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

R. A. G. E.
Radiotherapy Action Group Exposure

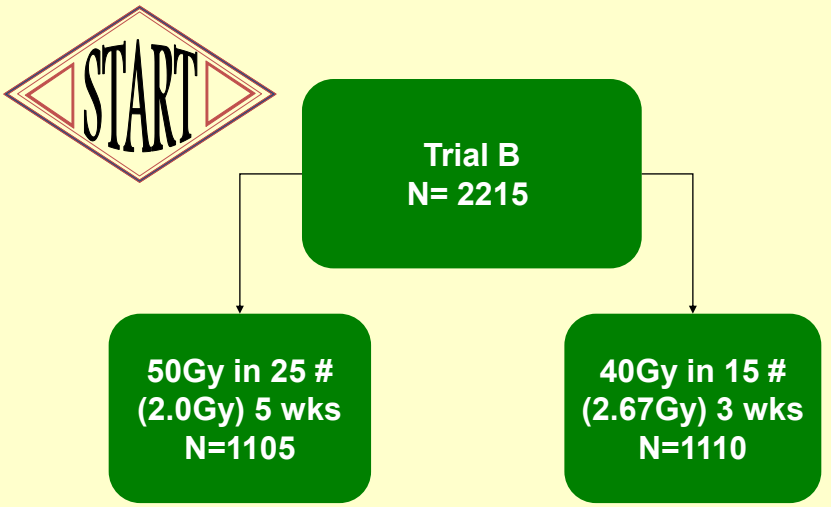
Why did this happen?

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



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

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Change practice

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

Site in relation to Primary tumour	Number (%)
≤ 2cm from scar	142 (74)
Other quadrant	43 (23)
Undetermined	6 (3)

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

Change practice

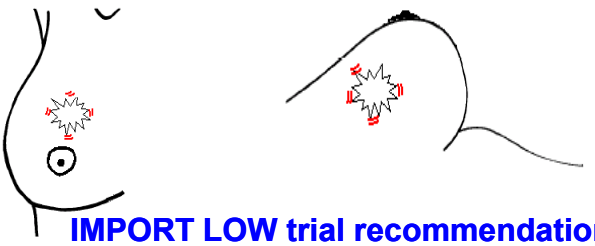
- Use of titanium clips insert into tumour bed at surgery

Clips should be used in **all** patients

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

Paired clips are positioned at the following sites:

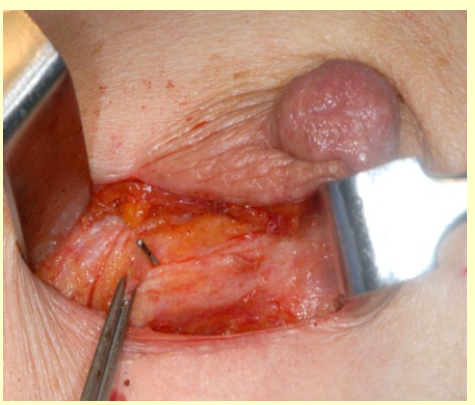
1. Medial, lateral, superior & inferior; half-way between skin & fascia
2. Deep: midpoint, usually the pectoral fascia (posterior)
3. Anterior: close to the suture line, avoiding skin dimpling

