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Clinical Oncology
The Royal College of Radiologists

# Postoperative radiotherapy for breast cancer: UK consensus statements

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Faculty of Clinical Oncology

# Contents

# UK consensus statements

## Cardiac sparing

**Cardiac-sparing radiotherapy should be considered the standard of care for patients with left-sided breast cancer.**

- The heart should routinely be excluded from the radiotherapy field.
- All UK radiotherapy departments should have a breath-hold technique available.
- A target mean heart dose would help departments to implement breath-hold.
- In left-breast-affected patients undergoing radiotherapy not including the internal mammary chain (IMC), >90% of patients should be treated to a mean heart dose of <2 Gray (Gy).

## Breast boost radiotherapy after breast-conserving surgery

**Tumour bed boost**

- A tumour bed boost should be considered for all patients with invasive breast cancer who are less than 50 years old.
- Consider the benefit of a tumour bed boost for those over 50 years with higher risk pathological features (especially Grade 3 and/or extensive intraductal component).
- A hypofractionated boost using a similar fraction size as the whole breast is acceptable; it should be equivalent to 16 Gray (Gy) in eight fractions.

**Breast-conserving surgery and tumour bed clips**

- Tumour bed clips should be considered the standard of care to improve planning (and delivery) of the boost.

## Safe omission of radiotherapy after breast-conserving surgery

**Avoidance of radiotherapy should be considered:**

- In women deemed to be at very low risk of local recurrence, for example 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-), Grade 1–2 tumours AND who are willing to take adjuvant endocrine therapy for a minimum of five years AND have regular mammograms for ten years. These criteria are best fulfilled within the UK PRIMETIME bio-marker directed study and participation is recommended.

## Internal mammary chain radiotherapy

- Internal mammary chain (IMC) radiotherapy should be considered in patients at high risk of recurrence (that is, T4 and/or N2–3 disease).
- IMC radiotherapy should be considered in patients at intermediate risk of recurrence (that is, 1–3 axillary macrometastases and central/medial disease, who have been recommended locoregional irradiation).
- IMC radiotherapy should be given using techniques which minimise doses to organs-at-risk. Every centre should have a breath-hold technique available for patients undergoing IMC radiotherapy.
- The following dose constraints are recommended for IMC radiotherapy: heart $V_{17\ Gray\ (Gy)}$ <10%, ipsilateral lung $V_{17Gy}$ <35%, mean contralateral breast dose <3.5 Gy; in patients at intermediate risk of recurrence, a mean heart dose <6 Gy is considered a reasonable objective.

## Hypofractionation

- There is no indication to use more than 15 fractions for the breast, chest wall or nodal areas for standard adjuvant treatment.

## Axillary management of sentinel lymph node-positive disease*

**Further local treatment for the malignant sentinel lymph node (SLN) in individuals with early invasive breast cancer:**

- **Sentinel nodes with isolated tumour cells and/or micrometastases** – no further axillary treatment is required in addition to breast-conserving surgery or mastectomy.
- **1–2 sentinel nodes with macrometastases** – further axillary treatment is no longer mandatory in breast conservation with whole-breast radiotherapy in patients who are postmenopausal and have T1, Grade 1 or 2, oestrogen receptor positive (ER+) and human epidermal growth factor receptor negative (HER2-) tumours. *These patients could also be entered into the POSNOC or equivalent clinical trial.*
- **Three or more sentinel nodes with macrometastases** – patients should usually be recommended to have further axillary treatment.
- **Further axillary treatment** should usually be recommended for patients undergoing mastectomy or with tumours with one or more of the following features: T3, Grade 3, ER- or HER2+.*These patients could also be entered into the POSNOC or equivalent clinical trial.*
- No consensus was reached on the management of the axilla for patients with one or more of the following features: premenopausal status, T2 tumours, lymphovascular invasion or extranodal spread.

## Partial breast radiotherapy after breast-conserving surgery

- Can be considered for patients ≥50 years, Grade 1–2, ≤3 centimetres (cm), oestrogen receptor positive (ER+), human epidermal growth factor receptor negative (HER2-), N0 with minimum 1 millimetre (mm) radial excision margins for invasive disease, using either (i) external beam radiotherapy with 40 Gray (Gy) in 15 fractions over three weeks or (ii) multicatheter brachytherapy using fractionation schedules as per the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) trial.
- Classical lobular cancer and/or lymphovascular space invasion should be excluded.

** These statements were agreed by the Trustees of the Association of Breast Surgery (ABS) following the ABS Multidisciplinary Consensus Meeting on the further management of the malignant axillary node, held in London on 26 January 2015.*

# Introduction

Radiotherapy is an important part of the multimodality treatment for breast cancer and plays a vital role in maximising local disease control, enabling safe breast conservation and contributing to increased survival. Overall cure rates for breast cancer are increasing and it is essential to minimise late side-effects of radiotherapy by consistently using the best techniques and equipment available.

As an oncology community comprising all the professional groups, commissioners and – above all – patients, we have an opportunity to clearly state the expected standard for breast radiotherapy across the UK. This should help ensure equity of treatment for all, regardless of postcode.

