

A good START for breast radiotherapy

A lower total dose delivered in fewer, larger doses (fractions) is likely to be as safe and effective as the international ‘gold standard’ for treating women with early breast cancer.

A long-standing collaboration exists between The Institute’s Sections of Academic Radiotherapy and Clinical Trials.

INTRODUCTION

The Institute’s Section of Academic Radiotherapy focuses on improving the delivery of radiotherapy to cancer patients, including working for many years on ways to:

- optimise the way radiotherapy is given to women with early breast cancer
- learn more about the relative sensitivity to radiotherapy of breast cancer tumours and healthy tissues in and around the breast.

Working as a scientific partner in this initiative are colleagues within the Section of Clinical Trials which hosts the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). Funded by Cancer Research UK, the ICR-CTSU is an academic clinical trials unit accredited by the National Cancer Research Institute to initiate, conduct and analyse large-scale trials of cancer treatments. As well as testing novel uses of drugs to treat cancer patients, evaluation of radiotherapy techniques is a strategic aim of the ICR-CTSU, which specialises in the areas of breast cancer and urology.

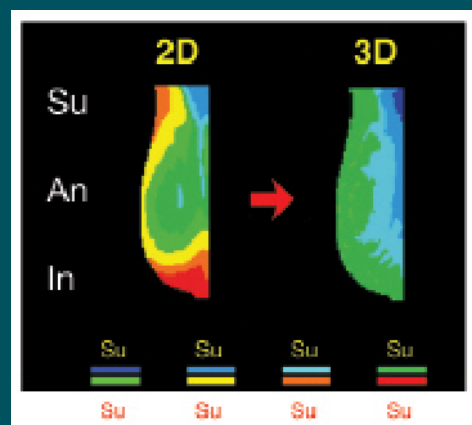
RADIOTHERAPY FOR BREAST CANCER

Standard schedules of curative radiotherapy for a wide range of cancers deliver multiple small (≤ 2.0 Gy) daily doses, called ‘fractions’, which are gentler on dose-limiting healthy tissues than they are on the cancer. As such, it makes sense to give many small fractions; however, if cancer is to be eradicated a high total dose has to be delivered. This way of treating cancer certainly works for squamous carcinomas of the head and neck, lung and cervix.

Interestingly, analysis of historical data led us to the hypothesis that a lower total dose in fewer, larger fractions would be just as safe and effective in women with breast cancer. In fact, schedules giving fewer,

The Section of Academic Radiotherapy, Section of Clinical Trials and the joint section of Radiotherapy and Physics have developed and successfully tested techniques for removing unwanted high dose (orange/red opposite) from standard 2D breast radiotherapy compared to new 3D techniques. The same technique is now used to vary fraction size across the breast according to cancer recurrence risk in the NCRI IMPORT trials led by our group.

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“Effective collaboration involving many researchers across UK radiotherapy centres has been key to a series of successful clinical trials conducted over many years.”

PROFESSOR JUDITH BLISS FRSS

Professor of Clinical Trials and Chairman of the Section of Clinical Trials at The Institute of Cancer Research.

PROFESSOR JOHN YARNOLD

MRCP FRCR

Professor of Clinical Oncology at The Institute of Cancer Research and a Consultant in Radiotherapy at The Royal Marsden NHS Foundation Trust.

larger fractions have long been used in the UK but without ever being formally tested against the international standard of 50 Gy in 25 fractions over five weeks. The Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) Trial set out to make this comparison.

The RMH/GOC trial randomised 1410 patients between 1986-1998 to the international standard schedule of 50 Gy in 25 fractions versus two 13-fraction regimens testing slightly larger fractions of 3.0 Gy or 3.3 Gy over five weeks, primarily to look at safety. This led to the development of a nationwide initiative called the Standardisation of Breast Radiotherapy (START) Trial, designed to adequately assess efficacy as well as safety.

STANDARDISATION OF BREAST RADIOTHERAPY (START) TRIAL.

In 1998, Professors John Yarnold (Academic Radiotherapy) and Judith Bliss (Clinical Trials) secured research funding from Cancer Research UK, the UK Medical Research Council and the UK Department of Health to conduct the largest evaluation of radiotherapy fractionation ever undertaken in women being treated for early breast cancer.

Ten years on, the principal results of the START trials have now been reported and published in the *Lancet* and *Lancet Oncology*. In total, 4451 women with early breast cancer were recruited into two trials comprising the initiative;

START A and START B between 1999 and 2002. At a median follow-up of five and six years respectively, the two trials have collected:

- annual clinical assessments on all women in the trials
- photographic assessments of radiotherapy adverse effects in 2400 women
- patient quality of life assessments in 2208 women.

