Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Standardised radiotherapy dose fractionation for breast cancer treatment

1. Summary of the impact

Clinical research led by The Institute of Cancer Research (ICR) has resulted in new standardised curative radiotherapy dose-fractionation regimens being adopted across the UK for over 25,000 women per year with early breast cancer. As a direct result of the trials led by the ICR, NICE introduced new guidance in 2009 recommending a 15-fractions-over-3-weeks radiotherapy regimen (hypofractionation) instead of the previous 25-fractions-over-5-weeks schedule. Patient welfare is substantially improved with savings in travel time and costs for attending treatment, and the NHS benefits from reduced treatment costs. This new treatment schedule is now being adopted internationally.

2. Underpinning research

Standard regimens of curative radiotherapy to the majority of primary cancers reflect a historical assumption that a high total dose delivered in multiple small doses (called fractions) maximises anti-tumour effect with the least damage to healthy tissues. While this assumption holds for most cancers, a retrospective analysis of treatment outcomes for breast cancer patients treated with a variety of different schedules, published in the mid-1980s, suggested that breast cancer may be an exception. This led to the initiation of underpinning research for the development of new radiotherapy dose-fractionation practices, led by Professor John Yarnold (ICR Faculty) in collaboration with Professor Judith Bliss (ICR Faculty) and the ICR's clinical partner, The Royal Marsden NHS Foundation Trust (RM). The team showed in the Standardisation of Breast Radiotherapy (START) pilot trial that normal breast tissues are more tolerant of lower total doses delivered in fewer, larger fractional doses. This was the first breast cancer radiotherapy fractionation trial to incorporate 2 experimental dose levels in its design, a feature that guaranteed reliable identification of equivalent normal tissue effects by interpolation. The START pilot hypofractionation trial recruited 1410 patients and the results published in 2006 challenged historical, highly conservative attitudes to radiotherapy dose-fractionation (Ref 1).

The Bliss and Yarnold teams subsequently designed and implemented the National Cancer Research Institute (NCRI) START trials (A & B), funded by Cancer Research UK, the Medical Research Council and the Department of Health (International Standard Randomised Controlled Trial Numbers: ISRCTN59368779 and ISRCTN59368779). These studies, led by the ICR/RM and involving 35 UK radiotherapy centres, recruited 4450 patients between 1998 and 2003 (Refs 2, 3). The results of these two parallel trials led to the recommendation, endorsed by NICE in 2009, that a 15-fraction regimen over 3 weeks (total 40Gy) should be the standard treatment protocol, replacing commonly-used 5-week schedules (total 50Gy). The START trials generated the only un-confounded estimates of fractionation sensitivity for any human cancer. One earlier trial testing this approach was a Canadian study (Ontario trial) that compared the same 25-fraction standard regimen against a 16-fraction test schedule. The results of this trial were consistent with the ICR's, but because treatment time as well as fraction number were varied in the test group, the Canadian study had very little explanatory value (Whelan et al. 2002).

The Bliss and Yarnold teams used the START pilot trial estimates of fractionation sensitivity of breast cancer to devise an experimental 5-fraction schedule, two dose levels of which were compared with the standard 25-fraction control regimen in 915 women, with dose-limiting adverse effects as the primary endpoint. The first results of this hypofractionation trial were published in 2011 (Ref 4) and they informed the design of the current NIHR FAST Forward Trial (target recruitment of 4000, International Standard Randomised Controlled Trial Number: ISRCTN19906132) testing a 5-fraction curative schedule of radiotherapy delivered in 1 week against the standard 3-week regimen. This trial is also being led by the same ICR teams.

Trial analysis by the Yarnold and Bliss teams has focused not only on disease outcomes but also on methodologies of recording normal tissue effects reported by patients and physicians and as scored from photographs (Ref 5). This work has shown patient reported outcome measures (PROMS) to be as sensitive as clinician assessments to small randomised differences in radiation dose intensity.

