Radiotherapy clinical trials

Charlotte Coles on behalf of the IMPORT Trialists
Radiotherapy for the lay representative
5th October 2012

Overview

• Why do we have clinical trials in radiotherapy (RT) ?
• What are the challenges ?
• What role can patient advocates play?
• Conclusions

Use breast RT trials to illustrate
Why do we have clinical trials in radiotherapy (RT) ?

- Improve patient safety: standardise RT
- Change practice
- Push forward new RT technology
- Improve cancer outcomes and reduce side effects

Improve patient safety: standardise RT

- In 1991 Lady Ironside took her doctor to court as a result of her severe RT side effects:
  - unrelieved neuropathic pain, paralysis whole arm & lymphoedema
- Became clear that others in UK were affected in similar way
- RAGE was formed & an investigation was launched
Why did this happen?

In 1980’s early 1990s
• Many different ways of giving breast RT, with different:
  – Patient positions
  – Doses (& prescription points)
  – Number of treatments (fractions)

• Non-standard approach prone to errors

Standardisation of RT technique
START Trial B

Trial B
N= 2215

50Gy in 25 #
(2.0Gy) 5 wks
N=1105

40Gy in 15 #
(2.67Gy) 3 wks
N=1110

1998- 2003

Prof J Yarnold, RMH

Positive outcomes: START Trial

• Revolutionised the way breast RT was given in the UK, as standardised:
  – Patient position
  – Target volumes
  – Dose and fractionation (NICE)
  – Prescription points
  – Quality assurance

• Brought together the clinical oncology community to deliver safer RT, with less morbidity

START Trialists, Lancet 2008; 371: 1098-107
Why do we have clinical trials in radiotherapy (RT)?

- Improve patient safety: standardise RT
- *Change practice*
- Push forward new RT technology
- Improve cancer outcomes and reduce side effects

Change practice

- Pattern of relapse after breast conserving surgery (BCS):
  - 2,544 patients treated by BCS +/-RT Milan 1970 – 89

<table>
<thead>
<tr>
<th>Site in relation to Primary tumour</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2cm from scar</td>
<td>142 (74)</td>
</tr>
<tr>
<td>Other quadrant</td>
<td>43 (23)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Salvadori B, BJS, 1999, 86, 84-87
Change practice

- Use of titanium clips insert into tumour bed at surgery

**Clips should be used in all patients**

Place clips **before** breast re-modelling is performed

**Paired** clips are positioned at the following sites:
1. Medial, lateral, superior & inferior; half-way between skin & fascia
2. Deep: midpoint, usually the pectoral fascia (posterior)
3. Anterior: close to the suture line, avoiding skin dimpling

C Chan, Cheltenham Hospital
Why do we have clinical trials in radiotherapy (RT)?

- Improve patient safety: standardise RT
- Change practice
- *Push forward new RT technology*
- Improve cancer outcomes and reduce side effects

IMRT creates steep dose gradients: matches dose to recurrence risk, IGRT needed to deliver
Detailed protocol & rigorous QA

30 page document

25 cancer centres & 25 units recruiting in UK

Can implementation of new RT technology through clinical trials benefit patients NOT treated in trials?
Availability of multi-slice planning

K Venables et al, Clin Oncol 2012

Availability of 3D dose compensation in centres

K Venables et al, Clin Oncol 2012
Timing of 3D planning

Why do we have clinical trials in radiotherapy (RT) ?

- Improve patient safety: standardise RT
- Change practice
- Push forward new RT technology
- *Improve cancer outcomes and reduce side effects*
Improving cancer outcomes - RT after breast conservation surgery: results from 10,801 women treated in 17 trials

Local relapse

Breast cancer mortality

~16% gain

~ 4 % gain

Reducing side effect: IMRT reduces unwanted high dose and gives a better breast appearance

EBCTCG Lancet 2011; 378: 1707-16

Donovan et al. Radiother Oncol 2007. 82; 254-264
What are the challenges of clinical RT trials?

- Slow recruitment due to implementation & QA of complex RT techniques
- Large numbers of patients required
- Long follow up essential

Slow initial recruitment due to implementation & QA of complex RT techniques

![Graph showing actual accrual and revised predictions for 2011 with sample size.]
...but implementation of RT technology through 1 trial, can help recruitment for the next

What are the challenges of clinical RT trials?

- Slow recruitment due to implementation & QA of complex RT techniques
- **Large numbers of patients required**
- Long follow up essential
Local recurrence (LR) rates are falling due to improvements in diagnosis and all aspects of treatment. The table below summarizes 5-year LR (%) for various trials:

<table>
<thead>
<tr>
<th>Trial</th>
<th>5-yr LR (%) BCS+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06 (1976-1984)</td>
<td>14.3</td>
</tr>
<tr>
<td>CRC, UK (1981-1990)</td>
<td>19.7</td>
</tr>
<tr>
<td>Ontario COG (1984-1989)</td>
<td>11</td>
</tr>
<tr>
<td>SCTBG (1985-1991)</td>
<td>5.8</td>
</tr>
<tr>
<td>INT Milan 3 (1987-1989)</td>
<td>5.8</td>
</tr>
<tr>
<td>NSABP B-21 (1989-1998)</td>
<td>2.8</td>
</tr>
<tr>
<td>Swedish BCG 91-RT (1991-1997)</td>
<td>4.0</td>
</tr>
<tr>
<td>Holli et al. (1990-1995)</td>
<td>6.3</td>
</tr>
<tr>
<td>Fyles et al. (1992-2000)</td>
<td>0.6</td>
</tr>
<tr>
<td>CALGB C9343 study (1994-1999)</td>
<td>1.0</td>
</tr>
<tr>
<td>BASO II (1992-2000)</td>
<td>0.4 pa</td>
</tr>
<tr>
<td>ABCSG study 8 (1996-2004)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Statistical Power Required for Non-inferiority Trials

Assume LR after breast RT is 2.5% at 5yr
For 90% power at 5% significance level:

<table>
<thead>
<tr>
<th>Inferiority to be excluded</th>
<th>1%</th>
<th>2%</th>
<th>3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. local relapses</td>
<td>294</td>
<td>96</td>
<td>53</td>
</tr>
<tr>
<td>No. patients</td>
<td>10,098</td>
<td>2,984</td>
<td>1,548</td>
</tr>
</tbody>
</table>

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What are the challenges of clinical RT trials?

• Slow recruitment due to implementation & QA of complex RT techniques
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Long follow up essential

Pre-RT

2 yrs post-RT

6 yrs post-RT
What role can patient advocates play?

- Essential for every stage of clinical trial development, implementation, follow up and reporting!
- Examples:
  - Lesley Turner & Hilary Stobart contributed to proposed PRIME TIME study grant application: made important recommendations about follow up mammograms & changed emphasis/wording to reassure patients in non-patronising way
  - Maggie Wilcox added outcome measures to IMPORT trials that were important to patients: “Can you find a bra that fits following your RT?”

Conclusions

- RT clinical trials aim to improve patient outcomes & safety; change practice and implement new RT technology for both trial & non-trial patients
- Patient advocates are essential for this process to ensure that patients are at the centre of any research
- RT clinical trials take time to implement and follow up & require engagement of the research community....
Breast RT trials: the 20 year plan

Acknowledgements