Indications for IMRT (Evidence Based Medicine) Part II – lessons learned from the ANROTAT project

A/Prof Annette Haworth & A/Prof June Corry

Clinical Research Physicist/ Chair, H&N Service

Peter MacCallum Cancer Centre

Regional Training Course on Basics of Intensity Modulated Radiotherapy

Melbourne Australia, 9-13 September 2015
STATEMENT:
IMRT is SAFE and compared with 3DCRT is CLINICALLY EFFECTIVE and COST-EFFECTIVE

How do we determine this statement is true?
ANROTAT Project

- 2010: Clinical trials group *TROG* commissioned by Australian Commonwealth Govt. (DoHA) ($1.6mil)

- ‘Assessment of New Radiation Oncology Technology and Treatments’ (ANROTAT) Aims
  - Develop and test a generic research framework
  - Rapid assessment of the safety, clinical efficacy and cost effectiveness
  - new radiation oncology technologies and treatments

- Completed in June 2012 (2 year time frame)
The Framework

Design a generic research framework

- Assess clinical efficacy, safety, cost effectiveness
- Easily and freely accessible for treatment centres
<table>
<thead>
<tr>
<th>STAGE</th>
<th>STEP</th>
<th>COMPONENTS</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PREPARATION</td>
<td>Define Question: Horizon scan, professional expertise</td>
<td>Patient Population, Intervention, Comparator, Outcome(s) of interest, Setting, Perspective</td>
<td>Clarity of question to be answered, Scope, goal posts &amp; limitations</td>
</tr>
<tr>
<td></td>
<td>Define technology</td>
<td>Include processes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Define evidence sources</td>
<td>Systematic review, Prospective data, Retrospective data, Expert opinion, Register (longitudinal data)</td>
<td>Agreed parameters, indicators, What data are required?</td>
</tr>
<tr>
<td>2. METHODOLOGY</td>
<td>Clinical requirements</td>
<td>Disease sites, Disease end points, Toxicity points (QoL), Dosimetric/DVH parameters</td>
<td>Robust and transferable disease indicators, Rapid (surrogate) indicators</td>
</tr>
<tr>
<td></td>
<td>Economic analysis</td>
<td>Costings, Utilities, Decision analytic model structure, Statistics</td>
<td>Valid and transferable model</td>
</tr>
<tr>
<td></td>
<td>Data Protocols</td>
<td>Prospective and/or retrospective data collection, Other protocols including Quality Assurance, Use of Register data</td>
<td>Population of genetic template</td>
</tr>
<tr>
<td>3. PROJECT MANAGEMENT</td>
<td>Timelines</td>
<td>Early discussion</td>
<td>Agreed and realistic</td>
</tr>
<tr>
<td></td>
<td>Resources</td>
<td>Staff, hardware, software, budget, other, Collaborations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Governance</td>
<td>Define responsibilities</td>
<td>Efficient project conduct</td>
</tr>
<tr>
<td></td>
<td>Communication</td>
<td>Communication</td>
<td>Effective communication and buy-in</td>
</tr>
<tr>
<td></td>
<td>Activation</td>
<td>Site recruitment, Ethics, Credentialing</td>
<td>Technical validity</td>
</tr>
<tr>
<td></td>
<td>Data Management</td>
<td>Collection (IT infrastructure), Centralisation, Quality Assurance</td>
<td>Data Validity</td>
</tr>
<tr>
<td>4. ANALYSIS</td>
<td>Modelling, statistics</td>
<td>Values of indicators</td>
<td>Informs cost utility equation</td>
</tr>
<tr>
<td></td>
<td>Sensitivity analysis</td>
<td>Effects of varying assumptions, Applicability</td>
<td>Clinical efficacy, Technical efficacy, Societal efficacy</td>
</tr>
<tr>
<td></td>
<td>Interpretation</td>
<td>Context, perspectives, Applicability, Justification, Report</td>
<td>Demonstration of benefit or otherwise, relative societal value in the health care context</td>
</tr>
<tr>
<td>5. EVALUATION</td>
<td>Review framework structure and function</td>
<td>Does it need adjusting?</td>
<td>Ongoing usefulness</td>
</tr>
<tr>
<td></td>
<td>Follow up</td>
<td>Phase 4 - real life application, Confirmation of utility</td>
<td>Ongoing informing of Health Technology Assessments</td>
</tr>
</tbody>
</table>
Five Stages of Technology/Technique Assessment

- **Preparation**
  - Define question/technology/comparator
  - What data already exists/what needs to be collected