The United Kingdom (UK) has made a major contribution to clinical research in breast radiotherapy due the commitment of multdisciplinary teams (MDTs): clinical oncologists, radiographers, dosimetrists, physicists and patient advocates. This has created a culture of improving radiotherapy quality through clinical trials. However, the highest standards of evidence-based breast cancer radiotherapy have not been introduced consistently in a timely and universal fashion due to limited resources and training.

## Why standards of care are needed – the patient/public perspective

Individuals faced with a diagnosis of breast cancer deserve the best, most effective, up-to-date and evidence-based treatment wherever they are treated. New innovative radiotherapy treatments, better equipment and many years of practice-changing research have brought improved effective outcomes for patients with reduced side-effects. Individuals have the right to know that their local cancer centre provides treatments based on the best-available evidence and takes part in research by offering clinical studies to patients where appropriate. Gaining agreement between clinical oncologists and the other specialist members of the breast MDT on specific areas of breast cancer care, in which radiotherapy might play a significant role, is to be welcomed. Barriers to equitable access and reluctance to change are not acceptable.

## Who this document is for

All those working clinically, commissioners and others in the NHS who are responsible for the provision of care for women with early breast cancer.

## How this document was produced

A core group consisting of patient representatives from 'Independent Cancer Patient Voice', a lay member from The Royal College of Radiologists (RCR), multidisciplinary breast cancer specialist health professionals representing therapeutic radiographers (The Society and College of Radiographers), clinical oncologists (the RCR and UK Breast Cancer Meeting), radiotherapy physicists (Institute of Physics and Engineering in Medicine) and breast surgeons (Association of Breast Surgery) and an NHS England commissioner, developed a series of short statements around optimal breast radiotherapy practice and a questionnaire about current practice in breast radiotherapy. The RCR's Clinical Oncology Heads of Service, representing all UK radiotherapy centres, were contacted and asked to identify a clinical oncologist, therapeutic radiographer and radiotherapy physicist with a specialist interest in breast cancer to review the first draft of the practice statements and complete the questionnaire.

Contacts were established with 53 out of 62 centres, of which 38 provided comments on the practice statements and 39 completed the questionnaire. Feedback was incorporated into presentations given by members of the core group at a consensus meeting held at the RCR in March 2016. Forty eight centres were represented at this meeting by at least one of the three disciplines that had been identified to review the first draft of the statements and complete the questionnaire. Electronic voting pads were used to vote on the statements, with one pad/one vote per centre. Before the meeting it was agreed that a vote of 70% or more would constitute consensus.

| Unanimous support | 100% |
|---|---|
| Very strongly supported | 90–99% |
| Strongly supported | 70–89% |
| Majority support | 60–69% |
| Equipoise | 50–59% |
| Rejected | <50% |

Evidence was presented to support practice statements and discussion was facilitated by core group chairs. Representatives were then asked to vote on behalf of their centre.

Members of the core group took notes of the discussion.

# 1. Cardiac sparing

**Discussion statement**

**Cardiac-sparing radiotherapy should be considered the standard of care for patients with left-sided breast cancer.**

## Background

- Long-term data show a linear relationship between mean radiation dose to the heart and late cardiac effects, including myocardial infarction, with no threshold dose below which a patient is at no risk from radiation. Radiation to the heart is a cardiac risk-factor equivalent to heart disease or smoking. Patients with pre-existing cardiac risk factors are at a greater risk of radiotherapy-induced cardiac morbidity.
- Multileaf collimator (MLC) cardiac shielding can be considered in patients with upper-half left breast tumours, in whom the tumour bed will not be shielded.
- Formal heart-sparing techniques, including breath-hold and prone treatment, reduce mean heart doses by around 50–60%.
- Breath-hold techniques are recommended for those with lower-half left breast tumours. Voluntary deep inspiration breath hold has been shown to be effective at reducing cardiac dose, is acceptable to patients and requires few additional resources and only slightly longer treatment times.
- Where the left internal mammary chain (IMC) is being treated, a formal cardiac-sparing technique (either breath-hold or rotational therapy) should be considered the standard of care.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| The heart should routinely be excluded from the radiotherapy field. | Unanimous support |
| All UK radiotherapy departments should have a breath-hold technique available. | Unanimous support |
| A target mean heart dose would help departments to implement breath-hold. | Strongly supported |
| In left-breast-affected patients undergoing radiotherapy not including the IMC, >90% of patients should be treated to a mean heart dose of <2 Gray (Gy). | Very strongly supported |

## Key points from consensus meeting:

- Where heart doses are reduced using adjustment of field angle or MLC, the tumour bed should be delineated to ensure that tumour bed coverage is not compromised.

## Key references:

1. Darby SC, Ewertz M, McGale P *et al.* Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; **368**(11): 987–998.

2. Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)* 2015; **27**(11): 621–629.

