3.
Breast cancer

Background

Breast cancer is the most common cancer in women in the UK and most patients are diagnosed at an early stage due the NHS Breast Screening Programme. Radiotherapy has long been established as an important treatment modality in the adjuvant and palliative setting in breast cancer. Technological advances and results of pivotal trials have led to significant changes in practice in the UK in the last few years.

Adjuvant radiotherapy to the breast or chest wall

Radiotherapy increases both local control and overall survival in the conservation management of primary breast cancer in selected patients after mastectomy (Level 1a).[1–3] It also reduces ipsilateral breast tumour recurrence following breast conservation in patients with a diagnosis of ductal carcinoma *in situ* (DCIS).[4,5]

Although radiotherapy reduces the risk of recurrence for both DCIS and invasive disease for all patient groups, given the small benefits of adjuvant radiotherapy following breast-conserving surgery in low-risk patient groups, it is reasonable to consider omission of radiotherapy in patients with oestrogen receptor positive, node negative tumours which are less than 3 centimetres (cm) in maximum diameter and who are aged over 70 years, with low-risk biological features such as low-grade, no lymphovascular invasion and HER-2 negativity (Level 1b).[3,6,7]

The previous standard breast fractionation was a regimen of 50 Gray (Gy) in 25 fractions over five weeks as reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials.[8] Currently the most widely used UK regimen is the hypofractionated regimen of 40 Gy in 15 fractions over three weeks as used in the UK START Study B.[9] Mature data from the START B trial and a Canadian study demonstrate the equivalence of hypofractionationed regimens to the previous standard of 2 Gy daily fractionation (Level 1b).[3,10]

There are no trials comparing 40 Gy in 15 fractions versus 50 Gy in 25 fractions following breast reconstruction, but there is no radiobiological reason to recommend 50 Gy in 25 fractions in this situation. The results of the START B trial demonstrate that 40 Gy in 15 fractions leads to fewer late effects.[9]

Recommendation

For adjuvant radiotherapy of breast or chest wall:

40 Gy in 15 daily fractions of 2.67 Gy over 3 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.[3]

Further hypofractionation for breast radiotherapy is currently under investigation. In the FAST study, 915 women aged ≥50 years with node negative early breast cancer were randomly assigned after microscopic complete tumour resection to 50 Gy in 25 fractions versus 28.5 or 30 Gy in five, once-weekly fractions of 5.7 or 6.0 Gy respectively, to the whole breast. The primary endpoint was two-year change in photographic breast appearance. At three years median follow-up, 28.5 Gy in five fractions was comparable to 50 Gy in 25 fractions, and significantly milder than 30 Gy in five fractions, in terms of adverse effects in

the breast. There were two local recurrences which were both in the 50 Gy in 25 fractions arm. Mature local recurrence and late effects data are awaited.[11]

The FAST Forward trial is investigating 40 Gy in 15 fractions vesus 26 or 27 Gy in five fractions over one week. The main trial closed in 2014. Five-year local control data will be available in 2019. The FAST Forward nodal study opened in 2015 with normal tissue endpoints.[12] In 2018, this was modified to a two-arm study comparing 40 Gy in 15 fractions over three weeks against 26 Gy in five fractions over one week.

Partial breast irradiation

It is recognised that whole-breast radiation (WBI) can cause significant toxicity in patients with large breasts. Partial breast radiation may improve this outcome, though accelerated partial breast irradiation (APBI) could reduce acute and late side-effects. A meta-analysis has shown that APBI is associated with a higher local recurrence rate, albeit still low, compared to WBI (Level 1a).[13] However, this meta-analysis included studies covering a broad range of APBI techniques and selection criteria. The UK Intensity Modulated and Partial Organ Radiotherapy Following Breast Conservation Surgery for Early Breast Cancer (IMPORT LOW) Trial compared two schedules of partial breast radiation versus whole-breast 40 Gy in 15 fractions and was presented at the European Breast Cancer Conference in March 2016.[14] For each of the test groups, non-inferiority, assessed against the prespecified 2.5% threshold, was demonstrated. Local relapse (LR) rates were very low across all groups, as were moderate/marked normal tissue events, with a statistically significant improvement for breast appearance and breast hardness (median follow-up 72 months) for partial breast radiotherapy.

