN stakeholders and interest groups, including consumers, and also has a limited overseas circulation.

Consultation and feedback

As stakeholders' acceptance of the guidelines is a critical first step towards their implementation, consultation is an essential part of the implementation process. ACN is developing an accreditation and credentialing program. Working Parties have been established to carry these processes and implementation activities forward.

Evaluation and updating

An essential part of the development and implementation of guidelines is to evaluate their effectiveness. An evaluation strategy will be drafted at the implementation stage and will include the collection of data to determine the impact of the guidelines on clinician behaviour and patient health outcomes.

The guidelines reflect the best available knowledge at the time of their publication. However, as new evidence emerges from systematic reviews, they will require regular revision in order to maintain validity. The ACN proposes to investigate the most cost-effective means of undertaking this.

References

1. National Health and Medical Research Council (NHMRC) guide to the development, implementation, and evaluation of clinical practice guidelines. AGPS Canberra 1998.

2. Cancer in Australia 2000. Canberra: Australian Institute of Health and Welfare, Australasian Association of Cancer Registries, 2003.

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APPENDIX 2 MEMBERSHIP OF THE AUSTRALIAN CANCER NETWORK DIAGNOSIS AND MANAGEMENT OF LYMPHOMA GUIDELINE WORKING PARTY AND PUBLIC CONSULTATION SUBMISSIONS RECEIVED

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A/ Professor Ken Bradstock, Haematologist
Mr Jeffrey Deslandes, Consumer
Dr David Ellis, Anatomical Pathologist
Professor Richard Fox (Chair), Medical Oncologist
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Dr Paula Marlton, Haematologist
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Dr Peter Bardy	Haematologist
Professor Bruce Barraclough	Medical Director, ACN / Surgeon
Professor Michael Barton	Radiation Oncologist
Mr Jeffrey Deslandes	Consumer
Dr David Ellis	Chair, Diagnosis Group Lymphoma Guidelines / Pathologist
Professor Richard Fox	Chair, Management Lymphoma Guidelines Group / Medical Oncologist
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Draft Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma
Public Consultation September 2004

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APPENDIX 3 ABBREVIATIONS

ABC	activated B-cell-like
ABVD	doxorubicin, bleomycin, vinblastine and decarbazine
ACVBP	doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone(chemotherapy regimen)
AE	adverse events
AgR	antigen receptor
ALCL	anaplastic large-cell lymphoma
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic lymphoma
ALLG	Australasian Leukaemia and Lymphoma Group
ANLL	acute non-lymphoblastic leukaemia
ASCO	Senior Adult Care Task Force of the National Comprehensive Cancer Network (NCCN)
ASCT	autologous stem cell transplantation
ATG	antithymocyte globulin
ATL	adult T-cell leukemia/lymphoma
auto-PBSCT	peripheral blood stem cell autologous transplant
B-ALL	precursor B acute lymphoblastic leukaemia
B-cell	Bursa-derived cell
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BFM	Berlin-Frankfurt-Munster
BL	Burkitt lymphomas
B-LBL	B lymphoblastic lymphoma
BMT	bone marrow transplant
BNLI	British National Lymphoma Investigation
C-ALCL	cutaneous anaplastic large-cell lymphoma
CAM	complementary or alternative medicine
CD	cluster differentiation (prefix descriptor for antigen type — followed by number).
CDR3	complementarity determining region 3
CEA	cost-effectiveness evaluation
CEOP	cyclophosphamide plus epirubicin
CER	cost-effectiveness ratio
CGH	comparative genomic hybridisation
Chl	chlorambucil
CHOEP	CHOP plus etoposide
CHOP	cyclophosphamide, doxorubicin, vincristine (oncovin) and prednisolone regimen
CHOP-R	cyclophosphamide, doxorubicin, vincristine (oncovin) and prednisolone (CHOP) regimen plus rituximab
CLL	chronic lymphocytic leukaemia
CMV	cytomegalovirus
CNS	central nervous system
COG	(United States) Children's Oncology Group
CR	complete remission

CR[u]	complete remission unconfirmed/
CSF	colony-stimulating factor
CSF	cerebrospinal fluid
CT	chemotherapy
CT	computed tomography
CTL	cytotoxic T cells
CVID	common variable immune deficiency
CVP	cyclophosphamide, vincristine and prednisolone
D+	seropositive donor
DALY	disability adjusted life years
DFS	disease-free survival
DHAP (or DHAC)	dexamethasone, high dose cytarabine and cisplatinum
DLBCL	diffuse large B-cell lymphoma
DSC	diffuse small cleaved cell
DSL	diffuse small lymphocytic
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ECP	extracorporeal photopheresis
EFS	event-free survival
ENT	ear, nose and throat
EORTC	European Organisation for Research and Treatment of Cancer
EPOCH	etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin
ESHAP	etoposide, cisplatinum, high dose cytarabine and methylprednisolone
ESR	erythrocyte sedimentation rate
EUS	endoscopic ultrasound
FBC	full blood count
FC	follicle center (lymphoma)
FCC	follicle center cell (lymphoma)
FCM	flow cytometry
FCM	fludarabine, cyclophosphamide and mitoxantrone
FDC	follicular dendritic cell
FDG	fluorodoxyglucose
FFP	freedom-from-progression
FFR	freedom from relapse
FISH	fluorescence *in situ* hybridisation
FL	follicular lymphoma
FLC	follicular large cell
FLIPI	follicular lymphoma international prognostic index
FM	follicular mixed
FNA	fine needle aspiration
FR3	framework region
FSC	follicular small cleaved cell
GC	germinal centre
GCB	germinal center B-cell-like
G-CSF	granulocyte colony stimulating factor
GELA	Groupe d'Etudes des Lymphomes des l'Adultes

GIT	gastro intestinal tract
GLSG	German Low Grade Lymphoma Study Group
GM-CSF	granulocyte macrophage colony stimulating factor
GnRH	gonadotrophin releasing hormone
GVHD	graft versus host disease
H pylori	Helicobacter pylori
H&E	haematoxylin and eosin
HAART	highly active anti-retroviral therapy
HD	Hodgkin's disease
HDC	high-dose chemotherapy
HDCT	high-dose chemotherapy
HDSG	Hodgkin Disease Study Group
HGL	high-grade lymphoma
HGNHL	high-grade NHL
HHV8	human herpesvirus-8
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HOVON	Stichting Haemato-Oncologie voor Volwassenen Nederland (Dutch haemato-oncology association)
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
HTLV	human T-lymphotrophic virus
ICE	ifosfamide, carboplatin and etoposide
ICER	incremental cost-effectiveness ratio
IELSG	International Extranodal Lymphoma Study Group
IFN	interferon
IgH	immunoglobulin heavy
IgL	immunoglobulin light (chain)
IgV(H)	Variable region of the immunoglobulin heavy chain gene
IPI	International Prognostic Index
IV	intravenous
J	joining
LDHL	lymphocyte depletion Hodgkin lymphoma
LL	lymphoblastic lymphoma
LOS	length of stay
LPD	lymphoproliferative disorder
LPD	Lymphoproliferative disease
LPHL	lymphocyte predominance Hodgkin lymphoma
LRCHL	lymphocyte-rich classical Hodgkin lymphoma
LyP	lymphomatoid papulosis
LYS	life years saved
MACOP-B	methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin
MALT	mucosa-associated lymphoid tissue
m-BACOD	(chemotherapy regimen of) methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone
MCHL	mixed cellularity Hodgkin lymphoma
MCL	mantle cell lymphoma

MDACC	MD Anderson Cancer Center
MDS	myelodysplastic syndrome
MF	mycosis fungoides
M-FISH	multi-colour fluorescence *in situ* hybridisation
MLBCL	mediastinal large B-cell lymphoma
MOPP	mechlorethamine, oncovin, procarbazine, prednisone (chemotherapy protocol for Hodgkin lymphoma)
MRD	minimal residual disease
MRDDM	minimal residual disease detection and monitoring
MSKCC	Memorial Sloan Kettering Cancer Centre
MU	million units
MZL	marginal zone lymphoma
NBS	Nijmegen breakage syndrome
NCB	needle core biopsy
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin's lymphoma
NHMRC	National Heath and Medical Research Council
NK-cell	natural killer cell
NLPHL	nodular lymphocyte predominant Hodgkin lymphoma
NM	nitrogen mustard (mechlorethamine)
NSHL	nodular sclerosis Hodgkin lymphoma
NST	non-myeloablative stem-cell transplant
O/E	(ratio of) observed to expected
OCT	optical cutting temperature
OR	overall response
ORR	overall response rates
OS	overall survival
PA	periodic acid-Schiff
PAGE	polyacrylamide gel electrophoresis
PARMA	a study initiated in Parma, Italy
PCBCL	primary cutaneous B-cell lymphomas
PCL	primary cerebral lymphoma
PCLBCL-leg	primary cutaneous large B-cell lymphoma of the leg
PCR	polymerase chain reaction
PD	progression of disease
PEL	primary effusion lymphoma
PET	positron emission tomography
PF	progression-free
PID	primary immune disorder
PMH	Princess Margaret Hospital
PMLCL	primary mediastinal large-B cell lymphoma
PR	partial remission
ProMACE-CytaBOM	prednisone, doxorubicin, cyclophosphamide, etoposide, followed by cytarabine, bleomycin, vincristine and methotrexate
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified
PTGC	progressive transformation of germinal centres