The 10-year results of the START trial were published in 2013 (Ref 6), and were presented by Yarnold at the San Antonio International Breast Symposium, December 2012. The results showed that the START pilot trial, START-A and START-B trials considered together, and the Ontario trial, all present robust evidence that hypofractionation is a safe and effective approach to breast cancer radiotherapy.

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.

1. Owen JR, Ashton A, **Bliss JM, Homewood J**, **Harper C**, **Hanson J**, **Haviland J**, Bentzen SM, **Yarnold JR.** 2006, Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial, Lancet Oncol. 7 (6), 467-471. (http://dx.doi.org/10.1016/S1470-2045(06)70699-4)
2. Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, **Bliss JM**, Brown J, Dewar JA, Dobbs HJ, **Haviland JS**, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, **Mills J**, Morgan DAL, Owen JR, **Simmons S**, **Sumo G**, **Sydenham MA**, Venables K, **Yarnold JR.** 2008, The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 371 (9618), 1098-1107. (http://dx.doi.org/10.1016/S0140-6736(08)60348-7)
3. Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, **Bliss JM**, Brown J, Dewar JA, Dobbs HJ, **Haviland JS**, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, **Mills J**, Morgan DAL, Owen JR, **Simmons S**, **Sumo G**, **Sydenham MA**, Venables K, **Yarnold JR.** 2008, The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 9 (4), 331-341. (http://dx.doi.org/10.1016/S1470-2045(08)70077-9)
4. Agrawal RK, Alhasso A, Barrett-Lee PJ, **Bliss JM,** Bliss P, Bloomfield D, Bowen J, Brunt AM, **Donovan E**, **Emson M**, Goodman A, Harnett A, **Haviland JS, Kaggwa R, Morden JP**, Robinson A, **Simmons S**, Stewart A, **Sydenham MA,** Syndikus I, Tremlett J, Tsang Y, Wheatley D, Venables K, **Yarnold JR**, 2011, First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015), Radiother Oncol. 100 (1), 93-100. (http://dx.doi.org/10.1016/j.radonc.2011.06.026)
5. **Hopwood P**, **Haviland JS**, **Sumo G**, **Mills J, Bliss JM**, **Yarnold JR**; START Trial Management Group. 2010, Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials, Lancet Oncol. 11 (3), 231-240. (http://dx.doi.org/10.1016/S1470-2045(09)70382-1)
6. **Haviland JS**, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, **Hopwood P**, Lawton PA, Magee BJ, **Mills J**, **Simmons S**, **Sydenham MA**, Venables K, **Bliss JM**, **Yarnold JR**, START Trialists' Group. 2013, The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials, Lancet. 14 (11), 1086-1094. (http://dx.doi.org/ 10.1016/S1470-2045(13)70386-3)

Selected research grant support

1. Bliss – "UKCCR Standardisation of Radiotherapy (START) Trial", Medical Research Council, 1997-2002 (£790k) and 2002-2008 (£1m).
2. Yarnold / Bliss – "Fast-Forward: a randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in women with early breast cancer", National Institute of Health Research, 2011-2020, £2.9m.
3. Yarnold – "Lymphocyte apoptosis and risk of chronic adverse effects in patients undergoing radical radiotherapy for breast and prostate cancers (FAST/CHHIP)", Department of Health, 2012-2014, £100k.

4. Details of the impact

Results from large-scale national trials led by the ICR and the RM testing hypofractionated breast radiotherapy (START trials Research Refs 1, 2, 3 and 6 above) have had a widespread impact on clinical practice in the UK and internationally. Radiotherapy dose fractionation is now standardised across the UK, as defined by the START team, involving a 15-fraction regimen delivered over 3 weeks. This regimen was approved by NICE in 2009 (NICE guideline CG80 [1]). The START trials (A and B) were led by Yarnold and Bliss as principal investigators and leaders of the Trial Management Group, with 35 participating clinical centres. Statistical analysis of the trials was carried out by Bliss and her team at the ICR, Bliss and Yarnold then produced the final report with the data interpretation. The results were more widely disseminated in a series of publications in medical journals, beginning in 2008, with Yarnold as the senior author (Research Refs 2, 3 and 6 above). As a result of the published outcomes, a Cochrane systematic overview of the 3 UK and 1 Canadian trial informed the updated (2009) NICE guidance on the management of early and locally advanced breast cancer, recommending 40Gy in 15-fractions (the START B trial test schedule) as the standard of care for these patients. This was immediately adopted nationwide, and remains a standard of care at all 61 UK radiotherapy centres.

