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Background

Breast cancer is the most common cancer worldwide, and most patients in the UK are diagnosed at an early stage. Radiotherapy has long been established as an important treatment modality in the adjuvant and palliative setting in breast cancer. The delivery of breast radiotherapy must be adapted based on the individual patients' risk of recurrence, and the risk–benefit ratio of treatment must be discussed with patients, enabling a shared care decision. Technological advances and results of pivotal trials have led to significant changes in practice in the UK in the past few years.

Adjuvant radiotherapy to the breast or chest wall

Radiotherapy can increase both local control and overall survival in the conservative management of invasive primary breast cancer and in selected patients after mastectomy (Level 1a).[1–4] It can also reduce ipsilateral breast tumour recurrence following breast conservation in patients with a diagnosis of ductal carcinoma *in situ* (DCIS).[5,6]

Evolution of hypofractionation from 50 Gray (Gy) in 25 fractions over 5 weeks to 26 Gy in 5 fractions over 1 week

Historically the 2 Gy per fraction regimen of 50 Gy in 25 fractions over 5 weeks was the standard of care as reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials.[7] There was a practice change following publication of the START trials, and the most widely used UK regimen was the hypofractionated regimen of 40 Gy in 15 fractions over 3 weeks as used in the UK START-B trial.[8–9] Mature data from the START-A, B and P trials and the Canadian OCOG study demonstrate the equivalence of hypofractionated regimens for efficacy with evidence of some reduced normal tissue effects compared with the previous standard of 2 Gy daily fractionation (Level 1b).[3,8–13]

Following the publication of the UK FAST-Forward trial in 2020,[14] there has been a rapid change in practice to delivering 26 Gy in 5 fractions over 1 week as the standard of care. The FAST-Forward trial was carried out in patients with early invasive breast carcinoma (pT1–3, pN0–1, M0) after breast-conserving surgery (BCS) or mastectomy.[14] Patients were randomised on a 1:1:1 ratio to 40 Gy in 15 fractions over 3 weeks (UK standard of care), 26 Gy in 5 fractions over 1 week or 27 Gy in 5 fractions over 1 week.

4,096 patients were recruited from November 2011 to June 2014 with a median follow-up of 71.5 months. The primary endpoint of 5-year ipsilateral breast tumour relapse was estimated as 2.1% (95% confidence interval [CI] 1.4–3.1), 1.7% (1.2–2.6) and 1.4% (0.9–2.2) after 40 Gy, 27 Gy and 26 Gy respectively.

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At 5 years, moderate or marked clinician-assessed normal tissue effects were observed in 98/986 (9.9%), 155/1,005 (15.4%) and 122/1,020 (11.9%) of the 40 Gy, 27 Gy and 26 Gy groups respectively, all less than observed in the START trials. The odds ratio versus 40 Gy across all clinician assessments in the 5-year period were 1.55 (CI 1.32–1.83, p<0.0001) and 1.12 (0.94–1.34, p=0.20) for 27 Gy and 26 Gy respectively. Assessments by patients and via photographs showed the risk of normal tissue effects was higher for 27 Gy, but not for 26 Gy, compared with the control group. Statistically the only significant difference between 26 Gy and 40 Gy was for moderate/marked breast induration outside the tumour bed, but this is highly unlikely to be clinically significant with small absolute numbers (2.1% for 26 Gy; 20 cases).

Following the publication of FAST-Forward[14] NICE guidance is to offer 26 Gy in 5 fractions over 1 week to the whole breast as the standard of care (Level 1b).[3,4]

Ductal carcinoma *in situ*

The FAST-Forward trial was not offered to patients with DCIS only;[14] however, this patient group can still be offered 26 Gy in 5 fractions over 1 week for whole-breast radiotherapy. This follows the similar pragmatic implementation of 40 Gy in 15 fractions over 3 weeks for DCIS following the UK START-B trial,[8–9] given breast radiotherapy for DCIS does not appear to have a survival advantage.[15] It would be challenging to carry out a trial of 26 Gy in 5 fractions over 1 week as the low anticipated local recurrence rate would require a very large number of participants and it is questionable whether there would be equipoise for randomisation in the UK. Furthermore, the BIG-TROG DCIS trial[16] demonstrated there was no difference in efficacy or side-effects with moderate hypofractionation versus 50 Gy in 25 fractions over 5 weeks. NICE guidance is to offer 26 Gy in 5 fractions over 1 week to the whole breast in patients with DCIS.[4]