PTLD	post-transplant lymphoproliferative disorder
PUVA	ultraviolet-A radiation
QALM	quality-adjusted life-months
QALY	quality of life on utility
R-	EBV seronegative recipient
R+	EBV-seropositive recipients
RAR	retinoic acid receptor
RDI	relative dose intensity
REAL	Revised European-American Lymphoma
RFS	relapse-free survival
RQ-PCR	real-time quantitative Polymerase chain reaction
RR	relative risk
RT	radiation therapy
RXR	retinoid X receptor
SB	Southern blot
SC	Sézary cells
S-CHOP	standard CHOP
SCT	stem cell transplantation
SEER	Surveillance Epidemiology and End Results
SFOP	French Society of Pediatric Oncology
SKY	spectral karyotyping
SLL	small lymphocytic lymphoma
SLP	standard local practice
SS	Sézary syndrome
STNI	subtotal nodal irradiation
SV40	Simian virus 40
SWOG	Southwest Oncology Group
T-ALL	T-cell variant of acute lymphoblastic leukaemia
TBI	total body irradiation
T-cell	thymus-derived cell (not really an abbreviation now)
TCR	T-cell receptor
TCRB	T cell receptor beta
T-LL	T-cell lymphoblastic lymphoma
T-NHL	non-Hodgkin lymphoma of T-cell type
TNI	total nodal irradiation
TPN	total parenteral nutrition
TSEB	total skin electron beam
UKCCSG	United Kingdom Children's Cancer Study Group
UVB	ultraviolet-B
UVR	ultraviolet radiation
V	variable
WAS	Wiskott-Aldrich syndrome
WHO	World Health Organization
XLP	x-linked lymphoproliferative disorder (Duncan syndrome)
YLD	years lost due to disability
YLL	years of life lost
ZAP-70	zeta-associated protein 70

APPENDIX 4 GLOSSARY

Abdomen	The part of the body between the chest and hips, which contains the stomach, liver, intestines, bladder and kidneys.
Adjuvant chemotherapy	Chemotherapy that is used in a supplementary but not dominant therapy.
Advanced cancer	Cancer that has metastasised and/or is unlikely to be cured
Adriamycin	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Aetiology	Cause or causality
Age-standardised rate	A procedure for adjusting rates eg death rates, designed to minimise the effects of differences in age composition when comparing rates for different populations.
Aggressive	A word for a fast-growing cancer.
Allogeneic	Tissue from a donor.
Alpha interferon	A glycoprotein used in the treatment of cancer. One of its effects is to inhibit cell growth.
Alternative therapies	A term used to loosely describe any type of therapy outside the orthodox circle of surgery, radiation or chemotherapy. Alternative therapies include things such as diet therapy, vitamins and herbs. *(See also Complementary therapies)*
Antibody	A protein that is made in lymph tissue to destroy infections and other potentially harmful 'invaders' in the body.
Anticoagulant	A substance that prevents blood clotting.
Anxiety	A diffuse highly unpleasant, often vague feeling of apprehension, accompanied by bodily sensations such as pounding heart or sweating. There is an associated anticipation of future misfortune or danger, external or internal.
Apheresis	The process in which blood is temporarily taken from the body, one or more parts of it removed, and the blood returned to the body.
Apoptosis	Process of cell death.
Autologous	Tissue graft, blood transfusion etc arising from the recipient.
Benign	Not cancerous. Benign cells are not able to spread like cancer cells.
Biopsy	The removal of a small sample of tissue from the body, for examination under a microscope, to help diagnose a disease
Bleomycin	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Bone Marrow	The soft, spongy tissue in the centre of large bones that produces white blood cells, red blood cells and platelets.
Cancer registry	A centre in each state and territory where details of cancers are collected to monitor trends.
Case control study	A study that starts with the identification of people with the

	disease of interest and uses a suitable group without the disease for comparison to assess possible factors involved in the development of the disease. Such studies are often called retrospective as they look back from the outcome to its causes.
Cells	The 'building blocks' of the body. A human is made of millions of cells, which are adapted for different functions. Cells are able to reproduce themselves exactly, unless they are abnormal or damaged, as are cancer cells.
Chemotherapy	The use of drugs (which are cytotoxic) or a combination of drugs to kill cancer cells or prevent or slow their growth
Chest cavity	The area enclosed by the ribs, above the diaphragm.
Chemo-responsiveness	The measure of how a tumour reacts when an anti-tumour drug is administered
Chlorambucil	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Cladribine .	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Clinical practice guidelines	The bringing together by a central authority of the best available evidence to support recommendations for the prevention, diagnosis and treatment of cancer.
Complementary therapies	A term used to refer to therapies, such as meditation and relaxation therapy, that can work alongside conventional therapy.
Counselling	Refers generically to a form of supportive care delivered by all health professionals. There are differing levels of sophistication depending on the training and experiences of the practitioner involved.
CT scanning	Computerised tomography is a technique for constructing pictures from cross sections of the body, by x-raying from many different angles the part of the body to be examined.
Cyclophosphamide	A cytotoxic agent used during chemotherapy to kill cancer or lymphoma cells.
Cytology	The study of the origin, structure, function and pathology of cells.
Dacarbazine	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Depression	A pervasive or sustained lowering of mood or the loss of interest in nearly all activities. When used clinically, it is a cluster of symptoms or a syndrome, whose other features may include: changes in appetite or weight, sleep or psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating or making decisions; or recurrent thoughts of death or suicide ideation, plans or attempts.
Diagnosis	The process of identifying a person's illness.
Diaphragm	A thin muscle below the lungs and heart. It separates the chest cavity from the abdominal cavity.
Doxorubicin/liposomal doxorubicin	Agent used in chemotherapy.

Efficacy	The ability of a drug or intervention to produce the desired beneficial effect under ideal conditions.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems.
FDG	Fluoro-deoxy glucose (see PET scanning)
First line therapy	The first administration of therapy such as chemotherapy following surgical removal of the tumour.
Fludarabine	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
FNA	Fine needle aspiration is a procedure in which a fine needle is used to suck up a few cells from a tumour, for biopsy
Frozen section	A specimen of tissue that has been quick frozen, cut and stained immediately for rapid diagnosis of malignant tissue
Gene	One of the biologic units of heredity which are situated in specific locations on particular chromosomes in the body. Genes make up the DNA molecules that control cell reproduction and function.
Genome	A complete set of hereditary factors in the chromosomes
Growth factor	A substance that stimulates cells to reproduce and rapidly multiply.
H&E sections	Use of a stain -Hematoxylin-eosin - for routine examination of tissue under a microscope. Cell nuclei are stained deep blue and the surrounds (cytoplasm) pink.
Histology	The study of the minute structure, composition and function of tissues.
Immune system	The body's natural defence system. It protects against anything it recognises as an "invader", for example, bacteria, viruses, transplanted organs and tissues, tumour cells and parasites.
Immunotherapy	Treatment with immunopotentials and immunosuppressnats.
Incidence	The number of new cases of illness or disease during a given period in a specified population.
Indolent	A word for a slow-growing cancer.
Interferon	A substance made by the body in response to viral infection. It inhibits virus multiplication and has shown some activity against a few uncommon cancers.
Infusion	Introduction of a fluid as a saline solution into the blood by gravity flow.
Intravenous chemotherapy	Administration of a chemotherapy using the veins
Laparoscopy	Examination by means of a laparoscope.
Laparotomy	Surgery where an incision is made through the abdominal wall to expose abdominal contents.
Lymph nodes	Also called lymph glands. Small, bean-shaped structures which form part of the lymphatic system. Lymph is the fluid that flows through this system and carries cells that help to fight disease and

	infection. The lymph nodes filter the lymph to remove bacteria and other harmful agents, such as cancer cells.
Lymphatic system	The lymphatic system is part of the immune system, which protects the body against 'invaders', like bacteria and parasites. The lymphatic system is a network of small lymph nodes connected by very thin lymph vessels, which branch into every part of the body.
Lymphocyte	A type of white blood cell formed in lymph nodes. It is part of the body's immune system which helps to fight infection.
Lymphoma	A general term for any cancer that starts in the lymph tissue.
MabThera (Rituximab)	An antibody made by genetic engineering technology that is toxic to lymphoma cells.
Malignant Cancerous	Malignant cells can spread (metastasise) and can eventually cause death if they cannot be treated.
Mediastinum	The area in the chest cavity between the lungs. It contains the heart and large blood vessels, the oesophagus, the trachea and many lymph nodes.
Meta-analysis	A statistical method used to combine the results of different studies on the same topic. Used to pool results from a number of small randomised controlled trials to provide an aggregate that will allow for demonstration of statistically significant results.
Metastasis	Also known as a secondary tumour. A tumour that develops when cancer cells break away from the original (or primary) tumour and are carried by the lymph and blood systems to other parts of the body.
Mitosis	The process of cell division where new cells are formed. Used by the body to replace dead cells.
Morbidity	Term used to report on illness. Can also be used to show persons who were ill, the period of illness and the duration of the illness.
Mortality	Death rate due to a particular cause or disease.
MRI	A special imaging technique used to image internal structures of the body. It uses the influence of a large magnet to polarize hydrogen atoms in the tissues and then monitors the summation of the spinning energies within living cells. Images are very clear and are particularly good for soft tissue, brain and spinal cord, joints and abdomen. These scans may be used for detecting some cancers or for following their progress.
Multidisciplinary care	Multidisciplinary care is the co-ordinated approach using a collaborative group of health professionals and a range of treatment modalities. The team as a whole is responsible for the diagnosis, continuing management and palliative care of the woman with ovarian cancer.
Multidisciplinary team	A group of clinicians and health professionals, from a number of disciplines, working together to manage the care of a patient. The members of the team may include: a gynaecological oncologist, gynaecological pathologist, medical oncologist with special experience in ovarian cancer, radiation oncologist with special experience in ovarian cancer, radiologist with a special interest,

