DRAFT FOR CONSULTATION

HSE National Clinical Guideline: Treatment of patients with breast cancer (radiation oncology)

Cover page

HSE National Clinical Guideline:
Treatment of patients with breast cancer (radiation oncology)
National Policy ☐ National Procedure ☐ National Protocol ☐ National Guideline ☐
National Clinical Guideline ☒

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Evidence-based recommendations on the treatment of patients with breast cancer with radiation therapy
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The purpose of this National Clinical Guideline is to provide evidence-based recommendations on the safe and effective treatment of patients with breast cancer using radiotherapy, maximising clinical effectiveness and minimising harm to patients.

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Disclaimer

This guideline ("the Guideline") was developed by a multidisciplinary guideline development group ("the Group") and is based upon the best clinical evidence available together with the clinical expertise of the Group members. The Guideline supersedes all previous Health Service Executive (HSE), National Cancer Control Programme (NCCP), and National Clinical Effectiveness Committee (NCEC) guidelines for the radiation oncology treatment of patients with breast cancer. The NCCP is part of the HSE and any reference in this disclaimer to the NCCP is intended to include the HSE. Please note, the Guideline is for guidance purposes only. The appropriate application and correct use of the Guideline is the responsibility of each health professional. The Group's expectation is that health professionals will use clinical knowledge and judgment in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances, and it may be necessary to deviate from this guideline. Clinical judgment in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary. The NCCP accepts no liability, nor shall it be liable, whether arising directly or indirectly, to the user or any other third party for any claims, loss or damage resulting from any use of the Guideline.

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1 Background

1.1 Purpose

The purpose of this National Clinical Guideline is to provide evidence-based recommendations for treating patients with breast cancer by radiation oncology. The guideline integrates the best research evidence with clinical expertise, and patient values and experiences. It aims to address areas of care with new and emerging evidence, reduce variation in practice, and improve patient experience and service delivery.

1.2 Mandate

The National Cancer Strategy 2017-2026 (Department of Health, 2017) states that: "The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards" (Recommendation 37).

1.3 Scope

The scope of the guideline is to provide clinical recommendations on the treatment of patients with breast cancer by radiation oncology. It does not cover the treatment of patients with other cancer types or by other modalities.

1.4 Target audience

The guideline was developed by a multidisciplinary guideline development group — a full list of members can be found in Appendix I.

This guideline is intended for all health professionals involved in the treatment of patients with breast cancer by radiation oncology. It is also relevant to those involved in clinical governance to help ensure that arrangements are in place to deliver appropriate care for the population covered by the guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with breast cancer and their significant others. The Plain language summary of this guideline outlines what is covered in the guideline along with a suggested list of questions you may want to ask your healthcare professionals (see section 2.4).

A full list of the abbreviations and a glossary of the terms used in this guideline can be found in sections 4 and 5, respectively.

While the Chief Executive Officer, General Manager and the Clinical Lead of the cancer centre/hospital have corporate responsibility for the implementation of the recommendations in this guideline, the multidisciplinary team is responsible for the implementation of the individual guideline recommendations.

1.5 Target population

The target population covered by this guideline are patients with breast cancer for whom radiotherapy is being considered as a treatment option.

1.6 Summary of changes from the 2023 Guideline

This guideline supersedes all previous versions:

- Treatment of patients with breast cancer: radiation oncology (National Clinical Guideline). Versions 1.0 – 3.1. (National Cancer Control Programme, 2023)
- Radiation Oncology (Section 2.5) of National Clinical Guideline No. 7. Diagnosis, staging and treatment of patients with breast cancer (Department of Health, 2015a)

Clinical questions are marked to indicate the year of the last evidence review. This guideline update retains all clinical questions addressed in Version 3.1 “Treatment of patients with breast cancer: radiation oncology (National Clinical Guideline)” (National Cancer Control Programme, 2023). Three additional clinical questions (clinical questions 2.3.3, 2.3.8 and 2.3.12) have been added to the guideline in this update, and the evidence for clinical question 2.3.6 was updated. The remaining questions and recommendations were considered and re-endorsed by the guideline development group and remain current.