# 2. Breast boost radiotherapy after breast-conserving surgery

**Discussion statements**

**A tumour bed boost should be considered for women less than 50 years old.**

**For those over 50 years old with higher risk pathological features (especially Grade 3 and/or extensive intraductal component [EIC]), consider the benefit of boost in context of both local recurrence and normal tissue toxicity risks.**

**Tumour bed clips should be considered the standard of care to improve planning (and delivery) of the boost.**

**Photon boost using intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) is recommended, including simultaneous integrated photon boost (SIB).**

**Electron and mini-tangents are acceptable alternatives when IMRT boost is not clinically appropriate.**

## Background and discussion

- The European Organisation for Research and Treatment of Cancer (EORTC) boost trial randomised 5,318 women with stage I/II breast cancer to boost (2,657) or no boost (2,661) following breast-conserving surgery and whole-breast radiotherapy. Whole-breast radiotherapy was 50 Gray (Gy) in 25 fractions over five weeks and the boost was 16 Gy in eight fractions delivered with electrons, photons or iridium$^{192}$ ($Ir^{192}$) implant. Adequate excision was deemed as no invasive tumour at inked margin.
- Rates of local breast recurrence as first failure of 9% (boost) versus 13% (no boost) (hazard ratio [HR] 0.65) have been reported with a median follow-up of 17.2 years. The salvage mastectomy rate was 79% in women who did not receive a tumour bed boost and 75% in those that did. Boost did not impact on overall survival. The absolute benefit was greatest in younger women with a reduction in local recurrence from 36% to 24.4% in those under 40 years. Severe fibrosis occurred in 5.2% of women who received a boost and 1.8% of those who did not.
- An EORTC subgroup analysis with central pathological review shows only high grade as an additional independent risk factor for recurrence other than young age.
- In a more recent update of this subgroup analysis, with 17.2 years of median follow-up, extensive intraductal component correlates with late recurrences. In patients ≤50 years with high-grade tumour and ductal carcinoma *in situ* (DCIS), a boost reduced 20-year local relapse from 38% to 9% (HR=0.21, p=0.002). Close surgical margins were not associated with increased relapse (the Association of Breast Surgery considers 1 millimetre [mm] to be an acceptable surgical margin for both invasive disease and DCIS).
- Both the pre-consensus meeting questionnaire (see *How this document was produced*) and the results of the national RCR breast audits (2011 and 2014) revealed that young age, high grade, margin status and the presence of lymphovascular invasion were the most common reasons given for clinicians recommending an additional tumour bed boost. Other indications given for tumour bed boost were node positivity and oestrogen receptor negative (ER-) status. Electrons

remain the most common technique used for a tumour bed boost but the RCR national breast audits show a shift towards increased use of photon boosts between 2011 and 2014. Overall, approximately 30% of UK patients receive a tumour bed boost after breast-conserving surgery with considerable variation in the dose/fractionation schedule used.

- Potential advantages of a simultaneous integrated photon boost (SIB) include greater conformity of dose to the tumour bed, reduced geographical miss compared with electron boost (due to the mandatory use of image guidance) and fewer visits to hospital for patients. Phase II data have been published on feasibility and acute toxicity for the combination of SIB and hypofractionation. The four large randomised controlled trials (RCTs) of hypofractionation (Ontario, Standardisation of Breast Radiotherapy [START] A and B trials and the Royal Marsden Hospital/Gloucestershire oncology Centre [RMH/GOC] trial) did not specifically evaluate the contribution of a boost.
- The German ARO-2010-01 phase II study demonstrated the feasibility of simultaneously delivering 40 Gy to the whole breast volume and 48 Gy to the boost volume in 16 fractions using three-dimensional (3D) conformal radiotherapy or intensity-modulated radiotherapy (IMRT) with 92% adherence to dose. Franco *et al* (2014) used tomotherapy to deliver 45 Gy in 20 fractions to the whole breast and 50 Gy in 20 fractions to the tumour bed reporting 94% maximum grade 0–1 skin toxicity. The phase III Radiation Therapy Oncology Group (RTOG) 1005 study randomises between sequential boost and simultaneous boost, delivering 40 Gy to the whole breast and 48 Gy to the tumour bed in 15 fractions using 3D conformal radiotherapy or IMRT. The study accrued 2,354 patients and is currently in follow-up. Many UK radiotherapy centres have developed experience in the planning, delivery and verification of SIB through participation in the IMPORT HIGH study. The aim of IMPORT HIGH is to test dose-escalated IMRT after conservation surgery for early breast cancer in women with higher than average local recurrence risk. This is a three-arm trial design as follows. The control group delivers 23 fractions: 40 Gy in 15 fractions to whole breast plus 16 Gy in eight fraction sequential photon boost to the tumour bed; test groups deliver 15 fractions, with differing doses delivered in a total of 15 fractions to different parts of the breast, 36 Gy in 15 fractions to whole breast; 40 Gy to partial breast plus 48 Gy (test group 1) or 53 Gy (test group 2) as a concomitant photon boost in 15 fractions to the tumour bed. This study has recruited 2,621 patients and is currently in follow-up. The three-year toxicity results will be reported in 2017–2018. These phase III studies will provide local recurrence outcomes as well as longer term toxicity for the combination of SIB and hypofractionation.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| A tumour bed boost should be considered for all patients less than 50 years old. | Very strongly supported |
| A tumour bed boost should be considered for all patients less than 50 years; for those over 50 years with higher risk pathological features (especially Grade 3 and/or extensive intraductal component), consider the benefit of boost in context of both local recurrence and normal tissue toxicity risks. | Very strongly supported |
| Tumour bed clips should be considered the standard of care to improve planning (and delivery) of the boost. | Unanimous support |
| A conformal photon boost, with appropriate technique-specific margins and image-guided radiotherapy (IGRT), should be the standard of care. Electrons and mini-tangents are acceptable alternatives if photon boost is not clinically appropriate. | Majority support |
| A simultaneous integrated boost using IMRT and IGRT should be an option for patients. | Equipoise |
| The boost fraction size should match the whole-breast fractionation and be radio-biologically equivalent to the 2 Gy per fraction boost. | Strong support |

| | | |
|---|---|---|
| If hypofractionating a boost to a small volume then it should be equivalent to | 10 Gy in five fractions<br><br>18% | 16 Gy in eight fractions<br><br>82% |