The quality of life data included patient self-assessments of late-occurring adverse effects of radiotherapy. In addition, a health economics evaluation was carried out in 2058 women, and 2798 women donated a blood sample for use in future translational research.

START A

In START A, 2236 women with early breast cancer at 17 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy versus 41.6 Gy in 13 fractions of 3.2 Gy versus 39 Gy in 13 fractions of 3.0 Gy. After a median follow-up of five years, the rate of local-regional tumour relapse was low in all groups, with 3.6% in the 50 Gy group, 3.5% in the 41.6 Gy group and 5.2% in the 39 Gy group (Figure 1a). This translates into an estimated maximum 2.1% and 3.2% absolute excess associated with 41.6 Gy and 39 Gy compared with 50 Gy, respectively.

Both photographic and patient self-assessments showed lower rates of late adverse effects after 39 Gy than with 50 Gy, with rates in the 41.6 Gy group appearing very similar to those in the 50 Gy group (Figure 1b).

The design of START A, using two dose levels of the 13-fraction schedules, made it possible to directly estimate parameters describing the fractionation sensitivity of breast cancer and late-responding normal tissues. Analysed in a meta-analysis with the RMH/GOC trial, the results show that breast cancer responds to radiotherapy fraction size in a very similar way to the late-reacting normal tissues of the breast. This changes the traditional view of radiotherapy treatment for early breast cancer. It means that continuing to use small fractions of ≤ 2.0 Gy spares the cancer as much as the healthy tissue, which is of no patient benefit. In addition, there are possible biological advantages of giving fewer, larger fractions, as well as obvious benefits in terms of convenience for patients (less visits to hospital).

Figure 1a: Kaplan-Meier plot of local-regional (LR) tumour relapse in 2236 START Trial A patients

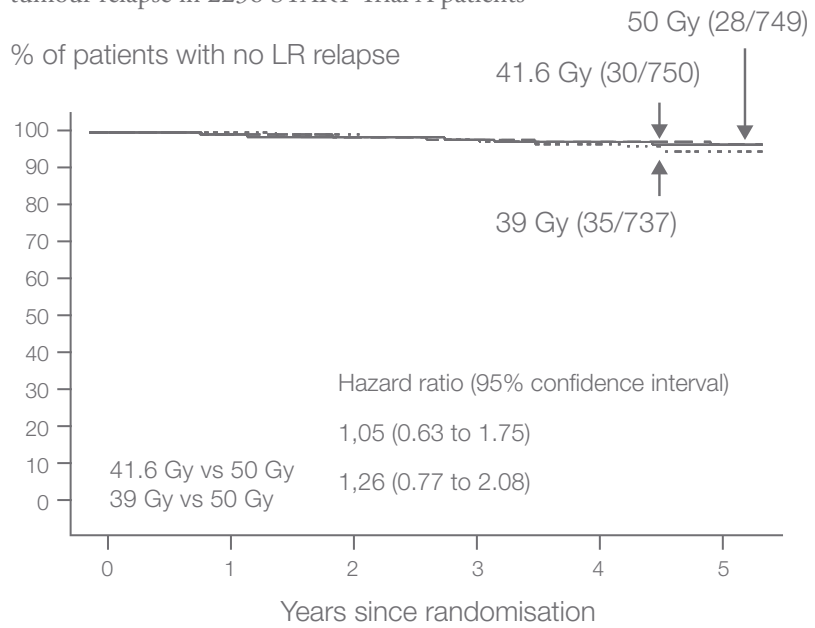


Figure 1b: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 1055 START Trial A patients with breast conserving surgery



START B

Meanwhile, START B randomised 2215 women with early breast cancer at 23 centres in the UK to receive either 50 Gy in 25 fractions of 2.0 Gy over five weeks or 40 Gy in 15 fractions of 2.67 Gy over three weeks. After a median follow-up of six years, the rate of local-regional tumour relapse was low in both groups, with 2.2% in the 40 Gy group and 3.3% in the 50 Gy group (Figure 2a). This translates into an estimated maximum 0.6% absolute excess associated with 40 Gy compared with 50 Gy.

Both photographic and patient self-assessments showed lower rates of late adverse effects after 40 Gy than with 50 Gy. This schedule appears to be gentler on the healthy tissues than 50 Gy in 25 fractions and at least as effective in terms of tumour control: a very good outcome for patients. The researchers concluded that after surgery for early breast cancer, a radiotherapy schedule delivering 40 Gy in 15 fractions over three weeks seems to offer local-regional tumour control and rates of late normal tissue effects at least as good as the accepted international standard of 50 Gy in 25 fractions over five weeks.

