Emmanuel van der Schueren lecture

E1. Research progress and priorities in breast radiotherapy

J. Yarnold*

Section of Radiotherapy, Institute of Cancer Research & Royal Marsden Hospital, Sutton, UK

This summary of progress and research priorities in radiotherapy for women with early breast cancer restricts itself to the role of adjuvant radiotherapy after breast conservation surgery. A systematic overview of whole breast radiotherapy by the Early Breast Cancer Trialists' Collaborative Group has reported outcome data on 7311 women entered into trials starting as early as 1976 and as recently as 1991.[1] For every 100 women allocated to radiotherapy, there were 20 fewer local tumour relapses than when no radiotherapy was given, translating into 5.1% and 7.1% reductions in 15-year breast cancer mortality in node negative and node positive patients, respectively. On average, one breast cancer death was prevented for every four local relapses prevented by radiotherapy. All-cause mortality was also reduced; the excess non-breast cancer deaths seen in an earlier era after post-mastectomy radiotherapy was no longer evident.

Over the last two decades, local relapse rates have fallen much more than expected from the demographic and tumour characteristics of the patients, and it is likely that greater attention to surgical excision margins and more effective adjuvant endocrine, cytotoxic and biological therapies have contributed.[2] Radiotherapy has also become more effective, partly due to the surgical practice of inserting titanium ligaclips to mark the anterior, posterior and four radial margins of tumour excision.[3] The clips allow the tumour bed to be reconstructed in 3D on radiotherapy x-ray computed tomography (CT) planning images and visualised during treatment using CT imaging capability incorporated in linear accelerators.

Progress has been made in identifying risk factors for local tumour relapse after breast conservation surgery and radiotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 trial evaluating the effects of a tumour bed boost dose after adjuvant whole breast radiotherapy has been most informative in this respect, identifying young patient age as an important independent risk factor for local relapse.[4] In addition, there is evidence that gene expression differences between tumours can discriminate high and low relapse risk subgroups.[5] A third example of progress relates to changes in fractionation. Four randomised trials ($N>7000$) tested a lower total dose delivered in fewer, larger fractions than the standard 5-week regimen. A Cochrane review confirmed the safety and effectiveness of this approach, and a 15-fraction schedule delivered over 3 weeks has become standard of care in the United Kingdom (UK).[6–8]

Research priorities include reducing the radiation exposure of women at low local relapse risk. Local relapse risk is not uniform across the breast, the majority appearing in the vicinity of the primary tumour. Partial breast radiotherapy restricted to the site of local tumour excision is under test in several ongoing randomised clinical trials.[9] The interventions vary from a 3-week schedule of external beam intensity modulated radiotherapy encompassing the index quadrant to a single intraoperative dose of radiotherapy restricted to the tumour bed. The expectation is that efficacy will not be compromised, and that the morbidity in terms of breast shrinkage and induration will be greatly reduced. For women at higher than average risk of local tumour relapse, the challenge is to increase the dose intensity to the tumour bed. One approach is to apply intensity modulated radiotherapy techniques to vary fraction size across the breast rather than giving additional fractions to the tumour bed. Randomised trials in the UK and the Netherlands are currently evaluating this approach.[10]

The incorporation of x-ray CT into linear accelerator design enables the accuracy of radiotherapy to be checked, allowing small variations in patient positioning to be corrected before treatment on a daily basis. This practice, called image guided radiotherapy, may allow a reduction in the safety margin of healthy tissue needed around the tumour bed, leading to worthwhile reductions in late side effects, especially breast hardness and pain. However, there is a potential downside. Repeated diagnostic imaging during radiotherapy delivers a small additional dose to internal organs that slightly increases the risk of rare radiation-induced second cancers. It is likely that the increased dose to internal organs is more than balanced by a reduction in scattered dose from smaller therapy beams.[11]

Other priorities for the coming decade include identification of low risk subgroups that need no radiotherapy after complete microscopic resection of primary tumour.[12–14] Women above the age of 70 years with oestrogen receptor-rich tumours prescribed adjuvant endocrine therapy represent a candidate group for this approach, which requires further systematic evaluation. Another priority is to identify predictors of

1359-6349/$ – see front matter

normal tissue response to radiotherapy, and international collaborations are currently undertaking genome wide association studies with the aim of identifying genetic polymorphisms associated with high or low risk of late adverse radiotherapy effects.

Finally, hypofractionation for whole breast radiotherapy justifies further investigation, since 15- or 16-fraction schedules are unlikely to represent the limits of this approach. Retrospective reports of once-weekly schedules suggest that a 5-fraction regimen can be delivered.[15] A UK randomised trial (N=915) identified a 5-fraction regimen equivalent to 50Gy in 25 fractions in terms of adverse effects at 2 years.[16] A larger trial is needed to test the long-term safety and effectiveness of this approach.

Conflict of interest statement

None declared.

References

[1] Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366(9503):2087–106.

[2] Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? *Radiother Oncol* 2009;90(1):14–22.

[3] Coles CE, Wilson CB, Cumming J, et al. Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery: audit on behalf of the IMPORT Trial Management Group. *Eur J Surg Oncol* 2009;35(6):578–82.

[4] Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007;82(3):265–71.

[5] Nuyten DS, Kreike B, Hart AA, et al. Predicting a local recurrence after breast-conserving therapy by gene expression profiling. *Breast Cancer Res* 2006;8(5):R62.

[6] James ML, Lehman M, Hider PN, Jeffery M, Francis DP, Hickey BE. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database Syst Rev* 2008;(3):CD003860.

[7] Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9(4):331–41.

[8] Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371(9618):1098–107.

[9] Mannino M, Yarnold J. Accelerated partial breast irradiation trials: diversity in rationale and design. *Radiother Oncol* 2009;91(1):16–22.

[10] Coles C, Yarnold J. The IMPORT trials are launched (September 2006). *Clin Oncol (R Coll Radiol)* 2006;18(8):587–90.

[11] Van Herk M. Different styles of image-guided radiotherapy. *Semin Radiat Oncol* 2007;17(4):258–67.

[12] Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351(10):963–70.

[13] Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351(10):971–7.

[14] Potter R, Gnant M, Kwasny W, et al. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007;68(2):334–40.

[15] Kirova YM, Campana F, Savignoni A, et al. Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 2009;75(1):76–81.

[16] Brunt AM, Sydenham M, Bliss J, et al. A 5-fraction regimen of adjuvant radiotherapy for women with early breast cancer: first analysis of the randomised UK FAST trial (ISRCTN62488883, CRUKE/04/015). *Eur J Cancer* 2009;7 (Suppl.):2.