	general practitioners, specialist nurses, physiotherapists, pharmacists, psychologists, social workers, genetic counsellors, geneticists, and palliative care specialists.
Mutation	A permanent and transmissible change in genetic material.
Myelosuppression	Suppression of bone marrow activity resulting in a decrease in the number of platelets, red cells and white cells.
Neo-adjuvant	Chemotherapy that is administered before the dominant therapy, for example, radiotherapy/surgery
Oral alkylating agent therapy	An anti-cancer or cytotoxic agent eg a platinum compound. An alkylating agent is one which substitutes an alkayl group for an active hydrogen in an organic compound.
Palliative care	The active total care of patients whose disease is not responsive to curative treatment. It encompasses the provision of co-ordinated medical, nursing and allied services to help relieve physical symptoms and to provide psychological, emotional and spiritual support.
Pathology	The study of diseases, especially their causes and nature.
Pathogenesis	The development of a disease, specifically the cellular events, reactions and other pathologic mechanisms that occur.
Peritoneum	The lining of the abdomen.
PET scan	Positron emission tomography. A technique that is used to build up clear and detailed cross-section pictures of the body. The person is injected with a glucose solution containing a small amount of radioactive material. The PET scanner can ‘see’ the radioactive substance. Damaged or cancerous cells show up as areas where the glucose solution is being used.
Phase I, II, III trial	The different stages of a clinical trial. Phase I is designed to evaluate the relationship between dose and toxicity. In Phase II new treatments are screened for their anti-tumour effect, to see which are worthy of further evaluation and in Phase III patients are randomly allocated to receive the new treatment or the best available standard treatment.
Platelets	Part of the blood. Platelets are important for blood clotting.
Ploidy studies	Identification of the number of genomes (complete set of chromosomes) it contains
Pooled data	Data from a number of studies combined for analysis to look for an effect/result
Prednisolone	A corticosteroid drug that is toxic to lymphocytes and lymphoma cells.
Prognosis	A forecast as to the probable outcome of a disease and the prospect of recovery based on the nature of the case.
Proliferating	Growth by reproduction of similar cells
Quality of life	A person’s view of their situation and well-being. It encompasses symptoms of disease, side effects of treatment, relationships, occupational and social functioning and a subjective evaluation of adjustment to daily life.

Radiotherapy	The use of radiation, usually x-rays or gamma rays, to kill cancer cells or injure them so they cannot grow and multiply. Radiotherapy treatment can also harm normal cells, but they are able to repair themselves.
Randomised controlled trial (RCT)	A study or experiment where subjects are allocated at random to receive or not receive the treatment, procedure or intervention. The results for each group are compared. Generally held to be the most scientifically rigorous method of testing an hypothesis.
Red blood cells	Blood cells that contain haemoglobin, which carries oxygen to the blood.
Reed-Sternberg cell	A malignant cell found in Hodgkin lymphoma (also known as Hodgkin's disease).
Relapse	The return of a disease after a period of improvement or remission.
Relative risk	The risk (of a disease or death) among those exposed to the risk compared to those who are not exposed to the risk.
Relative survival	Relative survival analysis aims to quantify how long someone with a specific disease might survive when compared to the "general population". The general population are matched to the "disease" cases by age, sex and year of diagnosis. Relative survival is thus the ratio of the proportion of survivors in the disease group to the proportion of survivors in a similar group of people without the disease. A relative survival of 100% would indicate that persons with disease do not die any more rapidly as they age than people without the disease whereas a result of less than 100% indicates that the disease is resulting in premature death, even when other causes of death have been accounted for.
Remission	The decrease or disappearance of the symptoms of a disease. A person is said to be in complete remission when there is no evidence of active disease.
Resection	Surgical removal of part of all of an organ or tissue.
Retroperitoneal lymph nodes	Lymph nodes situated external or posterior to the peritoneum.
Risk factor	Things that cause people to have a greater chance of developing an illness. Risk factors for cancer include exposure to harmful substances (such as asbestos, some viruses and cigarette smoke) and inheriting a predisposition to a cancer.
Spleen	An organ in the upper part of the abdomen on the left side, below and behind the stomach. The spleen produces lymphocytes, filters blood, stores blood and destroys cells that are ageing. It can mount an immune response to infections in the blood system.
Staging	Investigations to find out how far a cancer has progressed. This is important in planning the best treatment.
Stage/staging/stage distribution	The classification of a tumour according to its extent.
Stem cell	Any precursor cell; a blood cell progenitor or 'mother' cell, having the capacity for both replication and differentiation.
Thymus	An organ in the chest in front of the heart where lymphocytes

	mature and multiply.
Tissue	A collection of cells
Tissue biopsy	Examination of tissue, which has been removed from the body, under a microscope so that any abnormalities in the cells can be seen.
Toxicity	The quality of being poisonous,
Transformation	Change from benign or resting to dividing or malignant cell.
Transformed disease	Change from low grade or benign disease to a more malignant type.
Trephine	Core biopsy of bone marrow.
Tumour	Also called neoplasm. A new growth of tissue in which cell multiplication is uncontrolled and progressive. Tumours are classified in a number of ways the simplest being their origin and whether they are malignant or benign.
Tumour/tumourgenesis	The production of tumours.
Tumour marker	A substance found in the body that suggests the presence of a tumour.
Ultrasound	'Ultrasound' is sound waves of a very high frequency (higher than the human ear can hear). If ultrasound is directed at the body, it is reflected back differently by different types of tissue. In an ultrasound scan, these differences are measured and used to build up pictures of structures in the body. Ultrasound pictures are usually taken by an ultrasound technician, who guides the scanning by watching the images on a screen like a television.
Vinblastine	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
Vincristine	A cytotoxic agent or drug used during chemotherapy to kill cancer or lymphoma cells.
White blood cells	Also known as leucocytes. One of the two main types of cells present in blood. They play a major role in fighting infection.

Partly adopted from The Cancer Council Victoria handbook titled: 'Lymphoma, a guide for people with cancer, their families and friends'.

5.13 PRALATREXATE, solution for infusion, 1 mL vial, 20mg, Folotyn®, Mundipharma Pty Ltd.

1 Purpose of Application

1.1 Section 100, Authority Required, listing for pralatrexate for treatment of relapsed or refractory peripheral T-Cell lymphoma.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt	No. of repeats	Published DPMA	Effective DPMA	Proprietary Name and Manufacturer	
PRALATREXATE Pralatrexate 20mg in 1mL, solution for infusion (public hospital)	80mg	5	$[redacted]*	$[redacted]*	Folotyn®	Mundipharma
PRALATREXATE Pralatrexate 20mg in 1mL, solution for infusion (private hospital)	80mg	5	$[redacted]*	$[redacted]*	Folotyn®	Mundipharma

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Category / Program	Chemotherapy (Private and Public)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	~~Peripheral T-cell Lymphoma~~
Severity:	~~Patients who have~~ relapsed or chemotherapy refractory ~~disease~~
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	*Relapsed or chemotherapy refractory peripheral T-cell Lymphoma*
Treatment phase:	~~Initiation~~ *Initial treatment*
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	~~Patient must demonstrate relapsed or chemotherapy refractory disease to 1st line chemotherapy.~~

Clinical criteria:	Patient must have undergone appropriate prior front-line curative intent chemotherapy ~~AND~~ ~~Patient must demonstrate relapsed or chemotherapy-refractory disease~~
Population criteria:	~~Adults~~
Prescriber Instructions	Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed PTCL Pralatrexate PBS Authority Application - Supporting Information Form [to be determined] which includes the following: (i) The date of initial diagnosis of PTCL; (ii) Dates of commencement and completion of front-line curative intent chemotherapy; (iii) a declaration of whether the patient's disease is relapsed or refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory. ~~A maximum quantity and number of repeats to provide for an initial course of pralatrexate of 3 cycles will be authorised as part of the initiating restriction.~~
Administrative Advice	**Note** Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at: www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 ~~GPO Box 9826~~ HOBART TAS 7001 **Note** No increase in the maximum number of repeats may be authorised. **Note** No increase in the maximum quantity or number of units may be authorised. **Note** Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PRALATREXATE, 20mg in 1 mL, solution for infusion	80 mg	11	$[redacted] (public) $[redacted] (private)	Folotyn Mundipharma

Category / Program	Chemotherapy (Private and Public)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	~~Peripheral T-cell Lymphoma~~
Severity:	~~Patients who have~~ relapsed or chemotherapy refractory ~~disease~~
Condition:	Peripheral T-cell Lymphoma
PBS Indication:	Relapsed or chemotherapy refractory peripheral T-cell Lymphoma
Treatment phase:	Continuing ~~treatment~~
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	~~Patient must demonstrate relapsed or chemotherapy refractory disease to 1st line chemotherapy.~~
Clinical criteria:	Patient must not have progressive disease, And Patient must have previously been issued with an authority prescription for this drug.
Prescriber Instructions	
Administrative Advice	**Note** *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* **Note** No increase in the maximum number of repeats may be authorised. **Note** No increase in the maximum quantity or number of units may be authorised. **Note** Special Pricing Arrangements apply.

2.1 The requested listing (treatment in second line) is inconsistent with the clinical evidence presented in Section B of the Commentary. Patients in the primary study in Section B (PDX-008) had a median of 3 lines prior therapy. This was not explored in Section C of the submission.