- **Methodology**
  - Clinical
  - Economic

- **Project management**
  - Data collection
  - Who, what, when, how, ethics

- **Analysis**
  - Economic modelling
  - Statistics
  - Clinical interpretation
  - Safety

- **Evaluation**
  - Did the framework work?
  - Does the data collected in the short term reflect long term clinical outcomes?
Data Collection

- Review data available
  - Multi-centre Level III randomised clinical trial – preferable

- Collect data representing local practices (next slides)
  - Clinical data
  - QoL & costing for economic analysis

- Assess safety/education through benchmarking, physics QA review and dosimetry audits
Testing the Framework (IMRT) - Methods

- Collect data to support the assessment:
  - clinical efficacy,
  - safety,
  - cost effectiveness
- Comparator: 3DCRT
- New technology/tech: IMRT
- Clinical sites (selected by Govt):
  - Post-prostatectomy (PP)
  - NPC
  - Anal canal (AC)
- Image Guided Radiation Therapy (IGRT) in the Intact Prostate
Data Collection

• All data
  • Multiple centres (hospitals)
  • Retrospective & prospective
  • Representing ~30 patients/ study

• Clinical Efficacy
  – Planning studies (3DCRT vs IMRT)
    • Surrogate endpoints (DVH) to predict tumour control & toxicity

  – Safety
    • Credentialing & QA studies inc contouring, physics (patient specific QA & external dosimetry audits)

  – Cost effectiveness
    • Cost related to:
      – Service delivery
      – Patient costs
    • QoL
Economic analysis
Decision Analytic Models (DAM)

Markov Model
Decision Analytic Models

- Each health state is populated using evidence from the literature, expert opinion, or data collected
- Data used to calculate incremental quality adjusted life years (QALYs)
  - Not all years have same quality
- Time in each health state weighted by a health-related QoL value (utility)
  - death=0; full health=1
- Aims to reflect society’s preferences for different treatments and health outcomes
Study cohort (n=30):
- RAVES patients
- Prospective & retrospective

3DCRT & IMRT plans created
- 64 Gy & 70 Gy
- Predict tumour control & toxicity

Carter et al RO 2014
Results (prostate bed)

- 15/1000 IMRT patients would develop less late toxicity cf 3DCRT
- FFbF, OS etc same for both groups
- IMRT costs $226/pt more than 3DCRT @ 5-years
- @ 20 years mean incremental cost:
  - $32,816 IMRT
  - $33,917 3DCRT
- IMRT more effective & less costly than 3DCRT

Carter et al RO 2014
Results – IMRT benefit, IGRT marginal

• Post-prostatectomy
  – IMRT greater benefit at higher dose (70 Gy vs 64 Gy)
  – Lower toxicity = additional 0.02 QALY

• AC
  – Reduced local recurrence/ predicted cancer death
  – Reduced late femoral head fracture toxicity

• NPC
  – Reduced local recurrence/ distant mets
  – Reduced late toxicity

• IGRT
  – Safer than comparator
  – Marginally more costly
  – IMRT can’t be delivered without it
  – Despite slight increase in cost, overall societal benefit
Caveats

– Many uncertainties
– Very expensive & time consuming project
– Aust. Centres generally well educated & reasonably resourced
– IMRT anal cancer was a good example of limited experience but:
  • Practices varied widely
  • Results difficult to interpret
Safety assessment
Data quality

10 Benchmarking cases:
RT QA review by
Dr June Corry
Dr Anne Lee
Dr Louis WT Ng

30 Clinical cases:
Prospective and retrospective cases
All had RT QA review:
HN RO PMCC:
Dr Tsien Fua
Dr Mark Lee
Dr Chen Liu
Dr June Corry
Safety assessment / Data quality
A/Prof June Corry, Prof Anne Lee and Dr Louis WT Ng

IMRT/ NPC Study

10 sites involved: Public and Private, Large and Small, City and Rural

Only 4/10 cases had no major protocol violations

60% had major protocol violations (GTV, PTV or dose to critical organs)

Resubmitted after constructive feedback and 5 of the 6 were then compliant

EDUCATION re NPC CONTOURING IMPORTANT
Subsequent Clinical Cases:
3 from each centre – 30 cases
RT QA – Drs Mark Lee, Tsien Fua, Chen Liu, June Corry

RT QA in these cases showed NO major protocol violations in relation to GTV or PTVs

So constructive peer review of IMRT QA can significantly and durably improve RT protocol compliance
Recommendations/ Lessons Learned