Two trials of intraoperative radiation therapy (IORT) have reported: the External Radiotherapy for Early Breast Cancer (ELIOT) trial reported an ipsilateral breast tumour recurrence rate of 4.4% at five years with IORT and 0.4% with WBI.[15] This gave a hazard ratio for ipsilateral relapse with IORT of 9.3 (95% confidence interval [CI] 3.3–26.3) compared to WBI. The TARGIT A trial has insufficient median follow up to draw firm conclusions (Level 2b).[3,16]

Multicatheter interstitial brachytherapy is an alternative approach to APBI. One large non-inferiority trial has shown equivalence at five years with a predefined 3% difference comparing APBI with interstitial brachytherapy and whole-breast radiotherapy to 50 Gy in 25 fractions.[17]

Breast boost

Delivery of a boost to the tumour bed following whole-breast radiotherapy reduces the risk of ipsilateral breast cancer recurrence (Level 1b).[3,18] However, there is no impact on overall survival and it doubles the risk of moderate or severe fibrosis.

The proportional benefit is similar across all age groups but the absolute benefit falls with increasing age and hence the biggest absolute benefit is in women under 50 years of age. There is also a greater absolute benefit of boost in high-grade (G3) cancer.

Incomplete resection margins, where further surgery is not possible, are an indication for breast boost regardless of age. A boost dose of 16 Gy in eight fractions or equivalent is most commonly prescribed.[18]

A multidisciplinary consensus meeting held at The Royal College of Radiologists (RCR) in March 2016 concluded that it would be reasonable for the boost dose to be hypofractionated, as given in 40 Gy in 15 fractions breast dose, rather than 2 Gy fractionation. A dose of 16 Gy in eight fractions is equivalent to a hypofractionated dose of 13.35 Gy in five fractions of 2.67 Gy or 12 Gy in four fractions of 3 Gy assuming an alpha/beta value for breast carcinoma of 3 Gy.

Appreciation of the volume of the boost and the need for accurate delivery was emphasised. It is recognised that there is no direct clinical trial evidence for this approach.

The UK dose-escalated, intensity-modulated radiotherapy (IMRT) for women treated by breast conservation surgery and appropriate systemic therapy for early breast cancer (IMPORT-HIGH) trial closed in 2015. Patients were randomised to sequential versus simultaneous integrated boost (IMRT and image-guided radiotherapy [IGRT]) including dose escalation.[19]

The breast boost volume should be defined by localising the tumour bed. Surgical clips should be routinely placed during a wide local excision to aid localisation of the tumour bed.

There is currently insufficient evidence to recommend IORT for tumour bed boost; the TARGIT B trial is currently recruiting (Clinical Trials Group, University College London, UK Clinical Research Network ID 14208) and randomising to convention external beam boost versus IORT boost in high-risk disease.[20]

Radiotherapy technique

Two-dimensional (2-D) computed tomography-based planning is no longer recommended for adjuvant radiotherapy to the breast or chest wall.

Simple, forward-planned, field-in-field IMRT reduces the late toxicity and improves cosmetic outcome following adjuvant whole-breast radiotherapy (Level 1b).[3,21]

Breast radiotherapy may increase the risk of heart disease.[22,23] For most women irradiated in the UK, the absolute risk of developing radiation-induced heart disease is less than 1% at 20 years, but risk varies according to a woman's pre-existing risk of heart disease and her heart radiation dose. Techniques to limit heart dose without reducing target dose should be considered for women with left-sided breast cancer. These include multileaf collimation (MLC) cardiac shielding and voluntary breath holding (Level 2b).[3,24]

Recommendations

For boost after whole-breast radiotherapy in women with a higher risk of local recurrence:

16 Gy in 8 daily fractions of 2 Gy (Grade A) or an equivalent hypofractionated schedule:[3]
13.35 Gy in five fractions of 2.67 Gy or 12 Gy in four fractions of 3 Gy (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.[3]

Regional nodal irradiation

Axilla and supraclavicular fossa

Axillary sentinel lymph node biopsy (SLNB) is now the British Association of Surgical Oncologists (BASO) recommended standard procedure for axillary staging in early breast cancer with clinically negative lymph nodes. For most patients with clinically positive nodes a level III axillary lymph node dissection (ALND) remains the standard procedure.

Nodal irradiation is not recommended following a negative SLNB.