2.2 The requested basis for listing is cost-effectiveness compared with the nominated comparator.

3 Background

3.1 TGA status: Pralatrexate was approved by the TGA in January 2015 for adult patients with peripheral T-cell lymphoma who have progressed after at least one prior therapy. The ARTG entry date is 11 August 2015

3.2 Pralatrexate has not been considered by the PBAC previously.

4 Clinical place for the proposed therapy

4.1 Peripheral T-cell lymphoma (PTCL) comprises a group of heterogeneous non-Hodgkin lymphomas that develop from T-cells in different stages of maturity. The sub-types of lymphoma that are categorised as PTCL in the submission are (pA26 of the submission):

- Peripheral T-Cell Lymphoma (Not Otherwise Specified - NOS)
- Anaplastic Large-Cell Lymphoma (ALCL)
- Angioimmunoblastic T-cell lymphoma
- Primary cutaneous PTCL (primary cutaneous gamma delta T-cell lymphoma, primary cutaneous CD4+ small/medium T-cell lymphoma, and primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, Mycosis Fungoides (cutaneous T-cell Lymphoma) and Sézary Syndrome (cutaneous T-cell Lymphoma))
- Enteropathy-associated T-Cell Lymphoma (involvement of celiac)
- Hepatosplenic Gamma-Delta T-Cell Lymphoma
- Blastic NK-cell lymphoma
- Adult T-cell acute Lymphoblastic Leukemia/Lymphoma T-Cell Leukemias
- Subcutaneous panniculitis-like T-cell Lymphoma
- Extranodal NK (natural killer/T-cell lymphoma) - Nasal T-Cell Lymphoma
- Precursor T-Cell Acute Lymphoblastic Lymphoma or Leukaemia

4.2 It is proposed that pralatrexate will be administered in the second line for treatment of PTCL.

5 Comparator

5.1 The submission nominated a basket of treatments as the main comparator. The basket of treatments included DHAP, brentuximab, gemcitabine containing regimens, methotrexate, romidepsin (not PBS listed in Australia), ESHAP, and ICE. The ESC considered that this basket is the appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission is based on a naïve comparison of

- Pralatrexate: Study PDX-008 (n=[redacted]). A sub-group of patients from Study PDX-008 (n=[redacted]) was matched to a historical control cohort.
- Comparator treatments: Matched control analysis (MCA). A subset of patients from PDX-008 were matched *on a 1:1 basis* to a historical control cohort (n=[redacted]).

6.4 PDX-008 was a Phase 2, single-arm, open-label multi-centre study conducted in US, Canada and Europe for patients with relapsed or refractory PTCL. [redacted] patients were recruited, and [redacted] patients formed the efficacy evaluable population (received at least 1 dose of pralatrexate and histology was confirmed by central review).

6.5 The historical control cohort consisted of [redacted] patients that were consistent with the main PDX-008 inclusion criteria ([redacted]) were extracted.

6.6 Each PDX-008 patient (n=[redacted]), for whom a match could be obtained, was matched to multiple control patients (n=[redacted]). Patients were matched on the basis [redacted]. Patients were not matched on the basis [redacted].

6.7 Each PDX-008 patient (n=[redacted]) was matched with [redacted]

6.8 Patients with a 1:1 match were identified as a case match. Where cases had multiple control matches the control match was randomly selected. The total matched population was [redacted] cases and [redacted] controls.

6.9 Further details of the studies presented in the submission are provided in the table below.

Table 1: Studies and associated reports presented in the submission

Study	Description	Reports
Pralatrexate		
Nonrandomised studies		
PDX-008	Single arm, Phase 2 study evaluating efficacy and safety of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma	Allos Therapeutics PDX -008: A Multi-center, Phase 2, Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin (Pralatrexate) with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma. 29 April 2010 O'Connor, O. A., B. Pro, L. Pinter-Brown, N. Bartlett, L. Popplewell, B. Coiffier, M. J. Lechowicz, K. J. Savage, A. R. Shustov, C. Gisselbrecht, E. Jacobsen, P. L. Zinzani, R. Furman, A. Goy, C. Haioun, M. Crump, J. M. Zain, E. Hsi, A. Boyd and S. Horwitz. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 2011, 29(9): 1182-1189. O'Connor, O., P. L. Zinzani, T. Koutsoukos and B. Coiffier. Pralatrexate reverses the trend in progressive resistance with successive chemotherapy regimens in the treatment of relapsed or refractory peripheral t-cell lymphoma (PTCL). Haematologica, 2011, 96: 151-152. Foss, F. M., S. M. Horwitz, L. Pinter-Brown, A. Goy, B. Pro, B. Coiffier, L. Popplewell, K. J. Savage, A. Shustov, J. M. Zain, T. Koutsoukos, S. M. Fruchtman and O. A. O'Connor. Pralatrexate is an effective treatment for heavily pretreated patients with relapsed/refractory transformed mycosis fungoides (TMF). Blood, 2010, 116(21). Goy, A., B. Pro, K. J. Savage, N. L. Bartlett, M. J. Lechowicz, E. D. Jacobsen, F. Young, M. Crump, H. Borghaei, B. Link, S. M. Fruchtman and O. A. O'Connor. Pralatrexate is effective in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) with prior ifosfamide, carboplatin, and etoposide (ICE)-based regimens, 2010, Blood 116(21).
Main comparator		
Matched controls analysis	Individual patient historical control data matched to patients in PDX-008	Allos Therapeutics Ltd. Historical Controls Data Report, including Attachments. August 2013

Source: Table B.2.2, p B13 of the submission

6.10 The key features of the studies are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pralatrexate						
PDX-008	111	OL, MC, single arm 2yrs (up to 5 years for some patients)	High	Progressive disease after at least 1 prior treatment	ORR, OS, PFS	Survival
Pralatrexate vs comparator						
MCA	[redacted]	Historical database patients matched 1:1 to PDX-008	High	[redacted]	[redacted]	[redacted]

MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; ORR=overall response rate, MCA=matched control analysis

Source: compiled during the evaluation

6.11 The following issues were identified with regards to the study design:

- PDX-008 was a single arm study, without a comparator or randomisation and is therefore subject to considerable bias.
- Overall survival in the sub-group representing the matched cohort in PDX-008 was [redacted] months compared to [redacted] months in the overall efficacy evaluable population. It is possible that the matched population represent a healthier population than the overall efficacy evaluable population, biasing the hazard ratio in favour of pralatrexate.
- Patients in PDX-008 were not matched to historical controls on the basis of ECOG status. Given an inclusion criteria of PDX-008 was ECOG ≤ 2 it is likely that PDX-008 patients have a better performance status than the matched historical controls. Performance status is a predictive factor of improved outcomes so this has the potential to bias in favour of pralatrexate.
- The PSCR (p30) noted that the majority of patients with known ECOG performance status in the historical control cohort were ≤ 2, and would be willing to restrict the indication to this group.
- The ESC were concerned that the incremental survival of [redacted] months for pralatrexate compared to historical controls ([redacted] vs [redacted] months) appeared implausible when the median PFS for pralatrexate was only 3.5 months.
- The recruitment periods for the historical controls *([redacted])* were older than that of PDX-008 *(2006-2008)*. Survival outcomes in those recruited in later time periods may be improved due to advances in treatment options, advances in supportive care and the increasing use of stem cell therapy. The PSCR (p3) argued that the comparison was valid because there was significant overlap between the 2 cohorts, and cited a study of 153 patients (Mak JCO 2013) that did not find difference in survival rates for patients with PTCL not undergoing transplant treated 1980-2000 vs 2001-2011. However, the ESC remained concerned that differences in overall survival between pralatrexate and the comparators were highly uncertain and likely over-estimated.
- The submission presented 2 sensitivity analyses using different matching methodologies. The hazard ratio was sensitive to the matching methodology employed. The hazard ratio *for overall survival* in the base case was [redacted] (95%CI: [redacted], [redacted]) compared to [redacted] (95%CI: [redacted], [redacted]) and [redacted]

(95%CI: [redacted], [redacted]) in the sensitivity analyses.

Comparative effectiveness

6.12 Original results in PDX-008 were based on a follow-up period of 2 years post pralatrexate initiation. Updated survival data were obtained for [redacted] patients in the efficacy evaluable population of which [redacted] patients were in the matched PDX-008 cohort. Those patients for whom updated data were not received were censored at two years. Of those [redacted] patients, there were [redacted] deaths and the remaining [redacted] were censored [redacted]. The tail of the Kaplan-Meier curve for pralatrexate suggests a low death rate beyond [redacted] months however the incremental benefit should be interpreted with caution due to the small patient numbers and high rates of censoring. Furthermore, it is unknown whether the patients for whom updated data are received are representative of the overall efficacy population.

Table 3: Results of overall survival and progression free survival in the non-randomised studies

	PDX-008 N=109 (original results)	PDX-008 N=109 (updated* results)	Matched PDX-008 cohort N=66 (based on updated* results)	Matched historical control cohort N=66	Absolute difference	Hazard ratio (matched PDX-008 and matched historical control cohort)
Median PFS (95%CI)	3.5 (1.7-4.8)	NR	NR	NR	NR	NR
Median OS (95%CI)	14.5 (10.6-22.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table B.6.2, p B66, Figure B.6.3, pB79 of the submission and page 37 of clinical-overview-row.pdf
Abbreviations: CI – Confidence interval, OS – Overall survival, PFS – Progression free survival, NR – Not reported
*Updated results based on additional survival data obtained from [redacted] patients in the overall trial population. Additional survival data was up to a four year follow-up period

Figure 1: Overall survival for matched PDX-008 (updated results) versus control matched patients

[redacted]

6.13 The PSCR (p1) acknowledged that 3 and 4 year data is based on small patient numbers, but did not provide numbers at risk for the Kaplan Meier survival curve, nor additional data to support the sponsor's assertion that such patients are representative.