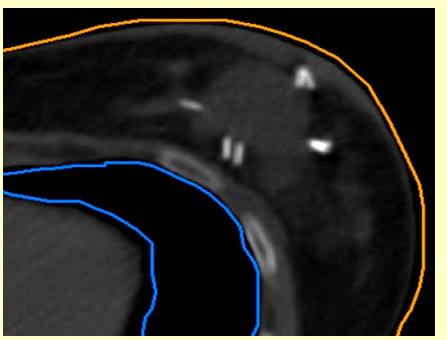


IMPORT LOW trial recommendations

Change practice

- Adopted by British Association of Surgical Oncologists as best practice





C Chan, Cheltenham Hospital

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

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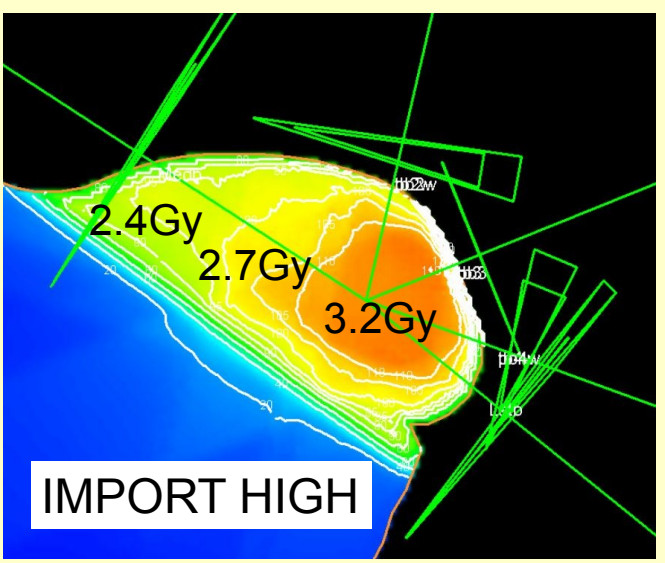
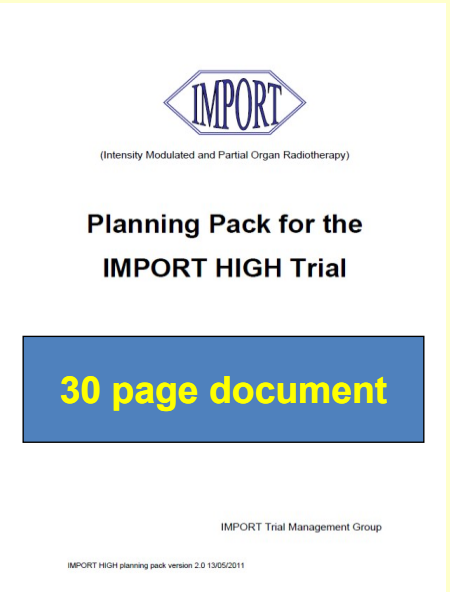
- ***Push forward new RT technology***
- Improve cancer outcomes and reduce side effects

IMRT creates steep dose gradients: matches dose to recurrence risk, IGRT needed to deliver