## Key points from consensus meeting

- If there is tumour at the inked margin then re-excision should be considered.
- The tumour bed boost dose should be the hypofractionated equivalent of 16 Gy in 2 Gy per fraction. (It is entirely reasonable to hypofractionate the boost schedule, for example, a five-fraction regimen of 2.67 Gy is equivalent to 14 Gy in 2.0 Gy equivalents assuming an alpha/beta value of 3.0 Gy).
- There was unanimous agreement that tumour bed clips should be the standard of care to improve the planning and delivery of the boost. It was recognised that oncoplastic techniques may introduce inaccuracy in clip placement – for example reduction mammoplasties using wider margins may make localisation more difficult, highlighting the importance of close dialogue with the operating surgeon.
- Discussion reflected the relation between increasing boost volume and possible poorer cosmesis.

## Key references:


1. Bartelink H, Maingon P, Poortmans P *et al.* Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; **16**(1): 47–56.

2. Jones HA, Antonini N, Hart AA *et al*. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol* 2009; **27**(30): 4939–4947.

3. Vrieling C, Van Werkhoven E, Poortmans P *et al*. *The impact of pathological factors on long-term local control in the EORTC boost no-boost trial*. European Cancer Congress 2015 (abstract).

4. Association of Breast Surgery at BASO 2009. Surgical guidelines for the management of breast cancer. *Eur J Surg Oncol* 2009; **35**(Suppl 1): 1–22.

5. 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 Oncology* 2009; **35**(6): 578–582.

6. Dellas K, Vonthein R, Zimmer J *et al.* Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01). *Strahlenther Onkol* 2014; **190**(7): 646–653.

7. Donovan EM, Cuirlionis L, Fairfoul J *et al.* Planning with intensity-modulated radiotherapy and tomotherapy to modulate dose across breast to reflect recurrence risk (IMPORT High Trial). *Int J Radiat Oncol Biol Phys* 2011; **79**(4): 1064–1072.

8. Franco P, Zeverino M, Migliaccio F *et al*. Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing statics ports of tomotherapy (TomoDirect): a prospective phase II trial. *J Cancer Res Clin Oncol* 2014; **140**(1): 167–177.

9. Harris EJ, Donovan EM, Yarnold JR, Coles CE, Evans PM, IMPORT Trial Management Group. Characterisation of target volume changes during breast radiotherapy using implanted fiducial markers and portal imaging*. Int J Radiat Oncol Biol Phys* 2009; **73**(3): 958–966.

10. Harris EJ, Donovan EM, Coles CE *et al*. How does imaging frequency and soft tissue motion affect the PTV margin size in partial breast and boost radiotherapy? *Radiother Oncol* 2012; **103**(2): 166–171.

11. Donovan E, Coles C, Westbury C, Yarnold J Breast In: Hoskin PJ (ed). *External Beam Therapy,* 2nd edn. Oxford: Oxford University Press, 2012.

# 3. Safe omission of radiotherapy after breast-conserving surgery

**Discussion statement**

**Avoidance of radiotherapy should be considered in women deemed to be at very low risk of local recurrence, for example, with T1N0 oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor negative (HER2-), Grade 1–2 tumours AND who are willing to take adjuvant endocrine therapy for a minimum of five years AND will have regular mammograms for ten years.**

## Background

- Local recurrence rates have fallen dramatically over the last 30 years, so that the absolute benefit of radiotherapy for some individuals may not outweigh the potential risks (normal tissue toxicity, cardiac morbidity, second malignancies).
- Randomised controlled trials (RCTs) to date show an increase in local recurrence without radiotherapy, but consistently show no increase in breast cancer death.
- RCTs to date fail to clearly identify which patients are at very low risk of recurrence, although unplanned subgroup analysis from PRIME II suggests that such a group can be identified. This is being tested in the UK PRIMETIME biomarker directed (IHC4+C) study that is expected to open in autumn 2016.
- Evidence shows that it is detrimental to avoid both radiotherapy and endocrine therapy (BASO II) so compliance with endocrine therapy should be strongly encouraged.
- It has been shown that the rate of local relapse in this group of patients is linear over time and therefore they should be followed up for ten years to salvage any local recurrences (repeat breast-conserving surgery and radiotherapy could be used at this time).
- The criteria in the statement above are best fulfilled with the UK PRIMETIME biomarker-directed study and participation is recommended.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| Avoidance of radiotherapy should be considered in patients deemed to be at very low risk of local recurrence, for example with T1N0 ER+, PR+, HER2-, Grade 1–2 tumours AND are willing to take adjuvant endocrine therapy for a minimum of five years AND will be followed up mammographically for ten years. These criteria are best fulfilled with the UK PRIMETIME biomarker-directed study and participation is recommended. | |
| Statement + ≥65 out of study and ≥60 in study. | Majority support |
| Statement + ≥70 out of study and ≥60 in study. | Strongly supported |

## Key points from consensus meeting

- If the breast multidisciplinary team (MDT) considers omitting radiotherapy after breast-conserving surgery, a radiotherapy consultation is required to discuss risks and benefits with the patient.
- Patients are still eligible for the breast screening programme when >73 years, but they need to self refer.
- Mammographic follow-up should take place annually for five years and ideally three yearly thereafter up to ten years.

