Understanding radiotherapy and its potential for use in novel combination trials

Breast cancer

Charlotte Coles,[1] Diana Ritchie,[2] Katherine Vallis[3]

1. Addenbrookes Oncology Centre, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK
2. Beatson Oncology Centre, Glasgow, UK
3. Cancer Research UK/MRC Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford, UK

UK incidence (2006 data)

Women: 45,500 per annum.

Men: 300 per annum.

Background, stage distribution at presentation and indications for radiotherapy

Breast cancer is the second-leading cause of cancer death among women after lung cancer. There will be an estimated 46,000 new cases of breast cancer in the UK in 2010 and an estimated 12,000 women are predicted to die from the disease. The prognosis for patients with breast cancer has improved in recent years due to early detection through mammographic screening and refinement of adjuvant therapies. Around 90% of women diagnosed with stage I breast cancer survive beyond five years and the five-year survival rate for all patients (diagnosed 2001–2003, England & Wales) was 80%.

Despite these encouraging trends, patients continue to present with or develop disseminated disease. For patients that develop metastases, the median time to treatment failure following chemotherapy or hormonal therapy is 8–9 months and median survival is less than 2 years. Recent models indicate that approximately two-thirds of breast cancer patients would benefit from radiation therapy (RT) during the evolution of their illness [1]. This figure may increase over the next five years because of the ongoing influence of screening and early detection, which make breast-conserving therapy (BCS) a viable alternative to mastectomy for many.

Adjuvant RT to the whole breast and, sometimes, the draining lymph nodes areas is a standard procedure after BCS for invasive cancer. Ductal carcinoma in situ (DCIS) is also often managed by BCS plus RT. RT is generally only omitted after BCS in patients who are at particularly low-risk of loco-regional recurrence. RT to the chest wall and, in some cases, the draining lymph node areas, is also recommended for patients with high/moderate risk of recurrence following mastectomy. Post-operative RT reduces the risk of loco-regional recurrence in breast cancer by 65–75%.

Recent data from Phase III trials and meta-analyses also indicate that RT has a substantial beneficial impact on survival, of up to 9–10% at ten years. On average, one breast cancer death is prevented for every four local recurrences avoided through the use of RT [2]. Results of some trials indicate that the proportionate survival benefit associated with RT may even be substantial in patients with a relatively low risk for loco-regional recurrence (those with 1 to 3 positive nodes) [3,4].

Stage at presentation

- Stage I: 50%
- Stage II, III: 45%
- Stage IV: 5%

Systemic therapy

Adjuvant endocrine therapy is recommended for most patients whose tumours are oestrogen receptor (ER) positive. Generally, tamoxifen and aromatase inhibitors are recommended for pre- and post-menopausal women, respectively. Trastuzumab (trade name Herceptin) is indicated in patients with human epidermal growth factor receptor 2 (HER2)-positive disease. Patients receiving Herceptin conventionally also receive chemotherapy. Chemotherapy is also generally offered to patients with triple-negative disease (i.e. those with tumours that are negative for oestrogen and progesterone receptors and for HER2). The recommendation for chemotherapy for patients with ER-positive, HER2-negative disease depends on their estimated risk of relapse (based on the precise stage using the TNM system, histological grade and presence of lymphovascular invasion [LVI]) and the estimated size of benefit attributable to chemotherapy. Chemotherapy most often consists of an anthracycline-containing regimen; FEC (5-fluorouracil, epirubicin and cyclophosphamide) is commonly used in the UK. Increasingly, taxane-containing regimens are being used particularly for women at moderate or high risk of recurrence. Adjuvant systemic therapy may be omitted in some patients with small primary tumours (pT1a, pN0 and ER negative).

Biology

Gene expression profiling has led to the discovery of molecular subtypes of breast cancer: luminal A, luminal B, basal like, and HER2 enriched. These subtypes have been found to be predictors for survival, recurrence and response to systemic therapy. The use of multigene assays to guide use of systemic therapy is being investigated in clinical trials. Genetic assays specifically to guide the use of RT are not available. Efforts to identify genetic determinants of individual variation in normal tissue radiosensitivity are under way (e.g. RAPPER – Radiogenomics: Assessment of Polymorphisms for the Predicting the Effects of Radiotherapy study).

Future directions in breast radiotherapy research

The current challenge in breast radiation oncology is to reduce late normal tissue side effects in patients at low risk of recurrence whilst maintaining excellent local control and survival. In addition, those patients considered to be at higher risk of recurrence should be targeted for escalation of treatment whilst minimising morbidity. The ultimate goal is to identify genetic and other biological determinants of outcome for both tumour and normal tissues, so that patients can receive individualised therapy. This approach requires the development of a range of radiation techniques, which may be used concomitantly with systemic therapies. The following themes are likely to be areas of future investigation.

