Radiotherapy following excision of early breast cancer

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Introduction
Breast cancer is the most common cancer in the UK. Most women diagnosed with breast cancer have early stage disease and will be treated with breast conserving surgery followed by whole breast irradiation to maximise local tumour control.

This review briefly outlines the rationale for our current management strategy in early breast cancer, the clinical indications for radiotherapy following excision of early breast cancer, technical advances in breast radiotherapy, dose-fractionation issues and future directions.

Evidence for current management of women with early breast cancer
In the 1980s, the standard surgical procedure for early breast cancer was the modified radical mastectomy, which involved removal of the breast and axillary nodal dissection with preservation of the major pectoral muscle. The incidence of local recurrence following this procedure was low in node negative patients, but the operation had a negative impact on body image.2,3

Efforts to improve the functional and cosmetic outcome of breast cancer surgery led to breast-conserving surgery, involving the removal of the tumour with a rim of normal tissue followed by adjuvant radiotherapy. Landmark studies compared breast conservation surgery followed by radiotherapy, with mastectomy alone, and reported equivalent survival.4,5

The Early Breast Cancer Trialists Collaborative Group systematic overview (2005) confirmed the benefits of radiotherapy following breast conservation surgery, with a three-fold reduction in local relapse risk at 10 years which translated into a reduction in breast cancer mortality of between 5% and 8%, depending on node status.6 For every 100 women randomised to radiotherapy, there were 20 fewer local relapses and five fewer breast cancer deaths compared with 100 randomised to no radiotherapy (Figure 1). Thus, avoiding four local recurrences prevents one breast cancer death, a benefit maintained at 15 years of follow-up. This 4:1 ratio is an average effect and is based largely on trials with no systemic chemotherapy. Sub-groups of patients with very poor prognostic factors, for example >10 nodes positive, are likely to derive much less benefit in terms of breast cancer mortality compared with subgroups with good prognostic factors in whom local control is of paramount importance in preventing first metastasis, and where the ratio might be ≤2:1 (prevention of ≤2 local recurrence saves one life).7

Clinical indications for radiotherapy following local excision of breast cancer
Recently updated NICE guidelines state that “patients with early invasive breast cancer who have had breast-conserving surgery with clear margins should have breast radiotherapy.” Adjuvant systemic therapies, including endocrine therapy, chemotherapy and biological therapy, eg trastuzumab, combines favourably with radiotherapy to further reduce local relapse risk following breast conservation therapy.8

NICE guidance states also that “an external beam boost to the site of local excision should be offered to patients with early invasive breast cancer and a high risk of local recurrence following breast-conserving surgery with clear margins and whole breast radiotherapy.” This guidance is based largely on the EORTC boost trial in which younger age was the strongest prognostic factor for local recurrence at 10 years.9 Rates of local tumour relapse following breast conservation therapy appear to be falling to <5% at five years. This improvement is probably due to a combination of factors, including improved surgical management of the primary tumour, more effective adjuvant systemic therapy, more older patients with low risk disease and technical advances in breast radiotherapy.10 While it is standard practice to give radiotherapy to all patients following breast conservation therapy, a research priority is to identify subgroups of women who can safely avoid radiotherapy.

Technical advances in breast radiotherapy
Our surgical colleagues have pioneered techniques to minimise the morbidity of breast cancer surgery, including sentinel node and reconstructive techniques where appropriate, without negatively impacting on local control or survival. Multi-disciplinary team working has encouraged closer collaboration between radiologists, pathologists, surgeons and oncologists. For example, it is now standard practice in many centres for titanium clips to be placed at the time of surgery, marking the wall of the excision cavity. The clips help oncologists to localise the tumour bed on radiotherapy planning CT scans, which is of help in identifying the boost site as well as being crucial in clinical trials of partial breast radiotherapy (Figure 2).

Improvements in radiotherapy technique have been made at each step in the radiotherapy pathway, including immobilisation (customised breast boards), treatment planning and verification (electronic portal imaging). Traditionally, conventional (2D) simulation has been used to plan breast radiotherapy. Many UK radiotherapy departments now routinely perform 3D planning using large-bore CT scanners, which has several advantages over 2D techniques. The time expenditure for both patients and clinical staff is reduced, due to fast capture of CT images and rapid reconstruction of images as well as automatic skin outlining. Other technical advantages include verification of beam coverage of target, as well as critical organ (eg heart and lungs) avoidance in three dimensions.11