## Key references

1. Hughes KS, Schnaper LA, Bellon JR *et al*. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; **31**(19): 2382–2387.

2. Blamey RW, Bates T, Chetty U *et al*. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial*. Eur J Cancer* 2013; **49**(10): 2294–2302.

3. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015; **16**(3): 266–273.

4. Kirwan CC, Coles CE, Bliss J; PRIMETIME Protocol Working Group; PRIMETIME Protocol Working Group. It's primetime. Postoperative avoidance of radiotherapy: biomarker selection of women at very low risk of local recurrence. *Clin Oncol (R Coll Radiol)* 2016; **28**(9): 594–596.

# 4. Internal mammary chain (IMC) radiotherapy

**Discussion statement**

**Internal mammary nodal radiotherapy should be given in patients at high risk of locoregional recurrence (that is, those with T4 disease and/or ≥4 axillary lymph node macrometastases). In patients with 1–3 axillary macrometastases who have been recommended locoregional irradiation based on risk factors (including age and tumour biology), inclusion of the internal mammary chain (IMC) in the target volume should be considered in those with central/medial disease. IMC radiotherapy should be delivered using techniques which minimise the dose to the heart and lungs.**

## Background

- The above recommendation is based on the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of outcomes in women treated with/without post-mastectomy locoregional radiotherapy including the supraclavicular fossa, axilla and IMC (8% reduction in breast cancer mortality at 20 years in patients with 1–3 positive lymph nodes), MA20 and EORTC internal mammary–medial supraclavicular (IM–MS) trials (3–5% disease-free survival benefit); and a Danish internal mammary node study (3.7% overall survival benefit with increased benefit in N2 disease, and in N1 disease with central/medial tumour location).
- Danish investigators have modelled risks versus benefits of widespread introduction of IMC radiotherapy. Number need to treat=14 patients (if treating only N2–3 and N1 med/central) and number needed to harm=10,000 (for patients without cardiac risk factors).
- It is strongly recommended that lymph nodes be defined according to the European Society for Radiotherapy and Oncology (ESTRO) guidelines (Offerson *et al*).
- It is recommended that the UK should adopt consistent technical approaches to treating the IMC that minimise dose to organs atrisk (particularly heart, lung and contralateral breast) but do not overwhelm current capacity. Wide tangents in breath-hold or rotational therapies are capable of meeting constraints in the majority of patients.
- It is recommended that centres treating the IMC should have a breath-hold technique available.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| Internal mammary nodal radiotherapy should be *offered* in patients at high risk of locoregional recurrence (that is, T4 and N2–3 disease). | Equipoise |
| Internal mammary nodal radiotherapy should be *considered* in patients at high risk of locoregional recurrence (that is, T4 and N2–3 disease). | Strong support |
| In patients with 1–3 axillary macrometastases who have been recommended locoregional irradiation based on risk factors, inclusion of the IMC in the target volume should be *considered* in those with central/medial disease. | Strong support |
| Internal mammary chain radiotherapy should be given using techniques which minimise doses to organs-at-risk. Every centre should have a breath-hold technique available for patients undergoing IMC radiotherapy. | Unanimous support |
| Where the IMC is included in the target volume, the use of the following dose constraints are recommended: heart $V_{17Gy}$ <10%, ipsilateral lung $V_{17Gy}$ <35%. Mean contralateral breast dose <3.5 Gy. In patients at intermediate risk, a mean heart dose <6 Gy is considered a reasonable objective. | Very strong support |

## Key points from consensus meeting

- The meeting recognised that there was a need for training of multidisciplinary teams in the delivery of IMN radiotherapy.

## Key references

1. Whelan TJ, Olivotto IA, Parulekar WR *et al*. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; **373**(4): 307–316.

2. Poortmans PM, Collette S, Kirkove C *et al*. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; **373**(4): 317–327.

3. Thorsen LBJ, Offersen BV, Danø H *et al*. DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2015; **34**(4): 314–320.

4. Offersen BV, Boersma LJ, Kirkove C *et al*. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 2015; **114**(1): 3–10.

5. Thorsen LB, Thomsen MS, Berg M *et al*. CT-planned internal mammary node radiotherapy in the DBCG-IMN study: benefit versus potentially harmful effects. *Acta Oncol* 2014; **53**(8): 1027–1034.

