An Australian Radiation Oncology Register Pilot: Development and Future Use

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Registry Special Interest Group AUGUST 2012
Background to the ANROTAT Project

• DoHA – ‘Better Access to Radiation Oncology’ Program
  – Objectives: to undertake research into new technologies and treatments in radiation oncology.

• MBS – Keep pace with new RO technology and treatments

• Value in developing a generic research framework

• TROG Invited to submit a proposal - May 2009

• ANROTAT Radiation Oncology Register Pilot (ARORP)
ANROTAT Project

Objectives

- Framework
- Pilot the Framework (ANROTAT Study)
- MSAC Application
- ANROTAT Radiation Oncology Register Pilot (ARORP)

Register for Health Technology Assessment (HTA) – the way for the future??
Why TROG?

- **TROG** – Collaborative clinical trials group
  - Invited to submit a proposal - May 2009
  - Peak body for Radiation Oncology research
  - Existing infrastructure, international and national networks and technical expertise
ANROTAT Framework

1. PREPARATION
   Define Question
   Define technology
   Define evidence
   Sources (register)

2. METHODOLOGY
   Clinical parameters
   Economic analysis
   Data Protocols (use of register data)

3. PROJECT PREPARATION
   Timelines
   Resources
   Processes
   Data Management

4. ANALYSIS
   Modelling, stats
   Sensitivity analysis
   Interpretation

5. EVALUATION
   Review framework
   Follow up (value of register)
Why radiotherapy?

Tomas Kron
Medical Physicist
Peter MacCallum Cancer Centre
on behalf of the ANROTAT team
Objectives

- Introduce Radiotherapy
  - Australian situation
  - Role and importance of technology
- Discuss the need for a registry
- Consider the international scene
Cancer incidence (WHO) 2000

World-Both sexes (All ages)
5-year prev. cases: 22406657

- Breast 2379033 (10.6%)
- Colon/Rectum 3860296 (17.2%)
- Prostate 2379033 (10.6%)
- Cervix uteri 1554742 (6.9%)
- Stomach 1401428 (6.3%)
- Lung 1398055 (6.2%)
- Bladder 1394417 (6.2%)
- Corpus uteri 999734 (4.5%)
- Oral cavity 716389 (3.2%)
- Other cancers 707148 (3.2%)

GLOBOCAN 2000
Cancer treatment modalities

- Surgery
- Radiation
- Chemotherapy
- Hormones
- Others
Radiotherapy utilization rates for cancer vary widely internationally. It has previously been suggested that approximately 50% of all cancer patients should receive radiation. However, this estimate was not evidence-based. The aim of this study was to estimate the ideal proportion of new cases of cancer that should receive radiotherapy at least once during the course of their illness based on the best available evidence. An optimal radiotherapy utilization tree was constructed for each cancer based upon indications for radiotherapy taken from evidence-based treatment guidelines. The proportion of patients with clinical attributes that indicated a possible benefit from radiotherapy was obtained by adding epidemiologic data to the radiotherapy utilization tree. The optimal proportion of patients with cancer that should receive radiotherapy was then calculated using TreeAge (TreeAge Software, Williamstown, MA) software. Sensitivity analyses using univariate analyses and Monte Carlo simulations were performed. The proportion of patients with cancer in whom external beam radiotherapy is indicated according to the best available evidence was calculated to be 52%. Monte Carlo analysts indicated that the 95% confidence limits were from 51.7% to 53.1%. The tightness of the confidence interval suggests that the overall estimate is robust. Comparison with actual radiotherapy utilization data suggests a shortfall in actual radiotherapy delivery. This methodology allows comparison of optimal rates with actual rates to identify areas where improvements in the evidence-based use of radiotherapy can be made. It provides valuable data for radiotherapy service planning. Actual rates need to be addressed to ensure better radiotherapy utilization. *Cancer* 2005;104:1129–37. © 2005 American Cancer Society.
Changes since 2000/2005

- Aging population
- Better diagnostics
  - Early detection (more localized disease)
  - Better patient selection
  - Better loco-regional targeting
- More combination treatment
- Smaller regional radiotherapy centres
Radiation Therapy

- Ionising radiation
- Using particles (ie. photons, electrons) to damage DNA in cancer cells
Radiation as the good guy
The aim of radiotherapy

- To kill **ALL** viable cancer cells
- To deliver as much dose as possible to the target while minimising the dose to surrounding healthy tissues
- A geometric problem, largely addressed by technology
Local control

Identification of the target

Delivery of radiation

Excellent dose distribution

Verifying delivery

IMRT

IGRT
Reliance on technology

- For target identification
- For modeling of treatment approach
- For delivery of radiation
- For verification and quality assurance

Control area of modern RT unit
Reliance on technology

- For target identification
- For modeling of treatment approach
- For delivery of radiation
- For verification and quality assurance

Increasingly personalised (no two patients are the same)
Key issues

- Cost of healthcare
  - RT outpatient procedure > 90%
  - RT equipment costs 30% of the total bill (?)
  - Complex funding model between federal and states

- Evidence sketchy
Where do Clinical Trials sit?