While recommendations retained from the 2015 guideline have maintained the grading system used at that time, all updates to this guideline published since 2023 have followed an amended GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Furthermore, in this guideline update, the term “conditional” has replaced the term “weak” in denoting the strength of a recommendation. Further detail is available in Appendix III Grading the recommendations in this guideline.

2 Clinical Guideline & Recommendations

2.1 Summary of Recommendations

Recommendation 2.3.1.1

Radiotherapy is recommended for all patients undergoing breast-conserving surgery for early breast cancer.

Grade of recommendation: A

Recommendation 2.3.2.1

In patients who have undergone breast-conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations.

Grade of recommendation: A

Recommendation 2.3.3.1

For patients with early breast cancer who have undergone breast-conserving surgery external beam partial breast irradiation should be considered in those who meet the following criteria:

- Tumour size ≤2cm
- Age ≥50 years
- Unifocal tumour
- Invasive ductal carcinoma or other favourable subtypes
- pN0 – pNmi
- Grade 1 – 2
- ER-positive and likely to be compliant on hormonal therapy
- HER2-negative
- No known pathogenic variant in a very high-risk cancer predisposing gene

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.3.2

For patients with early breast cancer who have undergone breast-conserving surgery and are receiving partial breast irradiation, an accelerated twice-daily fractionation schedule is not recommended.

Moderately hypofractionated or ultrahypofractionated schedules, as would be indicated for whole breast irradiation, are recommended.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.3.3

For patients with early breast cancer who have undergone breast-conserving surgery intraoperative radiotherapy (with photons or electrons) is not recommended outside of a clinical trial or prospective registry.

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.4.1

In patients with breast cancer who have undergone breast-conserving surgery and who require adjuvant radiotherapy to breast and nodal regions, a moderately hypofractionated regimen e.g. 40 Gy in 15 fractions is recommended.

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.4.2

In patients with breast cancer who have undergone breast-conserving surgery, and are having whole breast radiotherapy only (with no boost or nodal radiotherapy) an ultrahypofractionated regimen e.g. 26 Gy in 5 fractions should be considered.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.4.3

In patients with breast cancer who have undergone breast-conserving surgery, and are having whole breast radiotherapy with a boost (but no nodal radiotherapy) an ultrahypofractionated regimen e.g. 26 Gy in 5 fractions may be considered.

Quality of evidence: Low **Grade of recommendation: Weak**

Recommendation 2.3.5.1

In patients who have breast-conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis.

Grade of recommendation: A

Recommendation 2.3.5.2

Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high-grade invasive cancers).

Grade of recommendation: A

Recommendation 2.3.6.1

In patients with early breast cancer receiving a radiotherapy tumour bed boost, a simultaneous integrated boost should be considered, e.g. 48 Gy in 15 fractions with 40 Gy in 15 fractions to the rest of the breast.

Quality of evidence: Moderate **Grade of recommendation: Conditional**

Recommendation 2.3.7.1

All patients with ductal carcinoma in situ having breast-conserving surgery should be considered for adjuvant radiotherapy.

Grade of recommendation: A

Recommendation 2.3.8.1

In patients with ductal carcinoma in situ who have undergone breast-conserving surgery and are having whole breast radiotherapy not requiring a boost, an ultrahypofractionated regimen, e.g. 26 Gy in 5 fractions, may be considered.

Quality of evidence: Very low **Grade of recommendation: Conditional**

Recommendation 2.3.9.1

In patients with ductal carcinoma in situ who have undergone breast-conserving surgery and have high-risk features, a radiotherapy boost may be considered.

Quality of evidence: High **Grade of recommendation: Weak**

Recommendation 2.3.10.1

Post-mastectomy radiotherapy should be recommended in patients with lymph node-positive breast cancer if they have high risk of recurrence (≥4 positive lymph nodes and/ or T3/T4 primary tumour).

Grade of recommendation: A

Recommendation 2.3.10.2

Post-mastectomy radiotherapy should be considered in patients with intermediate risk of recurrence (1 – 3 nodes) and individual patients should be discussed at a multidisciplinary team meeting.