Observational/early phase (I or II) studies

a) *Tumour bed localisation*

It is recognised that following BCS the majority of true local recurrences occur in the region of the original tumour. For example, in the Milan trial, which compared 2,544 patients treated by BCS +/-RT from 1970–1989, 74% of recurrences were ≤2 cm from the excision scar [5]. It follows that accurate tumour bed localisation is important for patients being considered for partial breast radiation therapy (PBRT) and for patients at higher risk of recurrence where dose escalation (boost) is considered. The EORTC boost vs no boost trial showed an improvement in local control with a hazard ratio of 0.59 for boost [6]. This trial used clinical tumour bed localisation.

Various imaging modalities have been investigated as a means of improving accuracy of tumour bed target definition. Some imaging methods, such as ultrasound and computed tomography (CT), rely on locating seroma at the site of surgical excision. The presence and volume of seroma, however, varies depending on time from surgery and surgical technique used. Research using magnetic resonance (MR) imaging has shown concentric rings of different signal intensity, suggesting that granulation tissue is laid down within the cavity. This indicates that the true excision cavity boundary is outside the fluid-tissue interface [7]. A study using positron emission tomography-CT (PET-CT) showed that tumour bed volumes using functional imaging were consistently larger than CT-defined volumes. It was stated that the PET-positive tissue was likely to represent peri-tumour bed inflammation. Therefore, the tumour bed volume may be overestimated when defined using PET-CT [8].

Further research investigating the use of MR and functional imaging for tumour bed localisation compared with implanted and fiducial markers plus CT is warranted. Given that the tumour bed moves with respiration, the utility of four-dimensional (4D) imaging in this context should also be explored. Strategies to minimise intra- and inter-observer variation in tumour bed delineation should be investigated.

b) *RT treatment volumes*

Breast

The current international standard of care is whole breast radiotherapy (WBRT). However, improvements in local control rates have prompted several randomised trials to compare PBRT versus WBRT, with the aim of maintaining local control but decreasing side effects in lower risk patients. The UK IMPORT LOW trial is the only trial which tests the effect of volume, as treatment is delivered over 3 weeks in both the control and test arms. In all other trials of PBRT, accelerated RT is given in the non-standard arm.

Further research to investigate optimal clinical target volumes (CTV) and planning target volumes (PTV) is required. The IMPORT LOW trial aims to accurately map the location of any recurrences in relation to the RT volumes. Translational studies are needed to investigate the genetic and biological characteristics of true recurrences versus new primaries. In addition, the effect of WBRT on new primaries distant from the index quadrant is currently unknown.

The ultimate reduction in RT volume is complete omission of radiation. Phase III trials have demonstrated that risk of recurrence, even in the absence of RT, is very low in older women (>70 years), with small, ER-positive cancers [9]. However, many hold the view that it is still not possible to reliably identify a group where RT can be withheld [10]. At least one international trial is planned to investigate the effect of omitting RT, e.g. the proposed Trans-Tasman Radiation Oncology Group – Breast International Group (TROG-BIG) trial. This and trials of similar design should include a translational component to identify the genetic and biological predictors for recurrence.

Regional lymph nodes

The RT fields used to treat regional lymph nodes are often large, to encompass the cervico-axillary chain of nodes. Yet, the volume actually occupied by lymphatic tissue (the target) within these fields is small. The value of intensity-modulated radiotherapy (IMRT) for regional node irradiation has not been thoroughly tested. IMRT techniques to assure treatment of the supra clavicular, axillary and, sometimes, internal mammary node chains while minimising the volume of normal tissue irradiated would be beneficial.

Image-guided techniques using, for example, MRI-anatomical mapping of lymphatics or lymphatic contrast agents should be investigated. These could lead to more precise delivery of RT and, therefore, dose escalation.

c) Image-guided radiotherapy (IGRT)

Most centres currently use limited verification with 'portal images' taken on the treatment machine at the time of radiotherapy, which are based on bony anatomy and do not take into account possible independent movement of the breast. Accurate on-treatment verification with IGRT becomes particularly important as RT target volumes are reduced, as is the case for PBRT, and when dose to the tumour bed is escalated. One consequence of IGRT, however, is that some methods, such as cone beam CT and megavoltage (MV) CT, result in delivery of non-target radiation dose.