Chest wall ± reconstruction

The RCR consensus (2020)[17] states that 26 Gy in 5 fractions over 1 week should be offered for chest wall radiotherapy. Within FAST-Forward, participants who had mastectomies at baseline included 91 patients (6.7%) in the 40 Gy group, 89 patients (6.5%) in the 27 Gy group and 84 patients (6.1%) in 26 Gy group, with a solitary reported recurrence in a 40 Gy-treated patient.[14] Regarding reconstruction, the RCR consensus (2020)[17] is that 26 Gy in 5 fractions over 1 week should be considered for chest wall radiotherapy with reconstruction. Of note, the trial had immediate reconstruction rates of <1% across all groups; however, there is no biological reason why patients with immediate reconstruction should have a higher risk of normal tissue toxicity or capsular contracture with 26 Gy in 5 fractions (versus 40 Gy in 15 fractions). The consensus statement for chest wall irradiation with reconstruction is to consider the 5-fraction schedule and, if used, centres may wish to audit their practice. This is also reflected in the NICE guidance for early and locally advanced breast cancer: diagnosis and management (updated June 2023).[4]

Co-morbidity and frailty

For patients with co-morbidity and/or frailty, making daily radiotherapy difficult, the RCR consensus (2020)[17] is to consider 28.5 Gy in 5 fractions over 5 weeks as well as 26 Gy in 5 fractions over 1 week following on from the FAST results.[18] 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 5, once-weekly fractions of 5.7 Gy or 6.0 Gy respectively to the whole breast. The primary endpoint was a 2-year change in photographic breast appearance. The 10-year FAST trial results found no statistically significant difference in normal tissue event rates in the 28.5 Gy group versus the 50 Gy group,[18] although normal tissue event rates were higher in the 30 Gy group.

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Recommendation

For adjuvant radiotherapy of non-nodal breast or chest wall without immediate reconstruction:

- 26 Gy in 5 fractions over 1 week (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]

Partial breast irradiation (PBI)

PBI may be an option for patients with a low risk of local relapse. Risk of local relapse is highest in the region of the tumour bed,[19] therefore radiotherapy can be delivered to this region only, sparing the whole breast and potentially reducing side-effects.[20] A meta-analysis showed that PBI is associated with a higher local recurrence rate, albeit still low, compared with WBI (Level 1a).[3,21] However, this meta-analysis included studies covering a broad range of PBI techniques and selection criteria. Some of the trials have included older surgical and radiation techniques. Techniques used to deliver PBI include external beam radiotherapy (EBRT), brachytherapy and intraoperative radiotherapy (IORT).

PBI can be considered for patients ≥50 years, with low-risk tumour features as follows: Grades 1–2, ≤3 cm, oestrogen receptor positive (ER+), progesterone receptor positive (PR+) or human epidermal growth factor receptor negative (HER2-ve) node-negative tumours, as per the RCR consensus (2016).[22] The consensus is to deliver PBI using EBRT, as per the IMPORT LOW trial,[23] or multicatheter brachytherapy using fractionation, as per the GEC-ESTRO trial.[24] NICE guidance recommends using EBRT when delivering PBI.[4]

There are a number of international PBI trials using EBRT that have reported, but this discussion is focused on the UK-led IMPORT LOW trial, as this is the PBI technique most commonly used in the UK.[23] Within IMPORT LOW, 2,018 women were randomised to receive 40 Gy to the whole breast (control), 36 Gy to the whole breast and 40 Gy to the partial breast (reduced-dose group), or 40 Gy to the partial breast only (partial breast group) in 15 daily treatment fractions using simple field-in-field technique. Local relapse rates were 1.1% (95% CI 0.5–2.3), 0.2% (0.02–1.2) and 0.5% (0.2–1.4) in the WBI, reduced-dose and PBI groups respectively at 72 months (median follow-up). The dose/fractionation in all groups were identical meaning the irradiated volume was the only variable within the trial and significantly less toxicity was found in the two test groups versus the control group.