Detailed protocol & rigorous QA

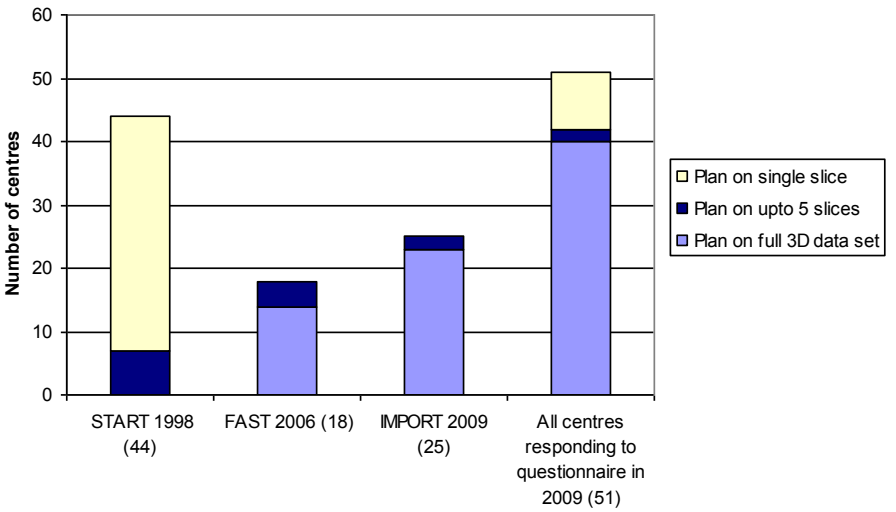


Radiotherapy Trials QA

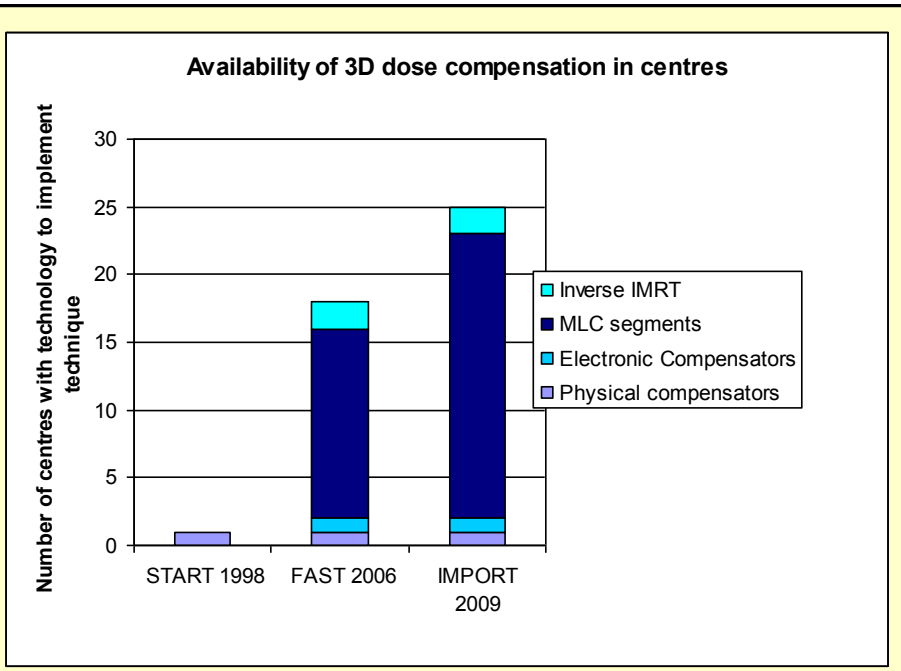
25 cancer centres &
25 units recruiting in UK

Can implementation of new RT technology through clinical trials benefit patients NOT treated in trials?

Availability of multi-slice planning

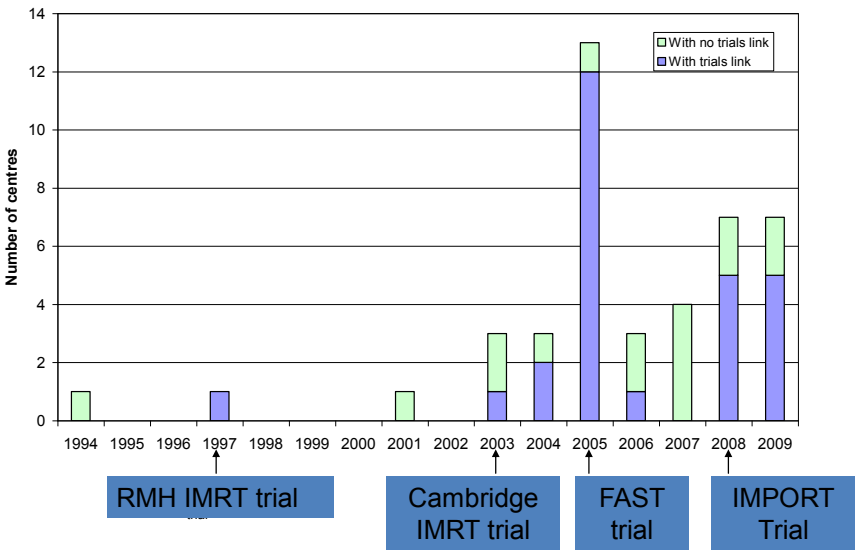


K Venables et al,Clin Oncol 2012



K Venables et al,Clin Oncol 2012

Timing of 3D planning



K Venables et al, clin Oncol 2012

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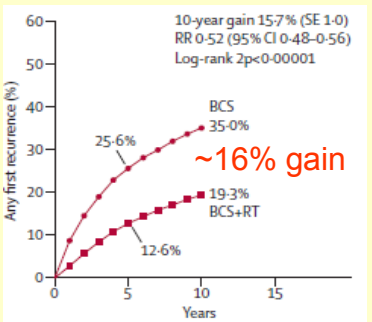
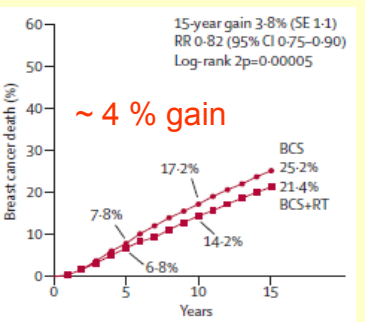
- Push forward new RT technology
- ***Improve cancer outcomes and reduce side effects***

Improving cancer outcomes - RT after breast conservation surgery: results from 10,801 women treated in 17 trials