Supportive evidence from study PDX-008 and a meta-analysis of fourteen single arm comparisons, utilising a variety of combination therapies examining refractory and or relapsed PTCL patients, indicated that the overall response rate for pralatrexate was not improved compared to brentuximab or the combination therapies, as acknowledged by the PSCR.

Figure 2: Overall response rate to pralatrexate, single agent (brentuximab) and combination regimens

The redacted figure above shows the primary measurement for the overall response rate for pralatrexate was29% (95% CI 21, 39%) which was compare with brentuximab, gemcitabine, DHAP, ESHAP, ICE and mixed pool analysis.

6.14 The ESC noted that the submission stated that pralatrexate had comparable efficacy to other single-agent regimens such as brentuximab (B.6.4.1 of the submission).

Comparative harms

6.15 The submission did not present a comparative safety analysis of pralatrexate and comparator treatments, sourced from randomised studies. It was acknowledged that there is little adverse event information published from RCTs about chemotherapy combinations. Patients in PDX-008 experienced a high burden of adverse events. Notably, 25% of patients had at least one serious adverse event that was treatment-related and 23% of patients in PDX-008 discontinued treatment due to adverse events. In PDX-008 the most commonly reported treatment-related adverse events were mucosal inflammation (68%), thrombocytopenia (40%), nausea (33%), anaemia (32%), fatigue (30%), neutropenia (24%) and epistaxis (23%). Nausea, anaemia, fatigue and epistaxis were generally mild in severity. Mucosal inflammation was common amongst patients and 22% of patients experienced Grade 3 or 4 mucosal inflammation. 31% of patients experienced grade 3-4 thrombocytopenia and 21% of patients experienced grade 3-4 neutropenia.

Benefits/harms

6.16 A summary of the comparative benefits and harms for pralatrexate versus the comparator is presented in the table below.

Table 4: Summary of comparative benefits and harms for pralatrexate and comparator

MCA	Pralatrexate (PDX-008 matched cohort n=[redacted])^	Comparator	Absolute Difference	HR (95% CI)
OS (median months)	19.0 (11.4,NE)	[redacted]	[redacted]	[redacted]

Harms	Pralatexate	Comparator	RR (95% CI)	Event rate/100 patients/ per 2 years		RD (95% CI)
				Pralatrexate	Comparator	
Treatment related neutropenia (all grades)						
PDX-008 efficacy evaluable population	27/111	NR	NE	[redacted]	NR	NE
Treatment related thrombocytopenia (all grades)						
PDX-008 efficacy evaluable population	44/111	NR	NE	[redacted]	NR	NE
Treatment related mucosal inflammation (all grades)						
PDX-008 efficacy evaluable population	76/111	NR	NE	[redacted]	NR	NE

Source: Table B.6.2, p B66, Figure B.6.3, pB79 of the submission and page 37 of clinical-overview-row.pdf
Abbreviations: OS = overall survival, HR= hazard ratio, NR = not reported, NE = not evaluable, MCA = matched control analysis
^ Based on updated results; additional survival data obtained from [redacted] patients in the efficacy evaluable population and [redacted] patients in the matched population

6.17 On the basis of the naïve comparison of pralatrexate and the comparator, there was approximately [redacted] months difference in overall survival. The ESC considered this survival benefit was likely over-estimated.

6.18 The difference in adverse events between pralatrexate and the comparator is unknown. The PSCR (p1) argues that pralatrexate has a more tolerable toxicity profile than the comparators, allowing responders to pralatrexate to continue therapy over a longer period extending disease control, but did not present additional data to support this assertion.

Clinical claim

6.19 The submission described pralatrexate as superior in terms of comparative effectiveness over single-agent and combination therapies. In terms of comparative safety the submission described pralatrexate as non-inferior to single agent regimens and superior to combination regimens. The ESC considered that claim for efficacy and safety was not adequately supported:

- The key study presented in the submission (PDX-008) is a non-randomised, single arm, open-label study. As such, the study is subject to considerable bias and the effectiveness estimates are subject to considerable uncertainty.
- The submission presented a naïve comparison of a matched sub-group of PDX-008 to a matched historical control cohort selected from 4 international lymphoma databases. The comparison is conducted by performing a 1:1 matched control analysis. Alternate approaches to conducting the matched controls analysis highlighted that the hazard ratio is sensitive to the matching methodology employed.
- The matched sub-group (n=[redacted]) in PDX-008 had a higher median overall survival (OS) ([redacted]) compared to the efficacy evaluable population (n=[redacted]) ([redacted]). This has the potential to bias the overall hazard ratio in favour of pralatrexate.
- Patients were not matched on the basis of [redacted]. An inclusion criterion of PDX-008 was an ECOG status of 2 or less. It is likely that PDX-008 patients have, on average, a better performance status than patients extracted from the databases. This has the potential to bias survival outcomes in favour of the treatment group.
- The submission did not present a comparative safety analysis of pralatrexate compared to comparator treatments.

6.20 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.

6.21 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.22 **Table 5: Summary of model structure and rationale**

Time horizon	10 years in the model base case versus 5 years in trial
Outcomes	Life years, deaths and QALYs
Methods used to generate results	Markov model with Monte Carlo simulation
Health states	Patients were modelled as alive or dead. Alive patients were partitioned into complete response, complete response (unevaluable), partial response, stable disease, progressive disease and unevaluable response.
Cycle length	One month
Transition probabilities	Parametric function is used to approximate the matched historical control cohort reference overall survival curve with the hazard ratio applied to approximate the overall survival curve in the pralatrexate arm. Proportion of patients in each alive health state assumed to be equal in each arm. Derived from PDX-008.

Source: constructed during the evaluation

6.23 The ESC noted that the Commentary had identified a number of technical issues with the model, including:

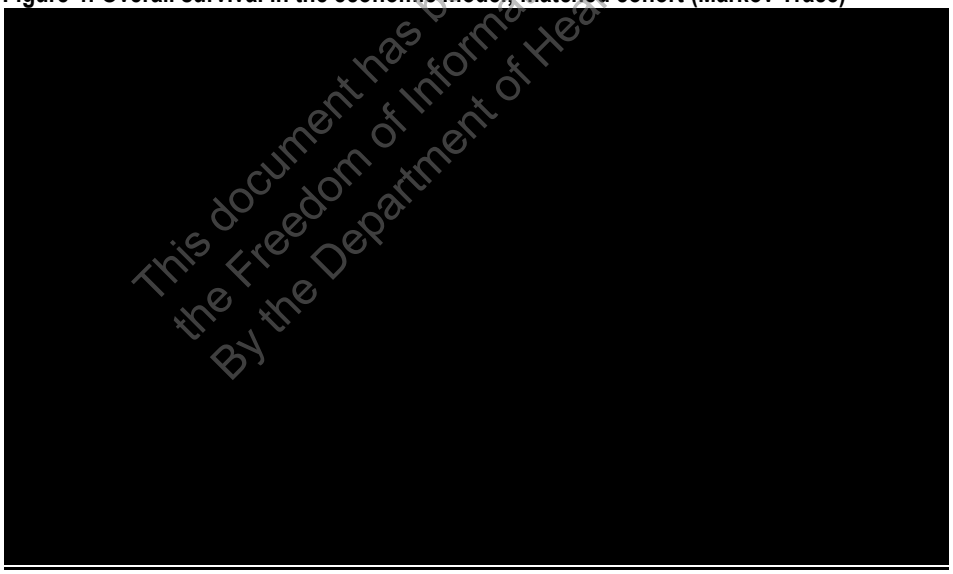
- All costs seem to be included as one off costs up front (hence the pralatrexate arm costs do not change from Step 2b onwards in the 'stepped economic evaluation' table below, even with discounting and a change in model time horizon), rather than accruing over time with treatment. The ESC considered this lead to implausible results that favour pralatrexate, whereby incremental costs for 5 years and 10 years follow up are identical, so incremental costs are not increasing over time, even though patients continue to accrue health outcomes.
- No variation of proportion of patients in each response state across treatment arms or with cycle. This result in the QALYs being driven by survival, rather than any changes in response to treatment.
- No inclusion of post-progression treatment costs and consequences, including stem cell transplant. The ESC disagreed with the PSCR (p5) when the response claimed that inclusion of these costs would define the resulting analysis as a 'cost of illness study'.
- Modelled overall survival estimates in the TreeAge economic model are inconsistent with the Kaplan Meier data. Survival estimates from the economic model show that [redacted]% of patients in the matched control cohort are alive after [redacted] years and [redacted]% of patients in the matched control cohort are alive at the end of the model. [redacted]% of patients in the matched pralatrexate cohort are alive after [redacted] years and [redacted]% of patients in the matched pralatrexate cohort are alive at the end of the model. These estimates are inconsistent with the Kaplan-Meier data ([redacted] year survival of [redacted]% in the matched control cohort and [redacted]% in the matched PDX-008 cohort). In addition, the model estimates that [redacted]% of pralatrexate patients and [redacted]% of matched cohort patients are alive at [redacted] years. The PSCR (p2) identified an error in the model that resulted in a modelled overall survival that is longer than would be anticipated from the Kaplan-Meier curves. The corrected model indicated that in the pralatrexate arm [redacted]% of patients are still alive and in the comparator arm[redacted]% of patients are still alive at the end of the model. After [redacted] years, [redacted]% of patients in the pralatrexate arm are still alive and [redacted]% of patients in the comparator arm are still alive. Despite correction in the revised model provided in the PSCR, the ESC considered that incremental survival was still overestimated in the model. Based on the information in the

submission, this inconsistency can be visualised by comparing the Kaplan Meier data and Markov traces (pralatrexate and control arms) from the model in the figures below.