PBI can be delivered in 1 week using the techniques in IMPORT LOW.[23] Both the FAST-Forward [14] and IMPORT LOW [23] trials were designed in parallel with the same dose/fractionation used in the control groups and with a pre-plan to consider the data together for 5 fractions of PBI. FAST-Forward showed non-inferiority with 40 Gy in 15 fractions for efficacy and similar toxicity. In addition, IMPORT LOW showed non-inferiority with 40 Gy in 15 fractions for efficacy *and* reduced toxicity. These results have enabled the FAST-Forward fractionation to be seamlessly adopted for PBI, and NICE guidance is to offer 26 Gy in 5 fractions over 1 week for partial breast radiotherapy.[4]

Regarding multicatheter interstitial brachytherapy, GEC-ESTRO randomly assigned women to PBI with interstitial brachytherapy, either high dose rate or pulsed dose rate versus WBI 50 Gy with a 10 Gy tumour bed boost.[24] At 10 years (median follow-up), the local recurrence rates were 1.58% (95% CI 0.37–2.8) in the WBI group and 3.51% (1.99–5.03) in the PBI group.[25]

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Difference in 10-year rates between the groups was 1.93% (95% CI −0.018–3.87; p=0.074). There was a significantly lower incidence of treatment-related Grade 3 late side-effects in patients in the PBI group compared with those in the WBI group. Fibrosis was the commonest Grade 3 adverse event in both treatment groups although overall numbers were very low.

With respect to IORT, the ELIOT[26] and TARGIT trials[27–28] used this technique with ELIOT delivering electrons (IOeRT) and TARGIT using photons. ELIOT randomised women to 50 Gy in 25 fractions over 5 weeks plus boost versus IOeRT 21 Gy to tumour bed.[26] The 5-year local relapse was 4.5% (95% CI 2.7–6.1) and 0.4% (95% CI 0.0–1.0) for the IOeRT and WBI groups respectively (hazard ratio [HR] 9.3; 95% CI 3.3–26.3). Local relapse rates in the IOeRT group were significantly greater than in patients receiving WBI but no difference in overall survival was seen. Of note, several patients in the trial had high-risk features and ELIOT (and other trials) began recruitment prior to the establishment of GEC-ESTRO/ASTRO guidelines.[29–30] Toxicity was not systematically recorded but a difference in skin toxicity favouring IOeRT was reported, although IOeRT patients were found to have increased fat necrosis.[26]

Participants within the TARGIT trial were randomised to IORT using 50 kV photons or WBI. The two strata within the trial consisted of pre-pathology where IORT was delivered at time of BCS, and post-pathology where IORT was delivered after BCS where the wound was reopened.[27–28] Patients receiving IORT in the pre-pathology strata required additional WBI (20% of patients) due to unfavourable histology results after final surgery.[27] There was no systematic collection of toxicity data. TARGIT-IORT is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour. NICE guidance recommends that if TARGIT-IORT is delivered it should only be done on machines that are already available and in conjunction with NHS England specified clinical governance, data collection and submission arrangements. Patients should be offered the NICE patient information and decision aid if being offered TARGIT-IORT.[31]

Recommendation

For partial breast radiotherapy using external beam radiotherapy:

- 26 Gy in 5 fractions over 1 week (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]

Safe omission of radiotherapy following BCS

Given the substantial reduction in local recurrences over the previous 3 decades in mostly high-income countries,[32] the risks of breast radiotherapy may outweigh the benefits for some patients at very low risk of local recurrence. These risks include normal tissue toxicities,[9] cardiac morbidity[33] and second malignancies.[34] In omission of radiotherapy RCTs conducted so far, an increase in local recurrence without radiotherapy has been demonstrated but without any increase in breast cancer death.[35–37] In addition, it has not been possible to identify which patients are at very low risk of recurrence, but an unplanned subgroup analysis from PRIME II suggested that such a group may be identified.[37] The 10-year update of PRIME II has now been reported.[38] At a median follow-up of 9.1 years, the cumulative incidence of local breast cancer recurrence was 9.5% (95% CI 6.8–12.3) in the no-radiotherapy group and 0.9% (0.1–1.7) in the radiotherapy group (HR 10.4; 95% CI 4.1–26.1; p<0.001). There was no statistical difference in overall or breast cancer-specific survival between groups.