Following a positive SLNB, the AMAROS trial demonstrated an axillary recurrence rate of 0.43% for ALND versus 1.19% for axillary radiotherapy after a median follow-up of 6.1 years.[25] The trial was underpowered for the planned non-inferiority test due to the low number of events. Axillary radiotherapy produced lower long-term toxicity compared to ALND (Level 2b), though the effects of RT on cardiovascular health and second malignancies in this study are not known.[3,25]

The American College of Surgeons Oncology Group (ACOS-OG) Z0011 trial demonstrated a low axillary recurrence rate of 0.9% versus 0.5% for SLNB + standard breast RT compared to SLNB followed by ALND + standard breast RT in a RCT comparing ANLD versus no axillary treatment in women with T1/T2 N0 breast cancer undergoing breast-conserving treatment.[27] Most patients were over 50 years of age and had grade 1 or 2, T1, oestrogen receptor positive, ductal cancer with no LVI (Level 2b).[3,26] However, there are significant methodological concerns about the Z0011 trial, including the statistical power of the study. There was a potential for bias in this study as the radiation oncologists were aware of the treatment allocation and it is unclear whether this influenced their decision about how much of the axilla to treat with tangential radiotherapy. Generalisability of the results is limited as some centres recruited fewer than five patients, axillary recurrence was not a prespecified endpoint, mastectomy patients were excluded and preoperative axillary ultrasound was not performed in contrast to standard UK practice.

The UK pragmatic, randomised, multicentre, non-inferiority trial (POSNOC) trial is currently recruiting patients with 1–2 positive sentinel lymph nodes and randomising them to standard adjuvant therapy *and* axillary treatment (ALND or axillary radiotherapy) versus standard adjuvant therapy alone. The primary endpoint is axillary recurrence at five years. When available, the results will provide a more definitive answer to the question of managing a positive SLNB axilla.[27]

Radiotherapy to the ipsilateral supraclavicular fossa (SCF) is recommended for N2 or N3 disease following ALND. Axillary radiotherapy following ALND produces significant toxicity and should only be recommended in women with very high risk of recurrence (high proportion of involved nodes, extensive extra-nodal disease or biologically aggressive cancer). There is no evidence that radiotherapy to the axilla following ALND improves overall survival from breast cancer.

The North American MA20 trial randomised node positive or high-risk node-negative patients to WBI versus WBI plus regional nodal irradiation (RNI) including the ipsilateral axilla, SCF and internal mammary chain, dose 50 Gy in 25 fractions.[28] It demonstrated improved disease-free survival (DFS) in the RNI group (82% versus 77%, hazard ratio [HR] 0.76, p=0.01) after a median follow-up of 9.5 years. The primary end point of improved overall survival was not met. There was a small absolute increase in the risk of acute pneumonitis and late lymphoedema in the RNI group (Level 1b).[3,28]

The EORTC 22922/10925 trial randomised patients with medial or centrally located breast cancers irrespective of nodal status or node-positive lateral tumours to WBI/chest wall irradiation versus WBI/chest wall irradiation plus RNI defined as ipsilateral medial SCF and internal mammary nodes, dose 50 Gy in 25 fractions.[29] After a median follow-up of ten years, it demonstrated an improvement in DFS in the RNI group (72.1% versus 69.1%, HR 0.89, p=0.04). The primary end point of improved overall survival was not met (Level 1b).[3,29]

Both the MA20 and EORTC 22922/10925 trials demonstrated improved distant-disease-free survival, but this did not translate to improved overall survival and the long-term effects of RNI on cardiovascular morbidity and mortality and second cancer rates in these trials is not known. However a meta-analysis of these studies published before the full results became available suggests an improvement in overall survival (Level 1a-), although this analysis was not conducted with patient level data. A Danish population based non-randomised cohort study has shown improved survival with internal mammary nodal (IMN) irradiation especially in women with larger (>50 millimetres [mm]) tumours or with more than four involved nodes (Level 2b).[3,30,31] Hence RNI to include the internal mammary chain along with ipsilateral axilla and SCF may be considered for patients fitting the MA20 and EORTC 22922/10925 criteria to reduce breast cancer recurrence, but careful patient selection is advised and the lack of data on cardiac effects of IMN irradiation and second cancers should be taken into account.[28–31]

Data for hypofractionated nodal irradiation is limited to small subsets of patients from RCTs (14% in START A, 7% in START B) but shows no increase in toxicity compared to standard fractionation nodal irradiation (Level 1b-).[3,32]

Recommendation

Where indicated, for regional nodal irradiation:

40 Gy in 15 daily fractions (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.[3]

Palliative treatment

There are no good-quality head-to-head trials evaluating the optimum schedules for palliative radiotherapy to the breast, chest wall or regional nodes. The most common doses range from 20 Gy to 40 Gy over 5–15 fractions. Weekly treatments over 5–6 weeks to a total of 30–36 Gy are also commonly used (Grade D).[3]

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