Department of Health statistics for 2012 report 37,000 attendances (courses) of radiotherapy delivered to breast cancer patients, involving a total of 510,000 exposures (fractions), of which up to 20% are palliative (fewer than 15 fractions). These statistics are consistent with the large majority of curative treatments being delivered to patients using the START trial 15-fraction regimen (see Table 2 [2]). This means that at least 25,000 women per year in the UK are treated with the START regimen, replacing a wide variety of pre-existing regimens, many of which involved 25 fractions delivered over 5 weeks. Women are spending less time and money travelling for treatment, and the cosmetic results have improved substantially without any loss of cancer control. In addition, the NHS is saving substantially on treatment costs.

There is evidence that ICR research into hypofractionated radiotherapy is having a substantial impact on the development of international healthcare practice in breast cancer treatment. Countries in mainland Europe and North America are either adopting the START regimen systematically (Canada, Netherlands, France) [3], conducting confirmatory trials (Denmark: corroborating source listed below [4], also see ClinicalTrials.gov NCT00909818), or adopting it piecemeal [5]. There is also rapid adoption in India (corroborating source listed below [6]). It should be noted that adoption in countries where healthcare insurance payments are linked to the number of fractions has been slower.

START provided evidence to support safe and effective delivery of hypofractionated radiotherapy, and led ICR teams to investigate this approach further in the NCRI FAST pilot trial, which, in turn, informed the design of the current NIHR (HTA) funded FAST-Forward trial [7]. This study will accrue 4000 women with early stage breast cancer by 2014, thereby benefiting a large number of patients by giving them the opportunity to take part in clinical trials – currently 200 UK patients per month are being recruited. Another trial that has followed from the ICR START studies is the NCRI IMPORT HIGH trial, currently recruiting 2800 patients across the UK [8].

The radiotherapy quality assurance (QA) programmes accompanying the fractionation trials led by the ICR and the RM have standardised radiotherapy techniques in the majority of the UK's 61 radiotherapy centres and have been the main vehicle for the safe introduction of advanced radiotherapy techniques, including intensity modulated radiotherapy (IMRT), across the UK. These benefits have remained in place after completion of trial accrual, as confirmed in a recent national survey [9]. The QA team has demonstrated the importance of centres participating in clinical trials, as these provide the framework and impetus for introducing more accurate radiotherapy for UK women with early breast cancer. The national radiotherapy QA team derives strong support from ICR staff in the Joint Department of Radiotherapy and Physics, whose members helped develop the protocols used in the breast fractionation trials.

5. Sources to corroborate the impact

[1] NICE Guideline CG80 – http://www.nice.org.uk/guidance/cg80

[2] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213151/Radiotherapy-Services-in-England-2012.pdf

[3] Besnard S et al. 2012, Radiotherapy of invasive breast cancer: French national guidelines, Cancer Radiothér. 16 (5-6), 503-513 (http://dx.doi.org/10.1016/j.canrad.2012.07.181)

[4] Radiation Oncologist, Aarhus University Hospital (Identifier 1)

[5] Smith BD et al. 2011, Fractionation for Whole Breast Irradiation: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline, Int J Radiat Oncol Biol Phys. 8 (1),59-68 (http://dx.doi.org/10.1016/j.ijrobp.2010.04.042)

[6] Director of Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre (Identifier 2)

[7] http://www.nets.nihr.ac.uk/projects/hta/090147

[8] http://www.controlled-trials.com/ISRCTN47437448

[9] Miles E and Venables K. 2012, Radiotherapy Quality Assurance: Facilitation of Radiotherapy Research and Implementation of Technology, Clin Oncol (R Coll Radiol). 24(10), 710-712 (http://dx.doi.org/10.1016/j.clon.2012.06.006)