Figure 3: Overall survival in the economic model; pralatrexate (Markov Trace)

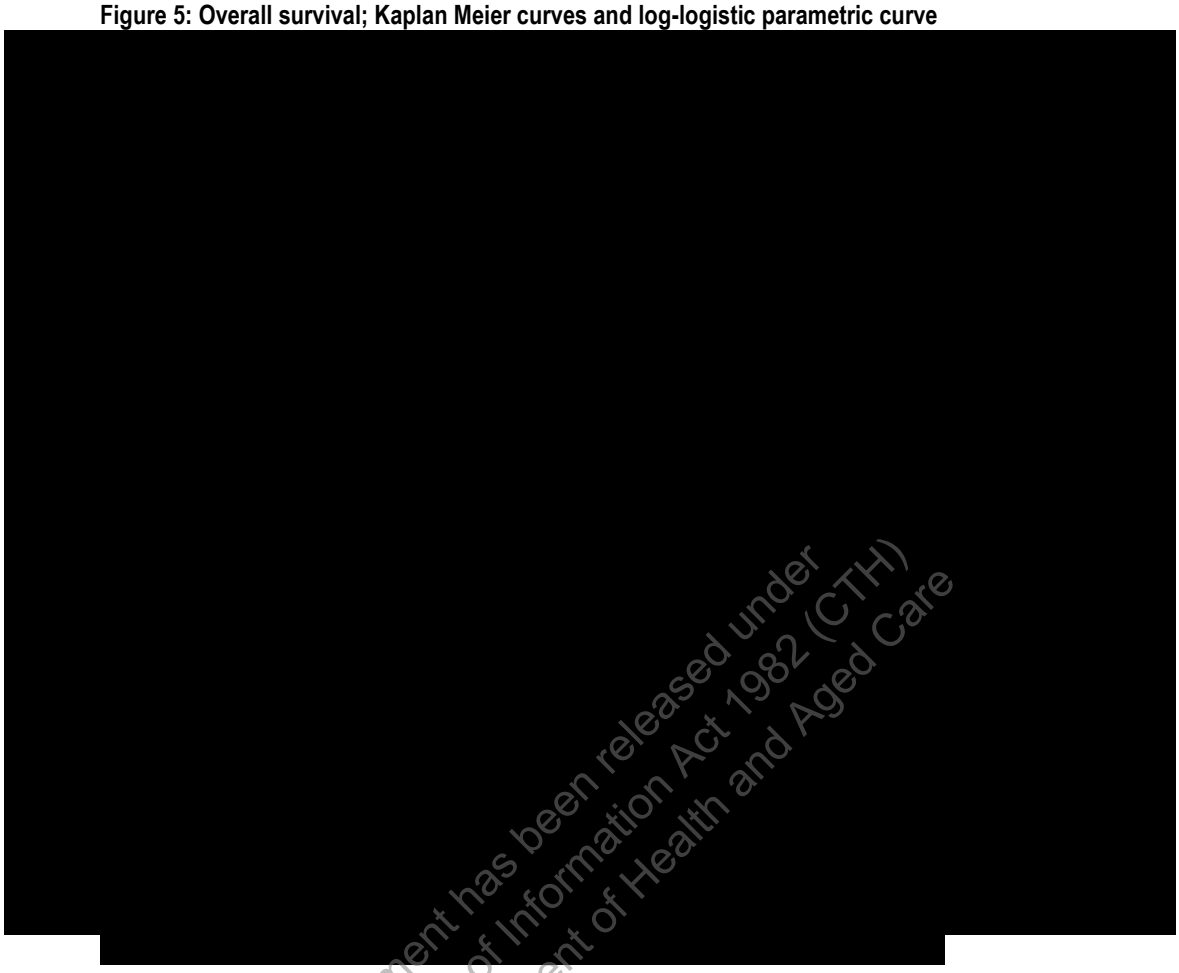
Source: Figure C(i).2.1of the Commentary. Extracted during the evaluation from the economic model (Folotyn Model FINAL (Step 5) Base Case.trex)

Figure 4: Overall survival in the economic model; matched cohort (Markov Trace)



Source: Figure C(i).2.2 of the Commentary. Extracted during the evaluation from the economic model (Folotyn Model FINAL (Step 5) Base Case.trex)

Figure 5: Overall survival; Kaplan Meier curves and log-logistic parametric curve



6.24 **Table 6: Key drivers of the model**

Description	Method/Value	Impact
Hazard ratio	[redacted] (matched control analysis)	High, favours pralatrexate
Dose of pralatrexate	Calculated based on mean total dose in PDX-008. Does not include wastage	High, favours pralatrexate
Cost of comparator chemotherapy regimens	Based on chemotherapy treatments in the matched historical control cohort (not include brentuximab)	Low, favours comparator
Utility values	Swinburn 2012	Moderate, favours pralatrexate
Costs of adverse events	Treatment related to neutropenia included, other adverse events excluded	Low
Choice of parametric function	Log-logistic	Low

Source: compiled during the evaluation

6.25 **Table 7: Results of the stepped economic evaluation**

Step and component	Pralatrexate	Comparator	Increment
Step 1: Trial-based outcomes			
Life years	[redacted]	[redacted]	[redacted]
Incremental cost/extra outcome gained			**NA**
Step 2a: Trial based costs and outcomes (pralatrexate and comparator drug costs)			
Costs	$[redacted]	[redacted]	$[redacted]
Life years	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			**$[redacted]/LYG**
Step 2b: Trial based costs and outcomes (pralatrexate and comparator drug costs, co-medication, admin and adverse event costs)			
Costs	$[redacted]	[redacted]	$[redacted]
Life years	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			**$[redacted]/ LYG**
Step 3a: Inclusion of utilities			
Costs	$[redacted]	[redacted]	$[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			**$[redacted]/ LYG**
Incremental cost/QALY gained			**$[redacted]/QALY**
Step 3b: Inclusion of discount rate			
Costs	$[redacted]	[redacted]	$[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			**$[redacted]/ LYG**
Incremental cost/QALY gained			**$[redacted]/QALY**
Step 4: Replacement of Kaplan-Meier curves with parametric curve for matched historical cohort and hazard rate applied to pralatrexate arm			
Costs	$[redacted]	[redacted]	$[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			**$[redacted]/ LYG**
Incremental cost/QALY gained			**$[redacted]/QALY**
Step 5: Modelled evaluation: model extended to 10 years			
Costs	$[redacted]	[redacted]	$[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/life year gained			**$[redacted]/ LYG**
Incremental cost/QALY gained			**$[redacted]/QALY**

Source: Table D.6.1, pD31, Table D.6.2, pD33, Table D.6.3, pD35 of the submission

6.26 The Kaplan-Meier estimates in the economic model were not able to be verified during the evaluation. The source of the estimates used in the pralatrexate arm was not able to be identified during the evaluation. In the comparator arm the Weibull survival curve was used instead of the Kaplan Meier curve. As a result the ICERs up to Step 3b are unable to be verified. The ESC noted that the PSCR indicated the estimates used were derived from the matched cohort report, however, the ESC could not identify the data in the sources stated in the PSCR to verity these estimates.

6.27 The PSCR (p2) corrected errors in the model, including the mortality estimates. The PSCR updated the base case ICER to be $45,000/QALY – $75,000/QALY.

6.28 The submission presented univariate and probabilistic sensitivity analyses. The evaluation conducted additional univariate sensitivity analysis to examine the impact of wastage, not considered by the submission. Including wastage the ICER increased to $75,000/QALY – $105,000/QALY.

6.29 The evaluation also explored the impact of using the alternate hazard ratios obtained in the sensitivity analyses of the matched controls analysis (MCA). This was considered important as the hazard ratio was sensitive to the matching methodology employed. Using these alternate hazard ratios the ICER increased to $75,000/QALY – $105,000/QALY.

6.30 The model was most sensitive to the dose (number of vials) of pralatrexate and the incremental survival gain.

Drug cost/patient: $[redacted]

6.31 The total cost of treatment was modelled to be $[redacted]. This was based on the total dose of treatment in PDX-008, an assumed body surface area (assumed separately for males and females, 1.8m^2 overall) and a gender ratio obtained from the matched control cohort. Based on the mean number of cycles in PDX-008 (3 cycles) the cost per cycle was $[redacted]. The total cost of treatment of the comparator was modelled to be $[redacted] (this cost was based on the basket of comparator therapies nominated in the clinician survey). Based on an average of [redacted] cycles the cost per cycle was $[redacted].

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC. The submission adopted an epidemiological approach. At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $20 – $30 million million.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (sALCL patients)	20%	30%	30%	30%	30%
Market share (all other patients)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Scripts*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table E.3.2, pE11 of the submission, Table E.6.3, pE38 of the submission, Folotyn – Section E Base Case (Ver10).xlsx, sheet Net Cost to PBS

*Assuming 14 scripts per person as estimated by the submission.

Abbreviations. sALCL - Systemic Anaplastic Large Cell Lymphoma.

6.33 The 6th Community Pharmacy Agreement which took effect on 1 July 2015, made some changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement.

In addition, some chemotherapy compounders will be paid a smaller fee and the DPMA that is published in the schedule will only include that smaller fee.

Under the finalised new arrangements:

a) The preparation fees paid to compounders who are licensed by the TGA to undertake such compounding are higher than those paid to compounders who are not licensed by the TGA, recognising that TGA licensed compounders incur additional costs in complying with the TGA's licensing requirements, as compared to chemotherapy compounders who are not TGA licensed;
b) The preparation fee paid to TGA licensed compounders remains the same as under the 5th CPA at $102.67* (indexed price for 2014/2015);
c) The preparation fees paid to a s90 Community Pharmacy (including s92 approved practitioners) and a s94 Approved Private Hospital Authority are the same as those paid to TGA licensed compounders to recognise the specialist nature of preparing chemotherapy medicines;
d) The preparation fee paid to non-TGA licensed compounders is $20 less at $82.67.
e) Where applicable, the $20 portion of the preparation fee will be paid directly to the compounder through Australian Healthcare Associates (AHA); and.
f) The $20 is not currently captured by the DMPA that is published in the Schedule of Pharmaceutical Benefits.