# 5. Hypofractionation

**Discussion statement**

**There is no indication to use more than 15 fractions for the breast, chest wall or nodal areas for standard adjuvant treatment.**

## Background

- In the Standardisation of Breast Radiotherapy (START) trial, no difference was found in the primary endpoint of local regional relapse. Normal tissue effects favour 40 Gray (Gy) in 15 fractions over 50 Gy in 25 fractions with a low rate of late events.
- Boost fractionation is additional to 15 fractions to whole breast if given sequentially.
- There have been no trials of hypofractionation in breast reconstruction patients but the START data suggest fewer side-effects with 40 Gy in 15 fractions compared to 50 Gy in 25 fractions.
- Data for hypofractionated nodal irradiation are limited to small subsets of patients from randomised controlled trials (RCTs) (14% in START A, 7% in START B), but show no increase in toxicity compared to standard fractionation nodal irradiation, and given START data on all patients, none would be expected.
- The Canadian study by Whelan used 42.5 Gy in 16 fractions.
- Meta-analysis of the START pilot study and the START trial, including approximately 6,000 patients, shows no difference based on tumour grade or subtype of breast cancer. A central histopathological review of the Canadian study (Bane *et al*) showed no difference but a trend towards Grade 3 being better with hypofractionation.
- With regard to heart and other late reacting normal tissues: if alpha/beta=3, 40 Gy is gentler on the heart and all other normal tissues; if alpha/beta=1.5, 40 Gy is still gentler on the heart.
- The FAST-Forward study of five fractions in a week is supported and is currently recruiting for patients undergoing nodal radiotherapy.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| There is no indication to use more than 15 fractions for the breast, chest wall or nodal areas. | Strong support |

*Note: pre-consensus meeting questionnaire indicated 100% agreement.*

## Key points from consensus meeting

- Ductal carcinoma *in situ* (DCIS) was not discussed separately but it is logical to treat as invasive cancer in terms of hypofractionation. There is no argument to support a different fractionation regimen.
- Hypofractionation should be at least as effective when irradiating nodal areas; trends on effectiveness favour hypofractionation.
- Normal tissue effects from hypofractionation do not cause specific concerns with regard to the brachial plexus.

## Key references

1. Haviland JS, Owen JR, Dewar JA *et al.* The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14**(11): 1086–1094.

2. Whelan TJ, Pignol JP, Levine MN *et al*. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362**(6): 513–520.

3. Bane AL, Whelan TJ, Pond GR *et al.* Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. *Ann Oncol* 2014; **25**(5): 992–998.

# 6. Axillary management of sentinel lymph node-positive disease

The following summary statement has been agreed by the Trustees of the Association of Breast Surgery (ABS) following the ABS Multidisciplinary Consensus Meeting on the further management of the malignant axillary node, held in London on 26 January 2015.

**Further local treatment for the malignant sentinel lymph node (SLN) in individuals with early invasive breast cancer**

• **Isolated tumour cells and micrometastases –** if the sentinel node(s) shows isolated tumour cells and/or micrometastases, no further axillary treatment is required in addition to breast-conserving surgery or mastectomy.

• **1–2 sentinel nodes with macrometastases –** further axillary treatment is no longer mandatory in breast conservation with whole-breast radiotherapy, in patients who are postmenopausal and have T1, Grade1 or 2, oestrogen receptor positive (ER+) and human epidermal growth factor receptor negative (HER2-) tumours.
*These patients could also be entered into the POSNOC or equivalent clinical trial.*

• **3 or more sentinel nodes with macrometastases** – patients should usually be recommended to have further axillary treatment.

• **Further axillary treatment should usually be recommended for patients undergoing mastectomy or with tumours with one or more of the following features: T3, Grade 3, ER- or HER2+.**
*These patients could also be entered into the POSNOC or equivalent clinical trial.*

• **No consensus was reached** on the management of patients with one or more of the following features: premenopausal status, T2 tumours, lymphovascular invasion or extranodal spread.

## Background

- The Z-11 trial conducted by the American College of Surgeons Oncology Group (ACOSOG) has suggested that small oestrogen receptor positive (ER+) tumours in postmenopausal women with macrometastases (deposits >2 millimetres [mm]) in the sentinel lymph nodes (SLNs) treated by breast-conserving surgery and whole-breast radiotherapy do not require axillary node clearance, but there are a number of shortcomings in this trial which limit these conclusions and suggest a need for caution.
- The POSNOC trial is recruiting patients in the UK and Australia with macrometastases in the SLNs who are randomised to receive further axillary local therapy (surgery or radiotherapy is permitted) or no further axillary treatment. Patients treated either by mastectomy or breast-conserving surgery are eligible.
- The AMAROS trial, assessing the effects of further axillary surgery or radiotherapy after a positive SLN biopsy, has demonstrated that axillary recurrence rates are very small and that radiotherapy and surgery have equivalent efficacy. The risk of lymphoedema was significantly lower after radiotherapy, although short-term shoulder stiffness was somewhat

worse than after surgery. The equivalence of surgery compared to radiotherapy has also been demonstrated in the older Edinburgh trial of axillary radiotherapy versus axillary node clearance in patients with a node positive axillary sample, and in the older trials of radiotherapy versus surgery in the Early Breast Cancer Trialists Collaborative Study Group (EBCTCG) analyses.