Since the START results were published, in March 2008, The Royal Marsden Hospital has changed from the current five-week regimen to a three-week schedule for most of its breast cancer patients. The same regimen is currently prescribed to the majority of British women, and the trial is likely to influence practices overseas.

Figure 2a: Kaplan-Meier plot of local-regional (LR) tumour relapse in 2215 START Trial B patients

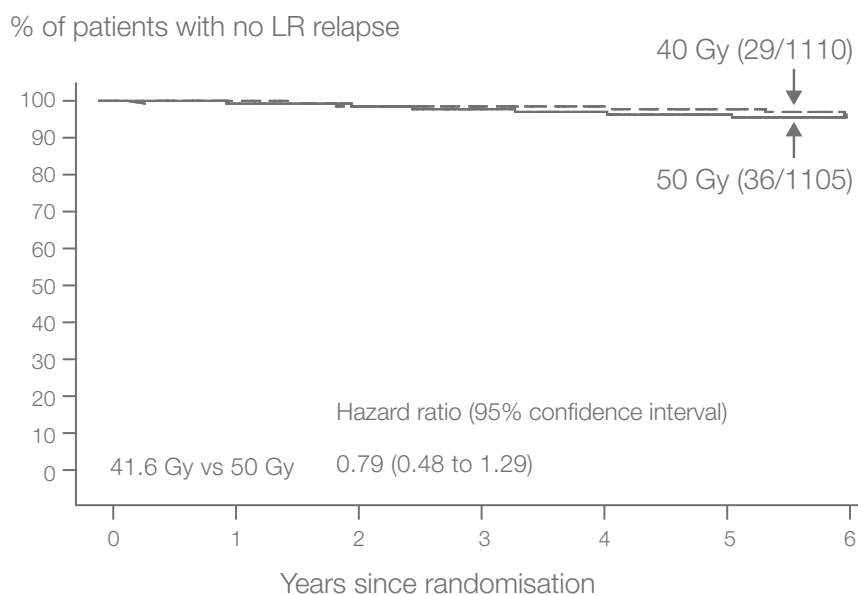
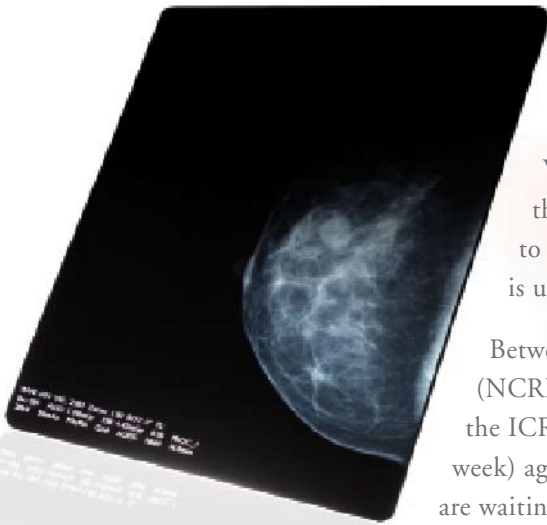


Figure 2b: Kaplan-Meier plot of mild/marked change in breast appearance (photographic) in 923 START Trial B patients with breast conserving surgery





THE FUTURE

Where do we go from here? Figure 3 shows a schema detailing the progressive nature of the radiotherapy fractionation trials to date and a possible future trial. A 15-fraction schedule is unlikely to represent the limits of this approach.

Between 2004 and 2007, the National Cancer Research Network (NCRN) FAST trial was set up by Professor John Yarnold and the ICR-CTSU to test a five-fraction regimen (treating once a week) against the international standard 50 Gy in 25 fractions. We are waiting for the first analyses of the 900 women on follow up.

Figure 3: Schema showing progression of breast radiotherapy trials co-ordinated by Professors Yarnold and Bliss