As the majority of chemotherapy preparations are compounded in settings where the $102.67 fee applies, this fee should continue to be used in PBAC submissions.

6.34 There is potential for the net cost to government to be greater than the estimate in the submission given that:

- The number of patients receiving treatment for PTCL in second line may grow.

- The estimated total number of vials per patient has been calculated incorrectly by the submission.
- The submission does not consider the number of vials administered per dose (i.e. wastage).
- The special pricing arrangements for brentuximab results in a reduced offset due to patients not using brentuximab.

Financial Management – Risk Sharing Arrangements

6.35 The submission requested a Special Pricing Arrangement such that the pricing of pralatrexate be published at no less than $[redacted] (ex. man - per 20mg vial). The submission proposed a risk share arrangement so that any additional cost to government as a result of a Special Pricing Arrangement is rebated to government.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC did not recommend Authority Required listing for pralatrexate for treatment of relapsed or refractory peripheral T-Cell lymphoma. In reaching this conclusion, the PBAC considered that there was insufficient evidence of the incremental clinical benefit against currently available treatments, concerns regarding a high burden of adverse events, and economic modelling was not reliable to enable the Committee to determine the cost-effectiveness of the pralatrexate in the Australian context.

7.2 The PBAC accepted that the basket of treatments was the appropriate the main comparator.

7.3 The PBAC noted that the PDX-008 trial of pralatrexate was a single arm study, which by its nature is subject to biases. The PBAC recalled that other submissions, including brentuximab for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma, have utilised a matched cohort analysis to quantify the comparative clinical efficacy of treatments in small patient populations. While the PBAC considered that this analysis was appropriate, the Committee was concerned about the methodology used in the submission, where the submission presented the most optimistic clinical benefit of a small sub-group of patients in the PDX-008 trial compared to the historical control cohort (median survival of 19 and [redacted] months respectively). The PBAC noted that the hazard ratio for overall survival in the base case matched controls analysis (MCA) was [redacted] (95%CI: [redacted], [redacted]) while using different matching methodologies, hazard ratio was [redacted] (95%CI: [redacted], [redacted]) and [redacted] (95%CI: [redacted], [redacted]).

7.4 The PBAC considered that there is a clinical need for new effective treatments for the relapsed or refractory peripheral T-Cell lymphoma, and noted that this view was reiterated in the pre-PBAC response. The PBAC considered that there was insufficient evidence of incremental benefit of pralatrexate versus comparators, based on evidence from study PDX-008, in which median progression-free survival was 3.5 months, and a meta-analysis of fourteen single arm comparisons indicated that the overall response rate for pralatrexate was not improved compared to

brentuximab or combination therapies. Overall, the PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data in the submission.

7.5 The PBAC noted study PDX-008 was associated with high burden of adverse events, where 25% of patients had ≥ 1 treatment-related serious adverse event, 23% of patients in PDX-008 discontinued treatment due to adverse events. The PBAC noted the discussion of comparative safety by the sponsor in the PSCR and the pre-PBAC response, but considered that the evidence presented in the submission did not support the claim of claim of non-inferior comparative safety in the submission.

7.6 The PBAC agreed with the ESC that there was insufficient clinical evidence to support the claim of superior efficacy and non-inferior safety, and therefore considered the economic evaluation presented in the submission was neither informative nor meaningful. The PBAC noted that, as presented in the submission, the ESC considered that the model was not sufficiently reliable to provide a plausible estimate of value for money for the listing of pralatrexate. The PBAC noted that of the many issues raised by ESC, the pre-PBAC response only addressed the issue of post-progression costs, which reiterated that these costs should not be incorporated into the economic modelling. The PBAC considered that a model should include post-treatment costs, as in the case of the economic model of brentuximab for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma, recommended at the March and July 2014 PBAC meetings.

7.7 The PBAC considered, at the price requested, that the net cost to government may be greater than the estimate in the submission.

7.8 The PBAC noted that patients in the PDX-008 trial had a median of 3 lines prior therapy, but considered that a second or later line listing as proposed in the submission was the appropriate clinical place for pralatrexate. The PBAC considered that the following would need to be addressed in a major resubmission: present more robust evidence to demonstrate the comparative efficacy and safety of pralatrexate over the comparators, ideally including other evidence of clinical benefit, such as Quality of Life data; and a substantially updated economic evaluation addressing the concerns of ESC and revised financial estimates. The PBAC recalled that brentuximab for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma was accepted in the ICER range of $45,000 to $75,000/QALY and the Committee considered, given uncertainty of clinical benefit, that an ICER at the lower end of this range would be needed in order for pralatrexate to be acceptably cost-effective.

7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to

recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

PTCL is a rare group of diseases. Once a patient becomes refractory or relapses from 1st line treatment they rely on combination treatments, whose evidence is with b-cell lymphoma patients, rather than in PTCL. Pralatrexate would provide a valid treatment option for these relapsed/refractory PTCL patients. The Sponsor will continue working with the PBAC in order to ensure that pralatrexate is made available to patients who currently have no targeted treatment for their cancer.

PUBLIC SUMMARY DOCUMENT
Product: Vorinostat, capsule, 100 mg, Zolinza®
Sponsor: Merck Sharp & Dohme Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an Authority Required listing for the treatment of advanced (stage IIB-IV) cutaneous T-cell lymphoma (CTCL) where treatment has failed with four systemic therapies.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Vorinostat was TGA registered on 15 December 2009 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease subsequent to prior systemic therapies.

4. Listing Requested and PBAC's View

Authority Required

Initial PBS-subsidised treatment, as monotherapy, in advanced stage (stage IIB - IV) Cutaneous T-cell Lymphoma, where treatment failure has occurred with four systemic therapies, unless contraindicated. At least one of these therapies should be a chemotherapy regimen.

Treatment failure is defined as:
(a) disease progression following treatment, or
(b) intolerance or toxicity to a particular treatment.

Patients will be eligible for a maximum of 3 scripts as initial therapy to enable their response to treatment to be assessed. If no response is achieved after 3 months, the patient is no longer eligible for PBS-subsidised treatment with vorinostat.

Authority Required

Continuing PBS-subsidised treatment, as monotherapy, in patients with advanced stage (stage IIB - IV) Cutaneous T-cell Lymphoma who have taken vorinostat for up to 3 months and whose disease has improved. Improvement is defined as a 50% reduction in the mSWAT score.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cutaneous T-cell lymphoma (CTCL) is collective term for a group of non-Hodgkin lymphomas (NHL) that initially present in the skin and may ultimately involve lymph nodes, blood and internal organs. CTCL is a rare disease and accounts for about 3.9% of all NHLs.

The disease initially presents as red or pink scaly patches, which evolve into skin tumours as the disease progresses. The tumours may ulcerate and result in secondary infection. The disease may also present as erythroderma, a mass of red lesions covering greater than 80% of

the body area which may or may not include clinically significant blood involvement. In addition to disfiguring, painful skin lesions, CTCL patients are often troubled with intense pruritus (itching).

Early stage disease is usually managed with topical steroids, topical nitrogen mustard, topical retinoids, phototherapy, localised radiotherapy or total skin electron beam (TSEB). Advanced stage disease is usually managed with systemic treatments such as interferon alfa (with or without phototherapy or acitretin), extracorporeal photopheresis, and single agent or combination chemotherapy.

The submission proposed that vorinostat would provide a further treatment option for patients with advanced stage CTCL when other alternative treatments have failed, prior to palliative care.

6. Comparator

The submission nominated palliative care, comprising of radiation; topical steroids; occlusive dressings, wet wraps, wound dressings and bandages; and related hospital admissions.

Although the submission presented multiple case series of various chemotherapy treatments used to manage advanced stage cutaneous T-cell lymphoma (CTCL), no formal comparison between vorinostat and these chemotherapies was conducted.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented one 'key' case series study (P001) of vorinostat and 13 supplementary open-label studies (one vorinostat dose finding study (P005), 8 case series chemotherapy studies, three non-randomised studies comparing different chemotherapies and one case series study of bortezomib (Zinzani (2007). The patient populations, study treatments, endpoints and follow-up varied considerably among these studies.