Grade of recommendation: B

Recommendation 2.3.11.1

In patients with breast cancer who have undergone mastectomy a boost is not routinely recommended.

Quality of evidence: Low **Grade of recommendation: Weak**

Recommendation 2.3.11.2

In patients with breast cancer who have undergone mastectomy and are considered to be at high risk for local recurrence a boost may be considered on a case-by-case basis.

Quality of evidence: Low **Grade of recommendation: Weak**

Recommendation 2.3.12.1

In patients with:

- early breast cancer (cT1 – 2)
- who have undergone upfront breast-conserving surgery or mastectomy
- and have had a positive sentinel lymph node biopsy (≤2 sentinel lymph nodes positive for macrometastases ± extracapsular extension)

axillary radiotherapy (as part of regional nodal irradiation) should be considered, avoiding axillary lymph node dissection.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.12.2

In patients with

- early breast cancer
- who have had a positive sentinel lymph node biopsy
- and do not meet the criteria listed in Recommendation 2.3.12.1

and are not proceeding to axillary lymph node dissection for a documented reason, axillary radiotherapy (as part of regional nodal irradiation) should be considered.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.13.1

In patients with N2 – 3 breast cancer at diagnosis radiation of the internal mammary chain is recommended.

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.13.2

In patients with N1 breast cancer at diagnosis and a central or medial tumour or multiple adverse factors, internal mammary chain irradiation should be considered.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.14.1

In patients with left-sided breast cancer deep inspiration breath hold should be considered as a cardiac-sparing technique.

Quality of evidence: Low **Grade of recommendation: Strong**

Recommendation 2.3.15.1

Women who have undergone surgery for breast cancer should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of surgery.

Grade of recommendation: C

2.2 Overarching practical considerations for patient care

The following practical considerations for patient care are applicable across all recommendations in this guideline:

- The patient should have access to an advanced nurse practitioner (ANP), clinical nurse specialist (CNS), or radiation therapist to address any concerns raised.
- The patient should be informed that they should continue with all physiotherapy exercises until all treatments have finished.
- It is important to counsel patients around the benefits of smoking cessation.
- Patients should be given skincare advice specific for the area being treated.

2.3 Clinical questions, evidence statements, and recommendations

2023

2.3.1 Clinical question: In patients with breast cancer who have undergone breast-conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome?

2015 Evidence statement

A meta-analysis (Darby et al., 2011) addressed this question.

A meta-analysis of individual patient data from 10,801 women in 17 randomised controlled trials (RCTs) has shown a significant reduction in breast cancer recurrence with radiotherapy given after breast-conserving surgery (BCS) (Darby et al., 2011). The rate of recurrence is approximately halved at 10 years from 35% to 19.3% (absolute reduction 15.7% (95% CI 13.7 – 17.7), 2p<0.00001). Radiotherapy also reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8% (95% CI 1.6 – 6.0), 2p=0.00005). The majority of women in this meta-analysis had node-negative disease. For these women, the absolute recurrence reduction varied according to age, grade, oestrogen-receptor status, tamoxifen use and extent of surgery. Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year ten.

Recommendation 2.3.1.1

Radiotherapy is recommended for all patients undergoing breast-conserving surgery for early breast cancer.

Grade of recommendation: A

Good practice point

- There may be a justification for avoiding adjuvant radiotherapy in certain patients with low-risk breast cancer, following discussion with the patient and at a multidisciplinary team meeting.

2023

2.3.2 Clinical question: In otherwise healthy breast cancer patients who have undergone breast-conserving surgery, are there any subpopulations in terms of age, tumour size and nodal involvement where radiotherapy is not necessary?

2015 Evidence statement

Three RCTs (Hughes et al., 2013, Fisher et al., 2002, Fyles et al., 2004) addressed this question.