- Axillary radiotherapy is therefore a reasonable option in patients with a macrometastatic SLN axilla if deemed to require further axillary treatment – particularly if radiotherapy is needed to the intact breast or post-mastectomy chest wall. It is permissible to advise axillary radiotherapy in the 'axillary treatment' arm of the POSNOC trial.
- The AMAROS trial did mandate (contoured) nodal volume definition and planning, and this is currently not commonly practised in the UK, where more often a field-placed approach is used without computed tomography (CT) definition of the nodal volume. This is potentially problematic and can lead to relatively poor dosimetry in some patients, particularly those with a high body mass index, where it is preferable to use CT definition of the nodal volume and consider intensity-modulated radiotherapy (IMRT) if coverage is poor with a direct anterior nodal field.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| If the sentinel node(s) shows isolated tumour cells and/or micrometastases, no further axillary treatment is required in addition to breast-conserving surgery or mastectomy. | Strongly supported |
| If the sentinel node(s) shows macrometastases, further axillary treatment is no longer mandatory for breast conservation patients receiving whole-breast radiotherapy, for T1, Grade 1 or 2, ER+, HER2- and postmenopausal.<br>*These patients could be entered into POSNOC or equivalent trial.* | Strongly supported |
| If the sentinel node(s) shows macrometastases, further axillary treatment should usually be recommended for patients undergoing mastectomy, or with tumours with one or the following features: T3, Grade 3, ER- or HER2+.<br>*These patients could be entered into POSNOC or equivalent trial.* | Very strongly supported |
| For the SLN+ patients with macrometastases (AMAROS eligible), axillary radiotherapy is a reasonable alternative to further axillary surgery. | Strongly supported |

## Key points from consensus meeting

- The meeting supported the Association of Breast Surgery Multidisciplinary Consensus Meeting guidelines.

## Key references

1. Giuliano MD, Hunt KK, Ballman KV *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis - a randomized clinical trial. *JAMA* 2011; **305**(6): 569–575.

2. Donker M, van Tienhoven G, Straver ME *et al*. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15**(12): 1303–1310.

# 7. Partial breast radiotherapy after breast-conserving surgery

**Discussion statement**

**Partial breast radiotherapy can be considered for patients ≥50 years, Grade 1–2, ≤3 centimetres (cm), oestrogen receptor positive (ER+), human epidermal growth factor receptor negative (HER2-), N0 using either (i) external beam radiotherapy with 40 Gray (Gy) in 15 fractions over three weeks or (ii) multicatheter brachytherapy using fractionation within Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) trial.**

## Background

**External beam radiotherapy:**

- The IMPORT LOW trial five-year results were presented at the European Breast Cancer Conference (EBCC) in March 2016. They showed that, for each of the test groups, non-inferiority, assessed against the pre-specified 2.5% threshold was demonstrated. Local relapse rates were very low across all groups, as were moderate/marked normal tissue events, with a statistically significant improvement for partial breast radiotherapy for breast appearance and breast hardness (median follow-up 72 months).
- The Danish partial breast phase II trial was also presented at EBCC in March 2016. This trial had a primary endpoint for late normal tissue toxicity at three years after treatment and used the same fractionation as IMPORT LOW test group 2 (40 Gy in 15 fractions over three weeks). It reported a very low rate of local relapse and normal tissue events with no difference between groups.
- The RAPID trial interim late toxicity results showed worse toxicity at three years in the accelerated partial breast irradiation (APBI) arm. This may be due to a higher dose/twice daily fractionation regimen, but longer term results for both local recurrence and toxicity are needed.

**Brachytherapy:**

- The five-year results of the GEC-ESTRO APBI trial confirm that adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery is as effective as whole-breast irradiation for selected patients with early-stage breast cancer (prespecified non-inferior criteria were reached, median follow-up 6.6 years). Significantly fewer late skin side-effects were observed in the APBI arm.

**Intraoperative radiotherapy (IORT):**

- The ELIOT trial showed a hazard ratio of 9.3 for IORT compared with whole-breast radiotherapy with median follow-up of 5.8 years; non-inferiority was not reached.
- The TARGIT A trial has insufficient follow-up (median two years five months) and the National Institute for Health and Care Excellence (NICE) is still ‘exploring options for evidence development’, therefore the timeline for provisional guidance has been extended.

Representatives at the consensus meeting were asked to vote on the following statements with the results shown below:

| Statement | Voting outcome |
|---|---|
| Partial breast radiotherapy can be considered for patients ≥50 years, Grade 1–2, ≤3 cm, ER+, HER2-, N0 using either (i) external beam radiotherapy with 40 Gy in 15 fractions over three weeks or (ii) multicatheter brachytherapy using fractionation within GEC-ESTRO trial. | |
| Statement + 2 millimetre (mm) minimum margins. | Very strongly supported |
| Statement + 1 mm minimum margins. | Strongly supported |
| Statement + classical lobular cancer should be excluded. | Strongly supported |
| Statement + lymphovascular space invasion. | Strongly supported |

## Key points from consensus meeting

- Some centres would be likely to change practice based on the IMPORT LOW abstract presentation rather than wait for publication of the full manuscript.
- It was discussed that implementation of IMPORT LOW type partial breast radiotherapy would not impact on resources and training, as it would use existing equipment and the standard technique of forward planned IMRT.

## Key references

1. Strnad V,Ott OJ, Hildebrandt G *et al*. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016; **387**(10015): 229–238.

2. Olivotto IA, Whelan TJ, Parpia S *et al*. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol* 2013; **31**(32): 4038–4045.

3. Veronesi U, Orecchia R, Maisonneuve P *et al.* Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; **14**(13): 1269–1277.