Local relapse

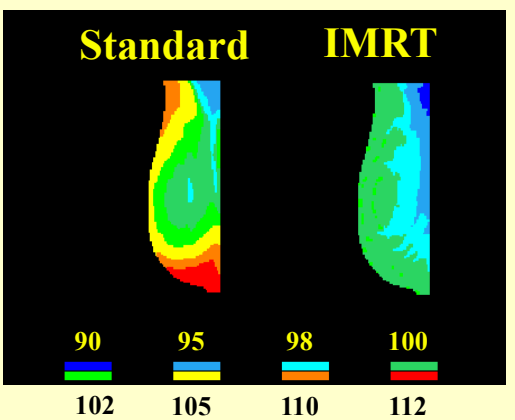


Breast cancer mortality



EBCTCG Lancet 2011; 378: 1707- 16

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

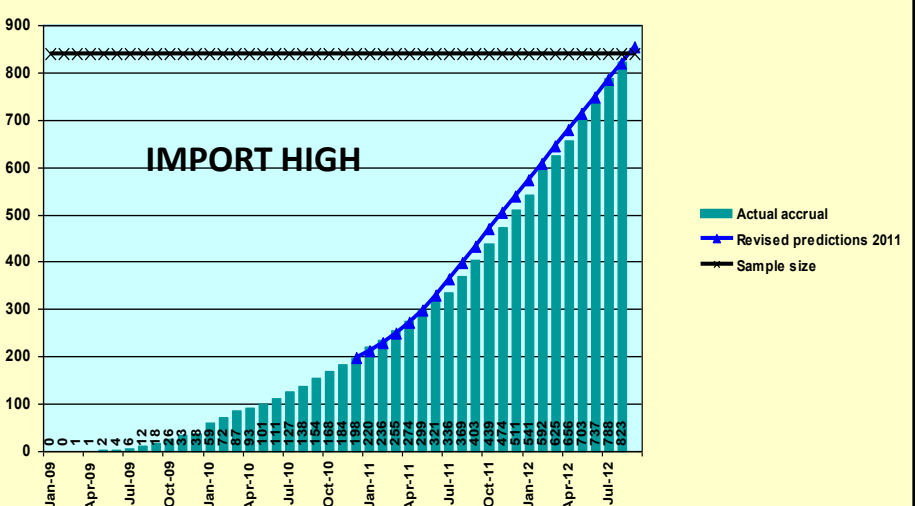


Donovan et al. Radiother Oncol 2007. 82; 254-264

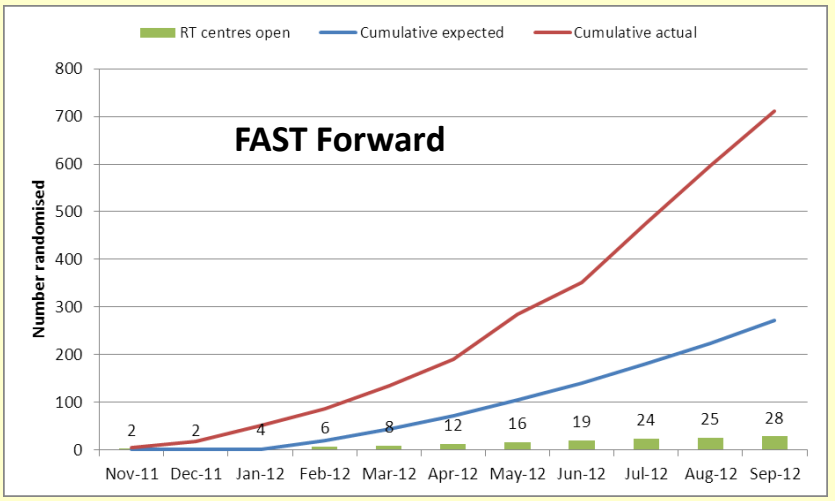
What are the challenges of clinical RT trials?

