Advanced Technology in Radiotherapy: How can we ensure benefit for patients?

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Medical Physicist
Peter MacCallum Cancer Centre
Possible Conflict of Interest

• I am a board member of the Transtasman Radiation Oncology Group

• I am an advisor to the Australian Clinical Dosimetry Service at ARPANSA
Contents

• What is advanced technology in radiotherapy?
  • IMRT
  • IGRT

• Why would a patient be interested in these?

• How can we introduce them efficiently and safely?
Local control

Identification of the target

Excellent dose distribution

Delivery of radiation

Verifying delivery

IMRT

IGRT
Traditional Radiation Therapy

Target

Courtesy of J Schreiner
Conformal Radiation Therapy
Conformal Radiation Therapy

Target

Multi-leaf collimator (MLC)
Why more than conformal?

patient

RT beams

target

Organ at risk
Why more than conformal?

patient

RT beams

Organ at risk

target

Beam fluence profile
Conformal Intensity Modulated Radiation Therapy (IMRT)
What characterizes an IMRT treatment?

- Many different MLC leaf positions (>10) for many gantry angles (>5)
- Field placement accuracy better than 2mm
- Segment size down to 1cm
- More than 10000 leaf positions
- Not intuitive
What is in it for patients?

- Better normal tissue sparing
What is in it for patients?

- Better normal tissue sparing - less toxicity
- Possibly higher dose to the target - higher chance of cure
- More dose in a fraction - fewer fractions
Is there clinical evidence for the use of IMRT?

Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies

Liv Veldeman, Indira Madani, Frank Hulstaert, Gert De Meester, Marc Mareel, Wilfried De Neve

Since its introduction more than a decade ago, intensity-modulated radiotherapy (IMRT) has spread to most radiotherapy departments worldwide for a wide range of indications. The technique has been rapidly implemented, despite an incomplete understanding of its advantages and weaknesses, the challenges of IMRT planning, delivery, and quality assurance, and the substantially increased cost compared with non-IMRT. Many publications discuss the theoretical advantages of IMRT dose distributions. However, the key question is whether the use of IMRT can be exploited to obtain a clinically relevant advantage over non-modulated external-beam radiation techniques. To investigate which level of evidence supports the routine use of IMRT for various disease sites, we did a review of clinical studies that reported on overall survival, disease-specific survival, quality of life, treatment-induced toxicity, or surrogate endpoints. This review shows evidence of reduced toxicity for various tumour sites by use of IMRT. The findings regarding local control and overall survival are generally inconclusive.

Lancet Oncology 9 (2008) 367
Figure 3: Evaluation tool for relevance of clinical statements reported in 56 studies of IMRT

BCS=best case series. CS=case series. NRCT=non-randomised controlled trial. RCT=randomised controlled trial. OS=overall survival. DSS=disease-specific survival. QoL=quality of life.
Achievable dose distributions

Bauman et al 2007

Vertebral body

Thyroid

Calvarial radiation
What are the draw backs?

- More complexity
- Need for new (and more accurate) equipment
- More need for QA
- Longer treatment times
- Higher risk of geographical miss
Local control

Identification of the target

Excellent dose distribution

Delivery of radiation

Verifying delivery

IMRT

IGRT
Image Guidance

• First X-ray in Australia (July 25, 1896)
• Bathurst: Father Slattery takes image of Eric Thomson’s hand.
• Eric Thomson had accidentally be wounded by a spring gun
Image guidance for RT

- At the time of delivery
- Must visualize the target (or relevant organ at risk)
- Must also provide information on radiation fields (eg isocentre)

3 gold fiducials implanted into the prostate gland
Image guidance tools on many linacs

- Visualization tools:
  - External (Lasers, markers)
  - Optical surface systems
  - Internal (Seeds)
  - EPID, portal imaging
  - $kV$ imaging
  - CT
    - Cone beam CT
    - CT on rails
    - MVCT
  - US
  - MRI?
Other X-ray image guidance solutions

- Siemens in-room CT
- Brainlab Exactrac
- Protons at PSI
- Tomotherapy MVCT
Like most veterinary students, Doreen breezes through Chapter 9.
What can we do with the images?

- Detect systematic error
- Position the patient, target, or organ at risk
- Modify the treatment plan or choose an appropriate plan
- Detect changes in patient or tumour size
Internal anatomy is changing

Start of treatment
7 days later
2 weeks later
3 weeks later
1 month later

Courtesy of Tim Holmes, St. Agnes Cancer Center, Baltimore, MD
Local control

Identification of the target

Delivery of radiation

Excellent dose distribution

Re-optimising
Verifying delivery

IMRT

 IGRT
Why would a patient be interested in this?
Obvious?

Complexity

Intuition/Obvious
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a doubleblind, randomised, placebo controlled, crossover trial of the parachute.

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes
The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.

Meta-analysis
Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results
Our search strategy did not find any randomised controlled trials of the parachute.
Obvious Evidence?

Parachute or not

Many drugs

Bland vs sharp scalpel

Intuition/Obvious

Complexity
IMRT/IGRT

• Is the outcome always obvious or predictable by other means?

Obvious Evidence?

Complexity

Intuition/Obvious

IGRT? IMRT?
Is it ethical to run a trial?

- Can we ‘randomise’ patients to receive
  - Conventional RT or IMRT?
  - Non-gated or gated RT
- What would I choose?
- Expected participation?
Why should it not work?

- Any hidden problems?
- Who can benefit?
- Can it be implemented widely? Access?
- Too complicated?
- Too expensive?
Can we trust what we see?