Research is needed to produce optimal IGRT protocols that result in minimum additional dose. This may be best achieved through observational studies or, possibly, as embedded IGRT studies within randomised controlled trials. Investigations into the consequences of intrafraction motion and how this can be accounted for in RT planning are also required. On-line planning strategies could be developed to accommodate real-time re-optimisation of the treatment at the moment of therapy. The implementation of a 4D planning approach would permit adaptation to changes in breast position and shape over a short course of therapy (which would be particularly important when hypofractionated regimens are used).

d) RT with concomitant systemic therapy in locally advanced breast cancer (LABC)

Much of the current breast RT research is concentrated on adjuvant treatment, with relatively few RT trials available for locally advanced breast cancer. Neoadjuvant chemotherapy is commonly used for

these patients, but some patients are relatively chemo-insensitive. The ideal protocol for combining neoadjuvant systemic treatment with RT has yet to be defined.

Research studies that investigate the use of neoadjuvant RT with systemic therapy are needed. Systemic therapy would include chemotherapy and also biological therapy (e.g. tyrosine kinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors, poly (ADP–ribose) polymerase (PARP) inhibitors, etc).

e) Studies to evaluate wound healing response

There is no clear relationship between excision margin width and local breast recurrence. This suggests that other tumour-host factors influence risk of recurrence. There is evidence that the wound healing response may play a part in tumour recurrence. Gene expression profiling has been studied in tumours classified as having an activated or quiescent wound response signature. It has been shown that the wound expression profile is a powerful predictor of local relapse [11]. In addition, increased proliferation in re-excision samples was found to be associated with HER2 positivity [12]. Intra-operative RT appears to modify the stimulation of proliferation associated with surgical wounding [13].

Research studies are needed to investigate whether peri-/intra-operative RT modifies the wound stimulating effects and thus decreases local recurrence. These studies could be designed to give peri-operative RT followed by conventional post-operative RT. Associated translational studies could provide greater understanding of biological and genetic factors influencing local recurrence.

f) Particle therapy

There have been a few reports of the use of proton therapy for breast RT. Dosimetry appears to be favourable when compared with IMRT.

Clinical trials of protons and other heavy ions are required to establish their efficacy in comparison with optimal photon therapy.

Long-term observational studies for late effect monitoring

In recent years, there has been a move away from traditional tangential field breast irradiations. Examples are 3-dimensional conformal RT for accelerated PBRT and IMRT for concomitant boost or internal mammary nodal irradiation. These techniques have been shown to provide excellent coverage of the target, with a reduction in the high dose regions to organs at risk (OARs). These techniques can result in a higher volume of normal tissue receiving a 'low dose bath' compared with tangential irradiation. A 2% incidence of symptomatic pneumonitis has been reported at a centre using accelerated PBRT with radiological lung changes all outside the high dose region [14].

Investigation into the normal tissue side effects of the newer RT techniques, including second malignancy, is required. This would require a co-ordinated effort to collect outcome data in a standardised format.

Possible areas for phase III trials

a) RT dose and fractionation

The results of three randomised controlled trials of WBRT involving more than 7000 patients indicate that protocols delivering 40–42.5 Gy in 15–16 daily fractions are as effective as the international standard of 50 Gy in 2 Gy daily fractions [15-17]. This suggests that breast cancer is as sensitive to RT fraction size as dose-limiting late adverse effects and therefore standard 2.0 Gy fractions may have only modest advantage in breast cancer RT. It is unlikely that 15 fractions is the limit of hypofractionation for WBRT. The FAST trial has shown that the hazard ratio for moderate/marked RT adverse effects for 28.5 Gy in 5 fractions vs 50 Gy in 2 Gy fractions is 1.20 (0.81–1.77, p=0.36) i.e. there is no statistically significant difference for late adverse effects. Further research is required to test the limits of hypofractionation on local control and normal tissue side effects. The UK FAST FORWARD trial will compare the UK standard for WBRT of 40 Gy in 15 fractions with two dose levels for 5 daily fractions. The primary endpoint will be tumour control.

Given that the response of breast cancer to RT fraction size is similar to that of late-reacting normal tissues, modification of dose intensity by adjusting fraction size rather than fraction number is an attractive solution. The UK IMPORT HIGH trial is currently testing dose escalation to the tumour bed using a concomitant IMRT technique. The primary endpoint is induration. Further research will be required after completion of IMPORT HIGH to establish the efficacy of dose escalation using hypofractionation for local control.

Palliative RT for breast cancer

RT is used extensively in the treatment of bone and other metastases in breast cancer. There has been recent interest in the strategy of radical treatment of oligometastases (<5 metastases) using stereotactic RT for brain metastases and other advanced techniques. Encouraging results for this approach have been achieved in breast cancer in particular [18]. A trial that compares radical RT for oligometastases versus the current standard of treating symptomatic lesions with a palliative dose would be of interest.