- Radiotherapy has a proud history
- Define clinical evidence
- No re-imbursement in Australia without evidence (MSAC)
  - Example: no re-imbursement for Intensity Modulated Radiation Therapy (IMRT) in Australia
Is it ethical to run an IMRT trial?

- Can we ‘randomise’ patients to receive
  - Conventional RT or IMRT?
  - Non-gated or gated RT
- What would I choose?
- Expected participation?
Considerations when raising a technological question

- Is a clinical trial ethical?
- Is it necessary to run a trial?
- Is a clinical trial the most effective way to test the question?
- Does a trial reflect clinical practice in all centres?
Randomized controlled trials in health technology assessment: Overkill or overdue?

Søren M. Bentzen*

Departments of Human Oncology, Medical Physics, Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Abstract

Evidence-based medicine has become a cornerstone in the development of radiation oncology and the randomized controlled phase III trial remains the gold standard for assessing differential benefits in clinical outcome between therapies. Health technologies aimed at improving treatment quality should primarily be tested using process measures or operational characteristics, the reason being that the sensitivity and specificity of clinical outcome is low for detecting quality improvements. The ongoing discussion of the relative merits of intensity modulated photon versus proton radiotherapy is used to illustrate these concepts. Concerns over clinical and individual equipoise as well as the potential limitations of health economics considerations in this setting are also discussed. Working in a technology and science based medical discipline, radiation oncology researchers need to further develop methodology for critical assessment of health technologies as a complement to randomized controlled trials.

© 2008 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 86 (2008) 142–147.

Keywords: Radiation oncology; Randomized trials; Health technology assessment; Proton therapy; Equipoise; Health economics; Operational characteristics

... refer also to presentation of TR Mackie
Obvious Evidence?
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 double blind, 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?

Intuition/Obvious

Complexity

Parachute or not

Bland vs sharp scalpel
Obvious Evidence?

- Parachute or not
- Bland vs sharp scalpel
- Complexity
- Intuition/Obvious
- Most drugs…
Technology

Is the outcome always obvious or predictable by other means?

Obvious Evidence?

- Most drugs
- Complexity
- Intuition/Obvious

RT Technology?
Technology

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

**Obvious Evidence?**

- Most drugs
- Complexity
- Intuition/Obvious

**Additional problem:**

Most recent technology advances are used to reduce toxicity, in particular late toxicity which occurs sometimes many years after radiotherapy delivery.
Is dose distribution a good surrogate?

- 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 dose distribution a good surrogate?

- 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)?
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>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;N</td>
<td>472</td>
<td>631</td>
<td>75%</td>
</tr>
<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
What happens in Australia in 2012?
A registry is needed

- Focus on technology
- Validation of surrogates
- Representative coverage
  - Regional
  - Public/private
  - Technology
Opportunities

- Good collaboration between professions
- Good clinical trials organisation with QA experience in radiotherapy (TROG)
- ANROTAT
- Only two commercial radiation oncology information systems (ROIS)
ROIS

- IT backbone of a radiotherapy department
- Scheduling
- Transfer of data
- Record and verify (some used for billing)
- Notes
Includes virtually all relevant technological information
What is happening overseas?

Practical Radiation Oncology (2012) 2, 10–17

Special Article

Developing a national radiation oncology registry: From acorns to oaks

Jatinder R. Palta PhD, Jason A. Efstathiou MD, PhD, Justin E. Bekelman MD, Sasa Mutic PhD, Carl R. Bogardus MD, Todd R. McNutt PhD, Peter E. Gabriel MD, Colleen A. Lawton MD, Anthony L. Zietman MD, Christopher M. Rose MD

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Similar attempts at data collection
Better funding of these efforts
Focus on Patient Recorded Outcomes (PRO)
Probably a bit behind ARORP at present
Clinical trials organisations

- Significant interest in registries
- Difficulties with conventional research grant funding mechanism
Without good data, it will be hard to get the true big picture...
ANROTAT RADIATION ONCOLOGY REGISTER PILOT (ARORP)

Methods

Results

Recommendations
ARORP Objectives

- Objectives
  - Develop and test a set of data variables and data collection tool
  - Feasibility in routine practice tested
  - Quantify opinion of system users
- Collected at one point in time
ARORP Methods

- Patients
  - Group A – first follow up post Tx
  - Group B – annual follow up
- Opt out consent procedure
- Six participating centres
  - Spectrum of operating environments
  - NSW, VIC, SA, NT
ARORP Methods