- We know:
  - The dose distribution LOOKS better

- We may want to know:
  - Is what we see what we get?
  - Is it safe, feasible and widely applicable?
  - Is it resource effective (cost/benefit)?
Is what we see what we get?

• Quality assurance
• Independent audit
• Documentation of outcomes
Radiological Physics Centre (Houston): Trial QA using phantoms
**RPC: Phantom Results**

Comparison between institution’s plan and delivered dose.

Criteria for agreement: 7% or 4 mm DTA (5%/5mm for lung)

<table>
<thead>
<tr>
<th>Site</th>
<th>Institutions</th>
<th>Irradiations</th>
<th>Pass rate</th>
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<tbody>
<tr>
<td>H&amp;N</td>
<td>472</td>
<td>631</td>
<td>75%</td>
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<tr>
<td>Pelvis</td>
<td>108</td>
<td>130</td>
<td>82%</td>
</tr>
<tr>
<td>Lung</td>
<td>67</td>
<td>77</td>
<td>71%</td>
</tr>
<tr>
<td>Liver</td>
<td>15</td>
<td>18</td>
<td>50%</td>
</tr>
</tbody>
</table>

Courtesy G Ibbott, April 2009
The dose bath...

- Due to increased mu per Gray there is more leakage
- Due to more beams dose is spread over larger volume
- Temptation to use conformal avoidance to spread high dose in critical structure somewhere else

David
### Estimate of risk for secondary cancers (Hall 2006)

<table>
<thead>
<tr>
<th></th>
<th>Estimated risk of fatal radiation-induced malignancies after RT for prostate cancer (%/Sv)</th>
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<tr>
<td><strong>Hall and Wuu (4)</strong></td>
<td></td>
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<tr>
<td>Conventional 6 MV</td>
<td>1.5</td>
</tr>
<tr>
<td>IMRT 6 MV</td>
<td>3.0</td>
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<tr>
<td><strong>Kry et al. (5)</strong></td>
<td></td>
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<tr>
<td>Conventional 18-MV Varian</td>
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<td>IMRT 6-MV Varian</td>
<td>2.9</td>
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<td>Siemens</td>
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<td>IMRT 10-MV Varian</td>
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<tr>
<td>IMRT 18-MV Varian</td>
<td>5.1</td>
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</tbody>
</table>

**Abbreviations:** IMRT = intensity-modulated radiation therapy; MV = megavoltage; RT = radiation therapy.
Is it ethical (not) to run a trial?

- Can we ‘randomise’ patients to receive
  - Conventional RT or IMRT?
  - Non-gated or gated RT
- What would I choose?
- Expected participation?
Elements of introducing new technology

- Needs analysis
- Multidisciplinary team
- Learning from others
- Procedures/protocols
- Quality assurance
- Evaluation
Training (here for adaptive RT for bladder cancer)
Proceed with caution...

**Clinical Investigation**

**Conformal Arc Radiotherapy for Prostate Cancer: Increased Biochemical Failure in Patients with Distended Rectum on the Planning Computed Tomogram Despite Image Guidance by Implanted Markers**

Benedikt Engels, M.D., Guy Soete, M.D., Ph.D., D. Verellen, Ph.D., and Guy Storme, M.D., Ph.D.

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**Purpose:** To evaluate the effect of rectal distention on the planning computed tomogram on freedom from biochemical failure (FFBF) of prostate cancer patients treated with image-guided conformal arc radiotherapy.

**Methods and Materials:** The outcomes of 238 patients with T1–T3N0M0 tumors were analyzed, with a median follow-up of 53 months (range, 24–93 months). In 213 patients, daily co-registration of X-rays and digitally reconstructed radiographs was used for positioning, whereas in 25 patients positioning was done using direct prostate visualization with implanted markers. The rectal average cross-sectional area was determined on the planning computed tomogram.

**Results:** The 5-year freedom from Grade 3 to 4 late gastrointestinal and urinary side effect, according to the Radiation Therapy Oncology Group criteria, was 100% and 99.4% respectively. The 5-year FFBF was 88.4%. On multivariate analysis the following variables were significantly related to worse FFBF: risk group according to the National Comprehensive Cancer Network (high- to very high risk vs. intermediate- to low-risk), dose (70 vs. 78 Gy), average cross-sectional area (≥16 vs. <16 cm²) and, unexpectedly, the use of implanted markers as opposed to bony structures for patient positioning. In retrospect, the margins around the clinical target volume appeared to be inadequate in the cases in which markers were used.

**Conclusion:** Overall, the outcome of patients treated with image-guided conformal arc radiotherapy is excellent. We were able to confirm the negative prognostic impact of a distended rectum on the planning computed tomoogram described by others. The study illustrates the potential danger of image guidance techniques as to margin reduction around the clinical target volume. © 2008 Elsevier Inc.
CLINICAL INVESTIGATION

CONFORMAL ARC RADIOTHERAPY FOR PROSTATE CANCER: INCREASED BIOCHEMICAL FAILURE IN PATIENTS WITH DISTENDED RECTUM ON THE PLANNING COMPUTED TOMOGRAM DESPITE IMAGE GUIDANCE BY IMPLANTED MARKERS

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Summary

• Radiotherapy practice relies on technology
• There is good reason to believe that improved technology will benefit patients
• There is a large variety of different approaches
• Multidisciplinary collaboration, training, quality assurance and discussion is needed
• Clinical trials are a method to test some aspects of technology
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