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The biomarker-directed PRIMETIME study (using IHC4+C incorporating Ki-67) investigating whether radiotherapy can be safely avoided in women with very low-risk breast cancer has now completed recruitment and we await the results.[39] The British Association of Surgical Oncology (BASO) II trial found avoidance of both radiotherapy and endocrine therapy to be detrimental; therefore; compliance with endocrine therapy should be encouraged, especially if radiotherapy is omitted.[36]

The RCR consensus (2016) is that avoidance of radiotherapy should be considered in patients ≥70 years out of a research study and ≥60 years in study with T1N0 oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor negative (HER2-ve) or Grades 1–2 tumours **and** who are willing to take adjuvant endocrine therapy for a minimum of 5 years **and** have regular mammograms for 10 years.[22] NICE guidance is similarly to consider omitting radiotherapy in women who have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours T1N0, ER-positive, HER2-negative and Grades 1–2) willing to take adjuvant endocrine therapy for a minimum of 5 years.[4] The predicted absolute risks and benefits of radiotherapy should be discussed with individual patients in order to reach a shared decision.

Breast boost

Delivery of a boost to the tumour bed following whole-breast radiotherapy reduces the risk of ipsilateral breast cancer recurrence (Level 1b).[3,40] However, there is no impact on overall survival, and it approximately 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.

Positive resection margins, where further surgery is not possible, are an indication for breast boost regardless of age.

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.[22]

Breast boost may be delivered as a sequential normofractionated or hypofractionated boost, or a 15-fraction simultaneous integrated boost (SIB); for example, 48 Gy to the boost volume and 40 Gy to the rest of the breast all over 3 weeks (as per IMPORT HIGH discussed below).[41]

Regarding dose and fractionation for the sequential boost, 13.35 Gy in 5 fractions of 2.67 Gy or 12 Gy in 4 fractions of 3 Gy assuming an α/β value for breast carcinoma of 3 Gy is similar to a dose of 16 Gy in 8 fractions.[22]

The UK IMPORT HIGH trial of simultaneous integrated boost (SIB) was carried out in women with early high-risk invasive breast carcinoma (pT1–3pN0–pN3aM0) after BCS.[41] Patients were randomised on a 1:1:1 basis between 40 Gy/15 fractions to whole breast (WB) + 16 Gy/8 fractions sequential photon boost to tumour bed (40+16 Gy; control), 36 Gy/15 fractions to WB, 40 Gy to partial breast + 48 Gy (48 Gy) or 53 Gy (53 Gy) in 15 fractions SIB to tumour bed. The primary endpoint was ipsilateral breast tumour relapse (IBTR) and 2,617 women consented to the trial. Smaller, more targeted boost volumes were used for all treatment groups with a median boost clinical target volume (CTV) of 13 cc. After a median follow-up of 74.0 months, the 5-year IBTR incidence was 1.9% (95% CI 1.2–3.1) for 40+16 Gy, 2.0% (1.2–3.2) for 48 Gy, 3.2% (2.2–4.7) for 53 Gy with 76 IBTR events (40+16 Gy: n=20, 48 Gy: n=21, 53 Gy: n=35). The estimated absolute differences versus 40+16 Gy were 0.1% (−0.8–1.7) for 48 Gy, 1.4% (0.03–3.8) for 53 Gy and the upper confidence limit for 48 Gy versus 40+16 Gy indicated non-inferiority for 48 Gy.

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For clinician-reported assessments, 5-year prevalence of moderate/marked breast induration was 6% (36/600) for 40+16 Gy, 5.2% (34/653) for 48 Gy and 8.9% (56/627) for 53 Gy. Comparisons were similar between groups for 5-year cross-sectional, time to event and longitudinal analyses, with similar levels of moderate/marked adverse events for 48 Gy versus 40+16 Gy and increased risk of adverse events for 53 Gy versus 48 Gy. Patient-reported moderate/marked breast hardness/firmness at 5 years was significantly lower for 48 Gy versus 40+16 Gy (RR 0.54, 95% CI 0.38–0.78, p=0.001) and higher after 53 Gy versus 48 Gy (RR 1.61, 95% CI 1.1.0–2.35, p=0.008).

The trial found that the local relapse event incidence is low in this higher-risk breast cancer group treated with small boost volumes and image-guided radiotherapy, whether the boost is delivered sequentially or simultaneously. Rates of 5-year moderate/marked adverse events were low.[41] SIB is a safe treatment with reduced patient visits, and further escalation of boost dose does not appear advantageous.