3D planning allows the spatial distribution of hot spots (volumes receiving a dose >105% of prescribed dose) to be evaluated. This information can be used to modify the treatment plan, by the use of physical compensators, or step-and-shoot MLC fields (Intensity Modulated Radiotherapy), in order to optimise dosimetry. Importantly, there is good evidence that the improvement of dosimetry that is now possible with IMRT, translates into improved clinical outcome for patients. A trial conducted at the Royal Marsden Hospital randomised patients requiring whole breast radiotherapy to standard 2D radiotherapy using wedge compensators (control arm) or 3D IMRT (test arm). The control arm patients were 1.7 times more likely to have a change in breast appearance (judged by clinical photographs) than the test arm patients (Figure 3). However, IMRT does increase the dose to other organs not normally considered in conventionally planned breast radiotherapy, eg contralateral lung and breast, thyroid, humeral head and oesophagus. The significance of this “low dose bath” effect is currently unknown, but the issue of possible late oncogenesis needs to be studied carefully.12
6097 women with BCS and node-negative disease

Five-year gain 16.1% (SE 1.0)

1214 women with BCS and node-positive disease

Five-year gain 30.1% (SE 2.8)

FIGURE 1

Survival curves showing the importance of breast radiotherapy after breast conserving surgery in reducing local recurrence rate and mortality.


FIGURE 2

Surface rendered view of surgical cavity clips. Note the clips of Patient B are positioned away from the surgical scar.


FIGURE 3

Examples of sagittal dose distribution for (a) standard wedged plan and (b) IMRT plan. Data are from the in-house programme for one patient. Colour scale: dark blue = 90%, mid blue = 95%, light blue = 98%, mid green = 100%, light green = 102%, yellow = 105%, orange = 110%, red = 112%.

Dose-fractionation issues

For many years, the international standard regimen for adjuvant breast radiotherapy has been 25 daily fractions of 2 Gy to a total dose of 50 Gy over five weeks. Alternative hypofractionated schedules have also been widely used in the UK and Canada on an empirical basis. The START B trial, a multicentre study that recruited over 2200 women, aimed to compare these commonly used regimens, and concluded that, following surgery for early breast cancer, a radiotherapy schedule delivering 40 Gy in 15 fractions over three weeks offers rates of loco-regional control and late normal tissue effects comparable with 50 Gy in 25 fractions. The recently updated NICE guidance endorses the use of 40 Gy in 15 fractions following breast conservation surgery for early breast cancer. This hypofractionated regime should result in considerable saving of resources, both human and financial, as well as being more convenient and acceptable to patients.

Future directions

There has been a recent trend to stratify patients post-surgery by their prognostic risk factors and to tailor their radiotherapy accordingly.

Low-risk patients

Partial breast irradiation is being evaluated for low-risk individuals, based on the observation that the majority of local relapses occur in the vicinity of the primary tumour or at least within the index quadrant of the breast. In addition, it is not clear that whole breast radiotherapy reduces the risk of ipsilateral breast tumour recurrence outside the index quadrant, a high proportion of which are probably new primary tumours. These two observations taken together raise the possibility that only partial breast irradiation is important in achieving local control following breast conservation surgery in low-risk cancer patients. Against this background, IMPORT-Low is a multi-centre randomised trial testing partial versus whole breast radiotherapy delivered with IMRT following complete local tumour excision of low-risk early stage breast cancer (figure 4).

Accelerated Partial Breast Irradiation (APBI) is also being evaluated in low-risk patients following breast conservation surgery. The MammoSite system employs a dual-lumen spherical balloon catheter which is placed in the surgical cavity and filled with water. A high-dose-rate (HDR) Iridium-192 source placed in the central lumen delivers the radiotherapy in 10 fractions over five days. The concept of APBI is also being evaluated in trials of intra-operative radiotherapy using either low energy x-rays (TARGIT) or electrons (ELIOT).

High-risk patients

The IMPORT-High study is currently open to recruitment for women at a higher than average risk of local recurrence. This randomised trial tests dose-escalated intensity modulated radiotherapy in eligible women after breast conservation surgery and appropriate systemic therapy.

Summary

Most women diagnosed with breast cancer have early stage disease and will be treated with breast conservation surgery followed by whole breast irradiation. A majority will have an excellent prognosis, and the challenge in this group of patients is to reduce treatment morbidity, without negatively impacting on local control or survival rates. In contrast, some women undergoing breast conservation surgery have poor prognostic factors and a higher than average risk of recurrence. The challenge in these women is to deliver more intense radiotherapy to improve local control and survival while maintaining acceptable late normal tissue toxicity. It is hoped that recent technological advances in radiotherapy techniques and well-coordinated clinical trials will help to meet these challenges.

References


FIGURE 4
Planning CT scan showing GTV (blue contour) marked by surgical clips, CTV (red contour) and PTV (lavender colourwash) of a patient receiving partial breast irradiation in the IMPORT Low trial.