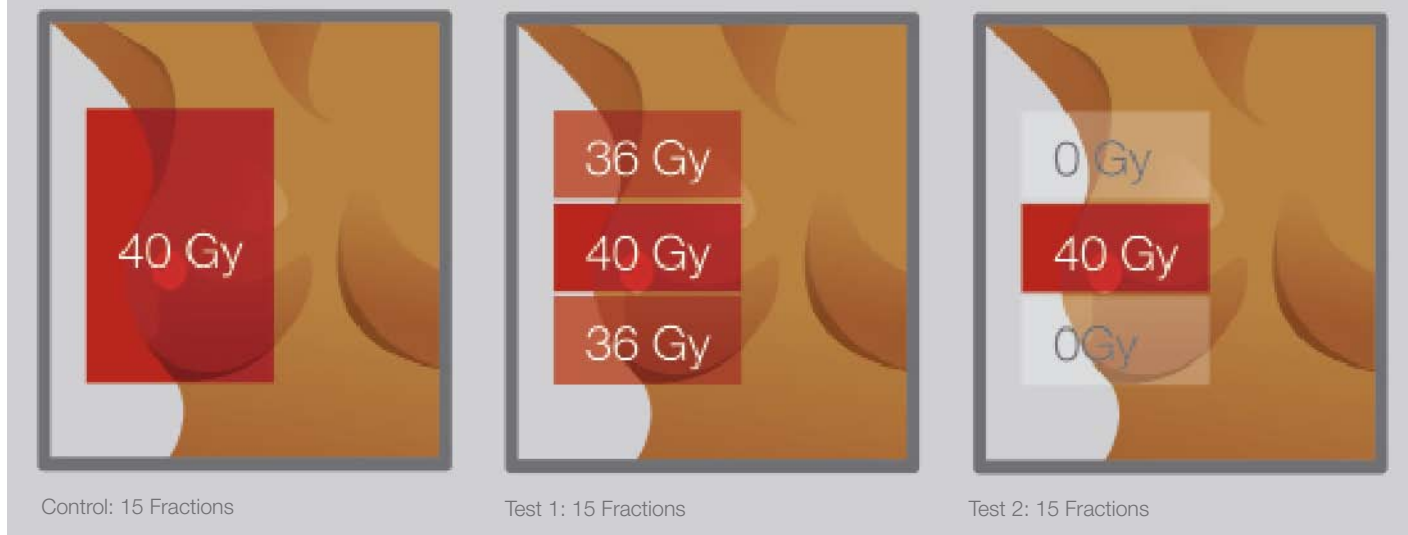
	Total Dose (Gy)	Number Fractions	Fraction Size (Gy)	Time (weeks)
	50.0	25	2.0	5
RMH/GOC (1986 – 98)	42.9	13	3.3	5
	39.0	13	3.0	5
	50.0	25	2.0	5
START A (1998 – 02)	41.6	13	3.2	5
	39.0	13	3.0	5
	50.0	25	2.0	5
FAST (2003 – 07)	30.0	5	6.0	5
	27.5	5	5.7	5
	50.0	25	2.0	5
possible future trial (2009 –)	30.0	5	6.0	5
	30.0	5	6.0	1
	27.5	5	5.7	1

We hope the next step will be to test a five-fraction regimen delivered in five days; a schedule that will really transform radiotherapy practices in breast cancer.

A five-day schedule may overcome a cause of radiation resistance related to the high speed at which some tumours grow, as well as being much simpler for patients. It would allow radiotherapy to be integrated more effectively with surgery and systemic therapies. It would also be used to treat patients suitable

for partial breast radiotherapy, which restricts radiotherapy dose to the area of the breast where the primary cancer used to be. This is under test in the NCRI Intensity Modulated and Partial Organ Radiotherapy (IMPORT) Low Trial (see Figure 4), also co-ordinated by Professor Yarnold and the ICR-CTSU.

Figure 4: Schema showing the trial design of the NCRI IMPORT Low Trial (N=1935)



Breast cancer is unlikely to be unique in responding to radiotherapy fraction size in this way. In fact, there are good indications that prostate cancer (which is also an adenocarcinoma) is also sensitive to fraction size. It is striking that the kinds of normal tissues that are spared by small fractions (eg, subcutaneous tissue, lung, kidney, brain) are all characterised by very low cell proliferative activity, rather like

breast and prostate cancers. By contrast, normal tissues that are not very sensitive to fraction size (eg, mucosal surfaces of mouth and bowel and epidermis of skin) have high cell proliferative indices, like squamous carcinomas.

Professor Yarnold is collaborating with colleagues at the Health Protection Agency at Harwell, and the Radiobiology Institute at

Oxford, to explore the molecular basis of these differences. One of the hypotheses being tested is that differences in DNA repair systems underlie differences in fractionation sensitivity. An aim of this research is to identify indicators of fractionation sensitivity that can be used to select the best radiotherapy fraction size for a particular cancer, of whatever type.

If the FAST and IMPORT trial results are as we hope, it means that women will be treated in a much more individualised way in future, with selection of partial breast treatment, total dose and fraction size each adjusted according to pre-treatment features.