- TROG Framework available:
  - Good starting point
  - Horizon scanning
- Source all available evidence
  - Fund a systematic review, clinical & economic data
- Data collection
  - Huge effort
  - TROG protocols available
  - Multi-centre
  - Requires rapid data collection & analysis
- Engage professional economist from the outset
- Don’t under estimate need for QA, peer review etc

Registry

Special Article
Developing a national radiation oncology registry: From acorns to oaks

Jatinder R. Palta, PhD\textsuperscript{a}, \textsuperscript{a} Jason A. Efslathiou, MD, PhD\textsuperscript{b}, Justin E. Bekelman, MD\textsuperscript{c}, Sasa Matic, PhD\textsuperscript{d}, Carl R. Bogardus, MD\textsuperscript{e}, Todd R. McNutt, PhD\textsuperscript{f}, Peter E. Gabriel, MD\textsuperscript{g}, Colleen A. Lawton, MD\textsuperscript{a}, Anthony L. Zietman, MD\textsuperscript{b}, Christopher M. Rose, MD\textsuperscript{h}

- Validates technology assessment
- Supports future technology reviews
- Automated data collection is preferable
- Needs collaborative support
- Address patient confidentiality/consent issues
- Industry collaboration essential
Conclusions

- IMRT more effective & less costly
  - Conclusion held in sensitivity analysis
- IGRT
  - Safer than comparator
  - Marginally more costly
  - IMRT can’t be delivered without it
  - overall societal benefit
- Surrogate end-points need to be validated
  - Relationship of DVH with TCP & NTCP complex
  - Registry
- Many uncertainties in data used in model
- Costly & time consuming exercise
  - Resources available
- Do a health economics course!!
  - And don’t forget to engage an economist 😊
Acknowledgements

The ‘Assessment of New Radiation Oncology Technology and Treatments Project’ (ANROTAT) is funded by the Australian Government Department of Health and Ageing (DoHA)

ANROTAT Exec: Prof Gillian Duchesne (Chair), Rowena Amin, Deidre Cornes, Annette Haworth, Tomas Kron, Bryan Burmeister

NHMRC Clinical Trials Centre, especially – Andrew Martin, Hannah Verry (nee Carter)
Project Team

Executive Advisory Group (EAG)
Chair: Prof Gillian Duchesne
Prof Bryan Burmesiter, Prof Tomas Kron, Assoc Prof Annette Haworth,
Mrs Rowena Amin, Ms Deidre Cornes, Ms Mel Grand

TROG Team
CEO (Rowena Amin), ANROTAT Project Team, TROG QA Team

IMRT Expert Group
Assoc Prof Annette Haworth (Chair)
June Corry, Michael Ng, Michael Jackson,
Phil Vial, Craig Everitt, Colin Hornby

IGRT Expert Group
Prof Tomas Kron (Chair)
Scott Babington, Farshad Faroudi, Charles Lin
Peter Greer, Martin Ebert, Aldo Rolfo
Bronwyn Hilder, Justin Dixon, Jim Frantzis

IMRT Nasopharynx Expert Sub Group
Assoc Prof
June Corry (Chair)
Annette Haworth, Chris Wratten,
Frank Gagliardi, Jeremy Booth,
Craig Everitt, Sheryn Campbell

IMRT Anal Canal Expert Sub Group
Chair: Dr Michael NG,
Annette Haworth, Sarat Chander,
Robert Lin, Alison Cray,
Elizabeth Brown,
Brinda Subramanian

IMRT Post Prostatectomy Expert Sub Group
Dr Michael Jackson (Chair),
Annette Haworth, Mark Sidhom,
Adrian Gibbs, Frank Gagliardi,
Colin Hornby, Maree Wood
References

Cost-effectiveness

A decision model to estimate the cost-effectiveness of intensity modulated radiation therapy (IMRT) compared to three dimensional conformal radiation therapy (3DCRT) in patients receiving radiotherapy to the prostate bed

Hannah E. Carter, Andrew Martin, Deborah Schofield, Gillian Duchesne, Annette Haworth, Colin Hornby, Mark Sidhom, Michael Jackson

*NHMRC Clinical Trials Centre, University of Sydney, Camperdown; a Sir Peter MacCallum Dept of Oncology, University of Melbourne; "Dept Physical Sciences, Peter MacCallum Cancer Centre, Melbourne; division of Radiation Oncology, Peter MacCallum Cancer Centre; b Liverpool Cancer Therapy Centre; and d Faculty of Medicine, University of New South Wales, Sydney, Australia

Testing the ANROTAT† Framework using the Evaluation of Post-Prostatectomy Radiotherapy techniques