4. Vaidya JS, Wenz F, Bulsara M *et al.* Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; **383**(9917): 603–613.

## Conclusion

This meeting appeared to address a need for consensus around what constitutes good practice in the breast oncology community. The major concerns were around implementing cardiac sparing and internal mammary node irradiation. Some centres have already implemented both these techniques, others are working towards this. Pragmatically the meeting was limited in scope and there remain other areas of breast radiotherapy practice that would benefit from a similar approach.

The reported issues around implementation of cardiac sparing were largely capacity and resource issues. Barriers to implementation of internal mammary node radiotherapy included capacity and resource, but also a request from some centres for support and training. There is a current bid for funding for an academic programme providing and evaluating support, and scope to include outlining training workshops in national professional meetings.

The consensus statements are suitable as a basis for departmental audit, the results of which can inform departmental priorities. These statements are the minimum standard of radiotherapy that centres should be working towards and any centres not delivering all elements should have a clear timetable for development and implementation. It is intended that these statements should inform future national quality standards.

Approved by the Board of the Faculty of Clinical Oncology: 5 October 2016.

# Acknowledgements


## Membership of core group

The production of *Postoperative radiotherapy for breast cancer: UK consensus statements* was undertaken by a core group comprising the following members:

- Dr David Bloomfield (Chair)
  Medical Director, Professional Practice, Clinical Oncology, The Royal College of Radiologists/Consultant Clinical Oncologist, Brighton and Sussex Universities Hospitals NHS Trust
- Professor Murray Brunt
  Consultant Clinical Oncologist, University Hospitals of North Midlands NHS Trust
- Mr Charlie Chan
  Association of Breast Surgery
- Dr Charlotte Coles
  Consultant Clinical Oncologist, Cambridge University Hospitals NHS Foundation Trust
- Dr Adrian Crellin
  Chair, Radiotherapy Clinical Reference Group, NHS England
- Professor David Dodwell
  Consultant Clinical Oncologist, St James Institute of Oncology, Leeds/UK Breast Cancer Group
- Ms Kim Fell
  Accountable Commissioner, NHS England
- Dr Anna Kirby
  Consultant Clinical Oncologist, Royal Marsden NHS Foundation Trust and Institute of Cancer Research
- Dr Imogen Locke
  Consultant Clinical Oncologist, Royal Marsden NHS Foundation Trust
- Ms Mairead MacKenzie
  Independent Cancer Patient Voice
- Ms Fiona MacNeill
  President, Association of Breast Surgery
- Mr Tony Murphy
  Lay Member, The Royal College of Radiologists
- Professor Heidi Probst
  Professor of Radiotherapy and Oncology, Sheffield Hallam University
- Neill Roberts
  Consultant Radiographer, St James Institute of Oncology, Leeds
- Ms Hilary Stobart
  Independent Cancer Patient Voice
- Jean Tremlett
  Research Radiographer, Brighton and Sussex Universities Hospitals NHS Trust
- Nikki Twyman
  Deputy Head of Physics, Cambridge University Hospitals NHS Foundation Trust
- Dr Karen Venables
  Head of Radiotherapy Physics, Mount Vernon Hospital, East and North Herts NHS Trust

The following centres were represented at the Consensus Meeting held at The Royal College of Radiologists on 23 March 2016:

Aberdeen Royal Infirmary
Addenbrooke's Hospital
Beatson West of Scotland Cancer Centre
Belfast City Hospital
Bristol Haematology & Oncology Centre
Castle Hill Hospital, Hull
Cheltenham General Hospital
Colchester General Hospital
Dorset Cancer Centre, Poole Hospital
Edinburgh Cancer Centre, Western General Hospital
Guy's & St Thomas' Cancer Centre
Imperial College Cancer Centre
Ipswich Hospital
Kent Oncology Centre, Maidstone
Lincoln County Hospital
Mount Vernon Cancer Centre
Musgrove Park Hospital
Northern Centre for Cancer Care, the Freeman Hospital
New Cross Hospital
Norfolk and Norwich University Hospital
North Middlesex University Hospital
Nottingham University Hospital, City Hospital Campus
Oxford Cancer Centre, Churchill Hospital, Oxford
Peterborough City Hospital
Portsmouth Oncology Centre, Queen Alexandra's Hospital
Queens Hospital, Romford
Raigmore Hospital, Inverness (NHS Highland)
Royal Berkshire Hospital
Royal Devon & Exeter Hospital (Wonford)
Royal Free Hospital
Royal Marsden NHS Foundation Trust
Royal Preston Hospital
Royal Shrewsbury Hospital
Royal Stoke University Hospital
Royal Sussex County Hospital
Royal United Hospital Bath
Southend Hospital
South Devon Hospital (Torbay and South Devon NHS Foundation Trust)
South West Wales Cancer Centre, Singleton Hospital, Swansea
St Bartholomews Hospital
St James Institute of Oncology, Leeds
The Christie Hospital
The Clatterbridge Cancer Centre
University College Hospital
University Hospital Southampton
University Hospitals, Coventry and Warwickshire
Velindre Hospital
Weston Park Hospital

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**The Royal College of Radiologists**
63 Lincoln's Inn Fields, London WC2A 3JW
**Tel:** +44 (0)20 7405 1282
**Email:** enquiries@rcr.ac.uk **www.rcr.ac.uk**

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