Radiotherapy technique

Two-dimensional (2-D) computed tomography-based planning is no longer recommended for adjuvant radiotherapy to the breast or chest wall. The ESTRO guidelines for volume-based breast radiotherapy planning are recommended for contouring breast, chest wall, nodal groups and organs at risk.[42]

Simple, forward-planned, field-in-field intensity-modulated radiation therapy (IMRT) reduces late toxicity and improves cosmetic outcome compared with a non-IMRT technique, following adjuvant whole-breast radiotherapy (Level 1b).[3,43]

Breast radiotherapy may slightly increase the lifetime risk of heart disease for some people.[33,44–45] For most women irradiated in the UK, the absolute risk of developing radiation-induced heart disease is less than 1% risk to age 80 years, but the risk varies according to pre-existing risk of heart disease and mean heart radiation dose. Techniques to limit heart dose without reducing target dose coverage should be considered for patients with left-sided breast cancer and those requiring internal mammary nodal irradiation. These include multileaf collimation (MLC) cardiac shielding and voluntary deep inspiration breath hold (DIBH) techniques (Level 2b).[3,45] Wide tangents technique or intensity-modulated arc techniques (IMAT), both using DIBH, are recommended.

Recommendations

For patients requiring a boost:

- 15 fractions SIB, 48 Gy to boost volume and 40 Gy to rest of breast (Grade A)
- 26 Gy in 5 fractions whole-breast radiotherapy plus either a sequential normo-fractionated boost or a hypofractionated boost (delivered in no more than 5 fractions); for example, 13.35 Gy in 5 fractions of 2.67 Gy or 12 Gy in 4 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]

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Regional nodal irradiation

Axilla and supraclavicular fossa

Axillary sentinel lymph node biopsy (SLNB) is the recommended standard procedure for axillary staging in early breast cancer with clinically negative lymph nodes.[46] Most patients with clinically positive nodes will require axillary treatment.

Nodal irradiation is not recommended following a negative SLNB.[4]

Following a positive SLNB, the AMAROS trial demonstrated an axillary recurrence rate of 0.93% for ALND versus 1.82% for axillary radiotherapy after a median follow-up of 10 years.[47] 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 with ALND (Level 2b).[3]

The American College of Surgeons Oncology Group (ACOS-OG) Z0011 trial demonstrated low axillary recurrence rates with no significant differences for SLNB plus standard breast radiotherapy compared with SLNB followed by ALND plus standard breast radiotherapy in an RCT comparing ALND versus no axillary treatment in women with T1/T2 clinically N0 but with 1–2 positive sentinel lymph nodes involved undergoing breast-conserving treatment at 10 years.[48] Most patients were over 50 years of age and had Grade 1 or 2, T1, oestrogen receptor positive, ductal cancer with no lymphovascular invasion (LVI) (Level 2b).[3,48] However, there are significant methodological concerns about the Z0011 trial.[49]

The UK randomised, multicentre, non-inferiority POSNOC trial has completed recruitment in patients with 1–2 positive sentinel lymph nodes, randomised to standard adjuvant therapy and axillary treatment (ALND or axillary radiotherapy) versus standard adjuvant therapy alone.[50] The primary endpoint is axillary recurrence at 5 years. When available, it is anticipated that the results may provide a definitive answer to the question of managing a positive SLNB axilla.

Radiotherapy to the ipsilateral supraclavicular fossa (SCF), now referred to as nodal levels 3 and 4, is recommended for N2 or N3 disease following ALND. Axillary radiotherapy following ALND produces significant toxicity if it specifically targets the operated nodal levels and should only be considered in patients with very high risk of recurrence (high proportion of involved nodes, extensive extranodal disease or biologically aggressive cancer) and high suspicion of residual cancer within the surgically operated nodal region. There is no evidence that radiotherapy to the operated axilla following ALND improves overall survival from breast cancer, but it increases the risk of lymphoedema.

The UK FAST-Forward nodal substudy is testing whether a 1-week schedule of adjuvant radiotherapy to Levels 1–3 axilla ± Level 4 (SCF) is non-inferior to a standard 3-week schedule in terms of patient-reported arm swelling and function in patients with early breast cancer.[51] The 1-week schedules were as per the main FAST-Forward trial, but the 27 Gy treatment schedule was closed early due to an increase in normal tissue effects from the main trial, which were statistically but not necessarily clinically significant. The definitive assessment of normal tissue non-inferiority will be at 5 years; however, preliminary descriptive 3-year data have shown that moderate/marked changes are low overall as assessed by patients and clinicians.[52] It should also be noted that this study did not include internal mammary chain (IMC) irradiation as this had not been widely adopted in the UK at the time of recruitment.