- ***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



…but implementation of RT technology through 1 trial, can help recruitment for the next



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Local recurrence (LR) rates are falling due to improvements diagnosis and all aspects of treatment

Trial	5-yr LR (%) BCS+RT
NSABP B-06 (1976-1984)	14.3
Uppsala-Örebro (1981-1988)	8.5
St. George's London (1981-1990)	13
CRC, UK (1981-1990)	19.7
Ontario COG (1984-1989)	11
SCTBG (1985-1991)	5.8
INT Milan 3 (1987-1989)	5.8
NSABP B-21 (1989-1998)	2.8
Swedish BCG 91-RT (1991-1997)	4.0
Holli et al. (1990-1995)	6.3
Winzer et al. GBSG (1991-1998)	3.7
Fyles et al. (1992-2000)	0.6
CALGB C9343 study (1994-1999)	1.0
BASO II (1992-2000)	0.4 pa
ABCSG study 8 (1996-2004)	0.4

Statistical Power Required for Non-inferiority Trials

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

	Inferiority to be excluded		
	1%	2%	3%
No. local relapses	294	96	53
No. patients	10,098	2,984	1,548

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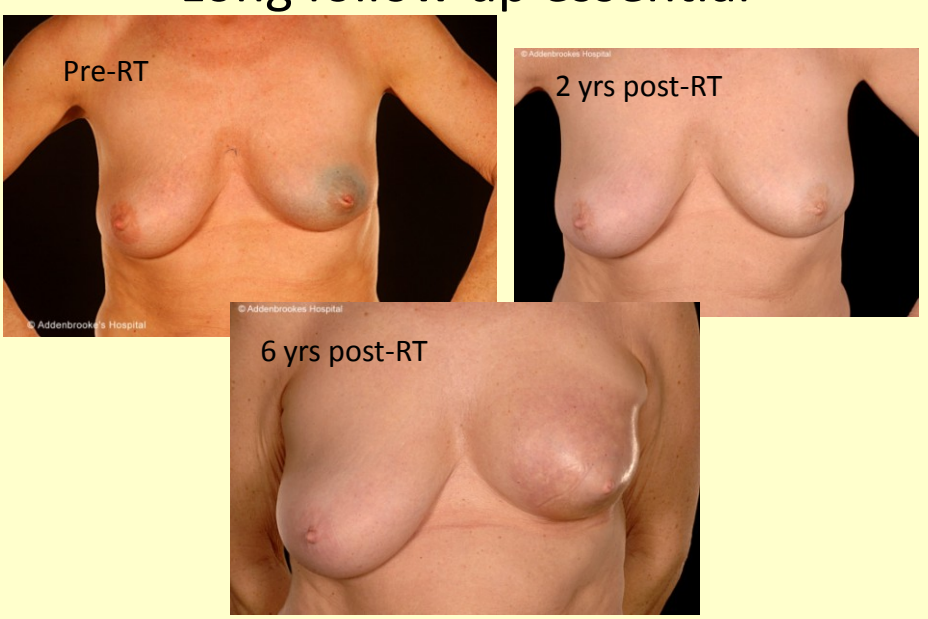
Long follow up essential

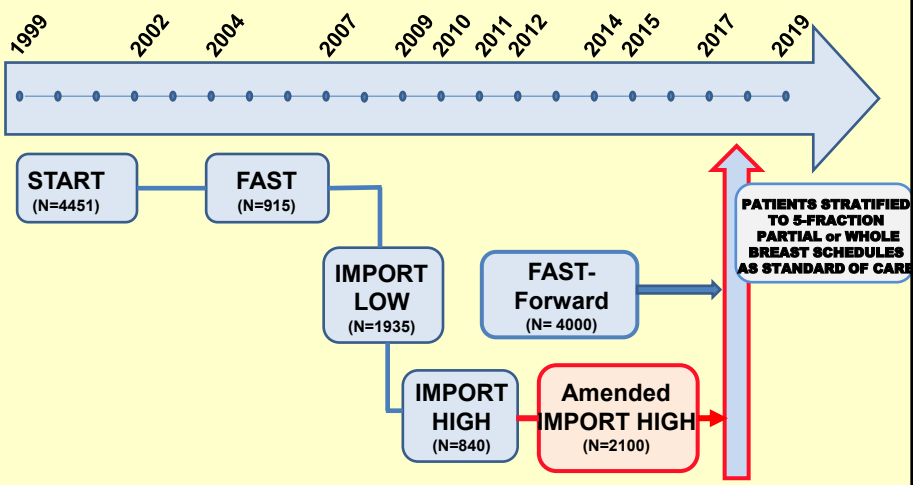


What role can patient advocates play?

- 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

START

CANCER RESEARCH UK

IMPORT

PATIENTS & research community

HTA Health Technology Assessment

FAST-Forward

The Institute of Cancer Research