The trials and associated reports published at the time of the submission are in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Single arm studies or single arms of studies presented in the submission		
"Key" Single arm study: Vorinostat		
P001 Olsen et al.	Phase II multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma.	J Clin. Oncology 2007; 25(21): 3109-15
Duvic M et al	The systemic effects of vorinostat in patients with cutaneous T-cell lymphoma (CTCL): Post-hoc analyses in patients with high blood tumor burden.	Blood 2009; ASH Annual Meeting Abstracts(114):1709.
Duvic M et al	Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma.	Clinical Lymphoma & Myeloma 2009; 9(6):412-416.
Supplementary single arm studies		
Vorinostat		

P005 Duvic et al	Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid, (SAHA)) for refractory cutaneous T-cell lymphoma.	Blood 2007; 109: 31-39
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and it variations: COP/ CVP (cyclophosphamide, vincristine, prednisone) or HOP (doxorubicin, vincristine, prednisone)		
Fierro et al	Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow-up study of 81 patients treated with COP or CHOP.	Leukaemia and Lymphoma 1998;34:583-588
Molin et al	Combination chemotherapy in tumour stage of mycosis fungoides with cyclophosphamide, vincristine, VP-16, Adriamycin and prednisolone (COP, CHOP, CAVOP) A report from the Scandinavian Mycosis Fungoides Group.	Acta Derm Verneol 1980;60:542-4
Fludarabine + cyclophosphamide or cladribine		
Mazur et al	Treatment of cutaneous T-cell lymphomas with purine analogues (fludarabine and 2-chlorodeoxyadenosine).	Journal of BUON 2003;8:247-251
Scarrisbrick et al	A trial of fludarabine & cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma.	British J Derm 2001;144:1010-1015
Kong LR et al	2-chlorodeoxyadenosine in cutaneous T-cell lymphoproliferative disorders.	Leukemia & Lymphoma 1997;26(1-2):89-97
Gemicitabine		
Duvic et al	Phase II evaluation of gemcitabine monotherapy for cutaneous T Cell lymphoma.	Clinical Lymphoma & Myeloma 2006;7(1):51-58
Zinzani et al.	Gemcitabine treatment in pre-treated CTCL. Experience in 44 patients.	Clin Oncology 2000;18(13):2603-2606
Zinzani PL et al	Therapy with gemcitabine in pre-treated peripheral T-cell lymphoma patients.	Annals of Oncology 1998;9(12):1351-1353.
Zinzani PL et al	Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome.	Annals of Oncology 2010;21(4):860-863
Bortezomib		
Zinzani PL et al	Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma.	Journal of Clinical Oncology 2007;25(27):4293-4297.
Liposomal doxorubicin		
Quereux G et al	Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary Syndrome.	Arch Dermatol 2008; 144(6): 727-733.
Pulini S et al	Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas.	Haematologica 2007; 92: 686-689.

8. Results of Trials

Study P001:

The results for the primary outcome, objective response and time to progressive disease, from the single vorinostat arm are summarised below:

Response rates:

The objective response rate (as measured by the modified Severity Weighted Assessment Tool (mSWAT) (a ≥ 50% reduction in skin disease from baseline using mSWAT) in advanced stage CTCL disease (Stage IIB or higher) was 29.5% (95% CI: 18.5, 42.6) and this exceeded the pre-specified criteria for vorinostat to be considered as an "active drug" defined

as a response rate of at least 20% with the lower limit of the confidence interval higher than and excluding 5%. Only one response (in patients with Stage IIB or higher) from the total number of objective responses (1/18) was a complete response (the rest were partial responses).

The median time to objective response was around 2 months for patients with Stage IIB disease or higher. The duration of objective response ranged from 34 - 322 days in all patients treated with vorinostat and from 34-280 days for patients with Stage IIB or greater disease.

Pruritus relief:
The PBAC noted of 59 patients, 18 (30.5%) with Stage IIB or higher disease had pruritus relief and 8 (13.6%) had complete resolution of their pruritus symptoms. Relief in pruritus was maintained for at least 4 weeks without any increase in pruritus medication.

Supplementary studies:
The PBAC noted there was substantial heterogeneity in the definitions of response and numerical estimates of objective response, partial response and complete response rates, among the supplementary studies included in the submission. The proportion of patients experiencing 1) an overall response varied from 24% in Kong (1997) to 84% in Pulini (2007), 2) a partial response varied from 8% in Scarrisbrick to 60% in Zinzanni (2000) and 3) a complete response varied from 0% (P005, Molin and Mazur) to 42% in Pulini.

Comparison of vorinostat with chemotherapy:
The PBAC noted that the submission presented one comparison analysis conducted by Prince et al (2010) to examine the effectiveness and safety of vorinostat compared to different chemotherapy regimens using different sources of clinical data (Combined Skin Lymphoma Clinic data).

For PBAC's view, see Recommendation and Reasons.

Overall, about 27% of patients had a serious adverse event and approximately 16% of patients discontinued vorinostat therapy due to an adverse event. Thrombocytopenia and anaemia were the most common haematologic toxicities. Other laboratory abnormalities reported included increased serum glucose in 69% of CTCL patients (59 of 86), transient increases in serum creatinine in 46.5% of patients (40 of 86), and proteinuria in 51.4% of patients (38 of 74). Serious adverse events included pulmonary embolism (4.7%); squamous cell carcinoma (3.5%); and anaemia (2.3%).

9. Clinical Claim

The submission described vorinostat as superior in terms of comparative effectiveness and inferior in terms of comparative safety over the main comparator of palliative care.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a partially modelled (primarily trial-based) evaluation. This is a cost-effectiveness model where in one arm (incremental) costs and effects are estimated from the single arm study P001, and other arm is assumed to have zero (incremental) costs/effects.

The time horizon of the evaluation is one year. The outcomes in the model are: the *incremental* cost per additional patient with response (≥50% and ≥25% decrease in mSWAT); and the incremental cost per additional year with response (≥50% and ≥25% decrease in mSWAT).

For the surrogate outcome number of patients with response (≥25% decrease in SWAT) in patients with stage IIB or greater disease, the submission estimated the incremental cost/additional responder to be in the range $75,000 to $105,000.

For the surrogate outcome years with response (≥50% decrease in SWAT) in patients with stage IIB or greater disease, the submission estimated the incremental cost/additional year of response to be greater than $200,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost per year to the PBS was estimated by the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the submission proposed palliative care as the comparator. However, the PBAC considered that a comparison with best available care, as represented by chemotherapy, is more appropriate than end-of life palliative care as the drug may not be used as last-line treatment. The PBAC noted that consumer comments and expert comments indicated that vorinostat would be used earlier in the treatment algorithm than proposed in the requested restriction (after failure of at least four systemic therapies) and that more toxic treatments would be reserved for patients with refractory disease.

The submission presented one 'key' case series study (P001) of vorinostat, several supplementary open-label and case series chemotherapy studies, three non-randomised studies comparing different chemotherapies and one case study of bortezomib. The objective response rate (a ≥ 50% reduction in skin disease from baseline using mSWAT) of Study P001 was 29.5%, (95% CI 18.5, 42.6) and only one response (in patients with Stage IIB or higher) from the total number of objective responses (1/18) was a complete response (the rest were partial responses). Of 59 patients, 18 (30.5%) with Stage IIB or higher disease had pruritis relief and 8 (13.6%) had complete resolution of their symptoms. The median duration of response was not reached but was estimated to be greater than 4 months with a range of 1 month to 9 months or more. The application would have been stronger if additional data about durability of benefit was presented. The PBAC noted that no survival data are available/ presented from Study P001 or from the non-comparative chemotherapy studies.

The PBAC noted that the quality of the data is extremely limited and the studies presented in the submission are small, non comparative and heterogeneous. The PBAC acknowledged that a meaningful comparison of the effectiveness of vorinostat relative to chemotherapy is difficult. A comparison analysis was conducted by Prince et al (2010) to examine the effectiveness and safety of vorinostat compared to different chemotherapy regimens using different sources of clinical data (Combined Skin Lymphoma Clinic data) but was methodologically flawed. The PBAC noted that better evidence about therapeutic advances

may be forthcoming as there are numerous clinical trials being undertaken which are recruiting patients with cutaneous T-cell lymphoma (Clinical trials.gov).

The submission claimed that vorinostat is superior in terms of comparative effectiveness and inferior in terms of comparative safety over the main comparator of palliative care. The PBAC agreed that vorinostat is an active drug that has superior efficacy to palliative care. However, no conclusion can be reached with respect to comparisons with other available therapies. The PBAC agreed that vorinostat has significant toxicities, and is inferior in safety to palliative care. However, expert testimony suggests it is less toxic than cytotoxic chemotherapies.

A partially modelled (primarily trial-based) evaluation is presented. This is a cost-effectiveness model where in one arm (incremental) costs and effects are estimated from the single arm study P001, and other arm is assumed to have zero (incremental) costs/effects. The PBAC noted that no studies identifying utility weights in CTCL health states were identified and that consequently, a cost-utility analysis could not be performed. The costs of vorinostat are modelled on the basis that patients without a 50% improvement in mSWAT will stop vorinostat treatment after 12 weeks (consistent with the requested restriction). The trial-based outcome (proportion of patients with response) is incorporated into the ICER. The ICER is calculable only for surrogate outcome measures of response and response duration and was therefore considered to be highly uncertain. The ICER was estimated by the submission to be in the range $75,000 to $105,000 per additional responder (surrogate outcome number of patients with response (≥25% decrease in SWAT) in patients with stage IIB or greater disease) to greater than $200,000 per additional year of response (years with response (≥50% decrease in SWAT) in patients with stage IIB or greater disease).

The PBAC noted that the total cost to the PBS was relatively low, however, the clinical place of the drug was uncertain and there was potential for use beyond the requested restriction. Therefore, the financial estimates were considered to be uncertain.

The PBAC acknowledged that that there was a high clinical need for vorinostat and a treatment benefit of around 30% in patients with cutaneous T-cell lymphoma. However, the incremental costs for measurable health gains far exceeded those accepted for other chronic, intractable diseases and other cancers. Cost offsets and toxicities of chemotherapies in the comparator arm may help improve the ICER, although some reduction in the treatment benefit would also need to be assumed.

The PBAC therefore rejected the submission on the basis of unacceptably high and uncertain cost-effectiveness ratios.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Vorinostat fulfils an unmet medical need by providing a treatment option for patients who have exhausted other effective systemic treatments. The negative impact of the disease on patient's quality of life and survival is significant and patients who respond to treatment with vorinostat experience significant relief from their symptoms.

The sponsor acknowledges that the data provided was limited. This is because the rareness of the disease and the individualised approach to treatment makes it difficult to conduct randomised controlled trials (RCT's) in this population.