- Select tumour sites
  - Intensity Modulated Radiation Therapy (IMRT) and Three Dimensional Conformal Radiation Therapy (3DCRT)
    - Post Prostatectomy
    - Anal Canal
    - Nasopharynx
  - Image Guided Radiation Therapy (IGRT) or non-IGRT
    - Intact Prostate
ARORP Methods

- ACSQHC ‘Operating Principles and Technical Standards for Australian Clinical Quality Registries’ utilised
- Advice from established clinical registries
- Level 2 Register – stand alone database
ARORP Methods

- Existing infrastructure used – CTDS
- Individual username and passwords
- Manual data entry only
ARORP Methods

- Monitoring Visits Undertaken
  - Data completeness
  - Data accuracy
  - Staff surveyed
Development of Data Variables

- Data variables collected
  - Demographics
  - Diagnostic
  - Staging
  - RT treatment (including submission of RT plan)
  - Systemic and Surgical treatment
  - Quality of life (QoL) – AQoL8D
  - Follow up information
  - Time taken to collect and input data
Development of Data Variables

- ARORP Development Group
  - Multidisciplinary – RT, RO, MP, Statistician, Health economist, Consumer, Project Manager.
- Data Dictionary
- User Manual
- Training package
ARORP Results
ARORP Outcomes and Results

➢ Feasibility

- **Recruitment** – Demographics analysis
- **Compliance** – Data completeness and accuracy
- **Functionality** – Use of the web-based tool (including modifications required for future use)
- **Feedback** – Participant feedback from surveys and workshops
## Results - Recruitment: Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Descriptive Statistics n = 59</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at treatment</strong></td>
<td>Mean = 66.1 years, Median = 67 years, (min-max: 45-82 years)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female n=2 (3%), Male n=57(97%)</td>
</tr>
<tr>
<td><strong>Tumour Site specific Distribution</strong></td>
<td>Anal Canal: n=6 (10%), Intact Prostate: n=31 (53%)</td>
</tr>
<tr>
<td></td>
<td>Nasopharynx: n=7 (12%), Post Prostatectomy: n=15 (25%)</td>
</tr>
<tr>
<td><strong>Group A and B Patients</strong></td>
<td>Group A: n= 16 (27%), Group B: n=43 (73%)</td>
</tr>
<tr>
<td><strong>Radiotherapy Technique Used</strong></td>
<td>IMRT: n=17 (29%), 3DCRT: n= 37 (63%), IMRT and 3DCRT: n= 2 (3%), Missing: n= 3 (5%)</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>IGRT : n = 31 (52%), Non-IGRT: n = 24 (41%), Missing: n = 4 (7%)</td>
</tr>
</tbody>
</table>
Results - Data Completeness and Accuracy

- Patients reviewed for completeness and accuracy during the monitoring visits
  - Quantified per patient and variable
  - 100% audit – 26 patients
  - Partial audit – 33 patients
  - 80% Completeness rate considered satisfactory
## Results - Data Completeness and Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Per Patient</th>
<th>Per Data Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completeness</td>
<td>Accuracy</td>
</tr>
<tr>
<td><strong>No of patients/variables</strong></td>
<td>59 patients</td>
<td>81 variables</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>91-100%</td>
<td>88%-100%</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>Percentage completeness 80% or greater</strong></td>
<td>100%</td>
<td>n/a</td>
</tr>
</tbody>
</table>
## Results - Time taken to collect and input data

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Time taken for data collection and submission (minutes)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min-Max</td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Submission of RT plan not required</td>
<td>12–178</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Submission of RT plan required</td>
<td>25-329</td>
<td>113</td>
<td>99</td>
</tr>
<tr>
<td>Overall Total</td>
<td>12-329</td>
<td>81</td>
<td>61</td>
</tr>
</tbody>
</table>
Results – Functionality and Feedback

- Online Survey - Feedback on access, data entry, navigation, training, support and overall ease of use
  - 100% return rate (n=14)
  - Interviews during monitoring visits
Results – Functionality and Feedback

▪ Results
  ▪ Data variables feasible to collect (75%)
  ▪ Online register feasible to use (83%)
  ▪ High level of satisfaction with structure and processes
  ▪ Further development required
Recommendations

- Require security of ongoing funding
- Define the Body responsible for the Register
- Automate data collection
- Optimise access through the web portal
- Opt out patient consent
- International collaboration
- Collaboration with industry partners
- Embed data collection in routine practice
Conclusion

- Register to complement the function of the Framework for evidence for HTA assessment
  - Patterns of care
  - Inform MSAC Applications
  - Cost analysis
  - Link short and long term endpoints
  - Validate predictive indicators
Acknowledgements

- Executive Advisory Group
- ARORP Development Group
- TROG ANROTAT Project Team/QA Team/Research Team
- Treatment Centres
- TROG Membership
- NHMRC Clinical Trials Centre
- NewtonGreen Technologies

“The Assessment of New Radiation Oncology Technologies and Treatments (ANROTAT) Project is funded by the Australian Government.”