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 IMC, dose 50 Gy in 25 fractions.[53] It demonstrated improved disease-free survival (DFS) in the RNI group (82% versus 77%, HR 0.76, p=0.01) after a median follow-up of 9.5 years.

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The primary endpoint 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).[3,53]

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.[54] After a median follow-up of 10 years, it demonstrated an improvement in DFS in the RNI group (72.1% versus 69.1%, HR 0.89, p=0.04). The primary endpoint of improved overall survival was not met (Level 1b).[3,54]

Both the MA20[53] and EORTC 22922/10925[54] trials demonstrated improved distant DFS, 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 are not known. 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 4 involved nodes (Level 2b).[3,55]

The EBCTCG carried out a regional nodal individual patient data meta-analysis consisting of 14,324 women participating in 16 trials.[56] Trials initiated between 1961 and 1978 were categorised as 'older' trials where participants were treated with historical radiation techniques using direct anterior radiation beams. Of note, radiation within this group did not usually involve radiotherapy to the chest wall in node-positive disease and was only given to the regional nodes in the interventional groups. In contrast, trials started between 1989 and 2008 were categorised as 'newer' trials and patients treated with more advanced radiotherapy techniques. It was found that in the 2,157 patients who participated in the 8 'older' trials, radiotherapy did not reduce breast cancer mortality (RR 1.04, 95% CI 0.91–1·20; p=0.55) but significantly increased non-breast cancer mortality. However, in the 12,167 patients who participated in the 8 'newer' trials, regional node radiotherapy significantly reduced recurrence (RR 0.88, 95% CI 0.81–0.95; p=0.0008). The main effect was on distant recurrence as few regional node recurrences were reported. In addition, radiotherapy significantly reduced breast cancer mortality (RR 0.87, 95% CI 0.80–0.94; p=0.0010) but there was no significant increase in non-breast cancer mortality. It is likely that the differences in findings between the 'older' and 'newer' trials are related to advancements in radiotherapy techniques over the decades, in addition to the inclusion of breast and chest wall radiotherapy, as well as regional nodal radiotherapy in the newer trials. Although rate ratio (proportional benefit) of regional radiotherapy is similar across all subgroups, the absolute benefit varies according to the individual patient's risk of recurrence. For example, for those patients with node-negative disease, 1–3 lymph nodes positive or 4 or more lymph nodes positive, the reduction in 15-year breast cancer mortality was 1–2%, 2–3% and 4–5% respectively.

Regarding data for hypofractionated nodal irradiation, the DBCG Skagen-1 trial is a phase 3 randomised trial of 40 Gy in 15 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks in 2,946 node-positive patients.[57] Tumour bed boosts were delivered as SIB using similar techniques to IMPORT HIGH. RNI included the IMC. The primary endpoint was the risk of ipsilateral arm lymphoedema ≥10% at 3 years after radiotherapy compared with the contralateral arm. The results presented in abstract form demonstrated low event rates and no differences between the patients receiving 40 Gy and 50 Gy. There was also no difference in locoregional recurrence, distant recurrence or overall mortality.[57] The Skagen-1 trial was the first RCT to report 40 Gy/15 fractions versus 50 Gy/25 fractions for RNI including IMC irradiation, and no increase in toxicity with 40 Gy in 15 fractions was observed.

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In addition, the HypoG-01 trial reported results in abstract form.[58] The HypoG-01 trial is a phase 3 randomised trial of 40 Gy in 15 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks in 1,265 patients. All patients received nodal and chest wall or breast radiotherapy. The primary endpoint was time to occurrence of arm lymphoedema after radiotherapy defined as ≥10% increase in arm circumference compared with the contralateral arm. At 3 years, ipsilateral arm lymphoedema rates were similar in both groups and it was found that 40 Gy/15 fractions is non-inferior to 50 Gy/25 fractions in terms of lymphoedema risk. Both HypoG-01 and DBCG Skagen-1 provide evidence supporting the use of 40 Gy in 15 fractions over 3 weeks with regard to lymphoedema risk.

Recommendation

For regional nodal irradiation:

- 40 Gy in 15 fractions over 3 weeks (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 is limited trial evidence 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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Acknowledgements

With thanks to lead authors Dr Indrani Bhattacharya (Cambridge University Hospitals NHS Foundation Trust), Prof Charlotte Coles (University of Cambridge) and Prof Murray Brunt (School of Medicine, Keele University) for reviewing and updating this chapter of the guidance.