Summary of breast RT trial concepts

1. Further research investigating the use of MR and functional imaging for tumour bed localisation compared with implanted and fiducial markers plus CT is warranted. Given that the tumour bed moves with respiration, the utility of 4D imaging in this context should also be explored. Strategies to minimise intra- and inter-observer variation in tumour bed delineation should be investigated.
2. Further research to investigate optimal clinical target volumes (CTV) and planning target volumes (PTV) is required. The IMPORT LOW trial aims to accurately map the location of any recurrences in relation to the RT volumes. Translational studies are needed to investigate the genetic and biological characteristics of true recurrences versus new primaries. In addition, the effect of WBRT on new primaries distant from the index quadrant should be established.
3. At least one international trial is planned to investigate the effect of having no RT (proposed TROG-BIG trial). This and trials of similar design should include a translational component to identify the genetic and biological predictors for recurrence.

4. For regional RT, image guided techniques using for example MR-anatomical mapping of lymphatics, or injectable lymphatic contrast agents should be investigated. The impact of delivery precision may allow dose escalation.

5. Research is needed to define optimal IGRT protocols with the minimum additional dose. This may be best achieved in observational studies or, possibly, as embedded IGRT studies within randomised controlled trials. Investigation is also required into the effects of and solutions for intrafraction motion. On-line planning strategies could be developed to accommodate real-time re-optimisation of the treatment at the moment of therapy.

6. Research studies investigating the use of neoadjuvant RT with systemic therapy are needed. In this context, systemic therapy includes chemotherapy and also biological therapy (e.g. tyrosine kinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors, poly—ADP ribose polymerase (PARP) inhibitors, etc.

7. Research studies are needed to investigate whether peri-/intra-operative RT modifies the possible wound stimulating effects of surgery and thus has the potential to decrease local recurrence. These studies could be designed to evaluate peri-operative RT followed by conventional post-operative RT. Associated translational studies could provide greater understanding of biological and genetic factors influencing local recurrence.

8. Clinical trials of protons and other heavy ions are required to establish their efficacy in comparison with optimal photon therapy.

9. Investigation into the normal tissue side effects of the newer RT techniques, including second malignancy, is required. This would require a co-ordinated effort to collect outcome data in a standardised format.

10. Further research is required to test the limits of hypofractionation on local control and normal tissue side effects. The UK FAST FORWARD trial will compare the UK standard for WBRT of 40 Gy in 15 fractions with two dose levels for 5 daily fractions. The primary endpoint will be tumour control.

11. Further research will be required after completion of the IMPORT HIGH trial to establish the efficacy of dose escalation using hypofractionation for local control.

12. A trial that compares radical RT for oligometastases versus the current standard of treating symptomatic lesions with a palliative dose would be of interest.

References

1. Williams MV, Drinkwater KJ. Radiotherapy in England in 2007: modelled demand and audited activity. *Clin Oncol (R Coll Radiol)* 2009;21:575–590.
2. 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;366:2087–106.
3. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997;337:956–62.
4. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641–8.
5. Salvadori B, Marubini E, Miceli R, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. *Br J Surg* 1999;86:84–7.
6. Poortmans PM, Collette L, Horiot JC, et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. *Radiother Oncol* 2009;90:80–5.

7. Whipp EC, Halliwell M. Magnetic resonance imaging appearances in the postoperative breast: the clinical target volume-tumor and its relationship to the chest wall. *Int J Radiat Oncol Biol Phys* 2008;72:49–57.

8. Ford EC, Lavely W, Frassica D, et al. Comparision of PET/CT and CT for delinieation of lumpectomy cavity for partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2006;66:S225–6.

9. 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;351:963–70.

10. 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;90:14–22.

11. 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:R62.

12. Tagliabue E, Agresti R, Carcangiu ML, et al. Role of HER2 in wound-induced breast carcinoma proliferation. *Lancet* 2003;362:527–33.

13. Belletti B, Vaidya JS, D'Andrea S, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clin Cancer Res* 2008;14:1325–32.

14. Recht A, Ancukiewicz M, Alm El-Din MA, et al. Lung dose-volume parameters and the risk of pneumonitis for patients treated with accelerated partial-breast irradiation using three-dimensional conformal radiotherapy. *J Clin Oncol* 2009;27:3887–93.

15. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143–50.

16. Owen JR, Ashton A, Bliss JM, et al. 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* 2006;7:467–71.

17. 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;9:331–41.

18. Milano MT, Philip A, Okunieff P. Analysis of patients with oligometastases undergoing two or more curative-intent stereotactic radiotherapy courses. *Int J Radiat Oncol Biol Phys* 2009;73:832–7.