The NSABP B-21 trial recruited women after lumpectomy with tumours ≤1cm in size. This trial was designed for the specific purpose of comparing the value of tamoxifen, radiotherapy or both in reducing the incidence of ipsilateral breast tumour recurrence (IBTR) or contralateral breast cancer (CBC) in this low-risk group. The cumulative incidence of IBTR at eight years was 16.5% with tamoxifen, 9.3% with adjuvant radiotherapy and 2.8% with both treatments. Survival was 93% – 94% in the three groups. The use of tamoxifen resulted in a significant decrease in the risk of CBC when compared with radiotherapy alone. The authors conclude that tumours <1cm recur with enough frequency after lumpectomy to justify considering radiotherapy, regardless of tumour oestrogen receptor (ER) status. (Fisher et al., 2002)

The CALGB trial recruited 636 women at least 70 years of age who had a clinical stage T1N0M0, oestrogen receptor-positive breast carcinoma treated by lumpectomy. Participants were randomised to receive tamoxifen and radiotherapy or tamoxifen alone. Median follow-up is now 12.6 years. At ten years, freedom from locoregional recurrence was significantly improved in women receiving radiotherapy and tamoxifen compared to tamoxifen alone (98% versus 90% (95% CI 85% – 93%)). There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer – specific survival, or overall survival (OS) between the two groups. Ten-year OS was 67% (95% CI 62% – 72%) and 66% (95% CI 61% – 71%) in the tamoxifen and radiotherapy and tamoxifen groups, respectively. Of the 636 women in this study, only 21 (3%) died as a result of breast cancer, whereas 313 (49%) died as a result of other causes (only 6% of deaths attributed to breast cancer). The authors conclude that, depending on the value placed on local recurrence, tamoxifen alone remains a reasonable option for women age ≥70 years with ER-positive early-stage breast cancer. (Hughes et al., 2013)

Fyles et al. (2004) in a Canadian study recruited women at least 50 years of age with node-negative breast cancer <5cm in size who had undergone lumpectomy. Participants were randomised to receive radiotherapy plus

tamoxifen or tamoxifen alone. At five years, only 0.6% of the women in the group given tamoxifen plus irradiation had a local relapse, whereas 7.7% of the women in the group given tamoxifen alone had had a recurrence in the breast. There was no difference in overall survival between groups, although the trial was underpowered to detect small differences in survival. (Fyles et al., 2004)

Adjuvant radiotherapy reduces the risk of recurrence in all subgroups; however, in some cases the benefit may be small. There may be very low-risk patients in whom radiotherapy can safely be avoided and tamoxifen therapy alone considered. Age, tumour size, lymphovascular invasion status, hormone-receptor status, tumour grade, comorbid conditions and performance status need to be considered in individual cases.

2023 Updates to the evidence statement

One systematic review (Chesney et al., 2017) and three RCTs (Killander et al., 2016, Kunkler et al., 2015, Tinterri et al., 2014) give additional evidence to answer this question, which is consistent with earlier findings.

In a high-quality systematic review of four studies (including Fisher et al. (2002) and Fyles et al. (2004)), Chesney et al. (2017) demonstrated that tamoxifen plus radiotherapy reduced in-breast recurrence at five years compared to tamoxifen alone in elderly women (≥70 years old) with early stage breast cancer following breast-conserving surgery (relative risk (RR) 0.18 (95% CI 0.10 – 0.34), p<0.001). The benefit of radiotherapy remained significant at ten years (RR 0.27 (95% CI 0.13 – 0.54), p<0.001). There was no significant difference between the two treatment groups in terms of OS at five years (RR 0.98 (95% CI 0.79 – 1.22), p=0.89).

Tinterri et al. (2014), Kunkler et al. (2015), and Killander et al. (2016) all concluded that adjuvant radiotherapy reduced the rate of IBTR in older patients when compared with patients who did not receive radiotherapy.

Kunkler et al. (2015) showed actuarial IBTR at five years in women aged >65 years was 1.3% (95% CI 0.2 – 2.3) in women allocated to radiotherapy compared with 4.1% (95% CI 2.4 – 5.7) in those assigned no radiotherapy (log-rank p=0.0002). Killander et al. (2016) showed that low-risk patients (defined as >64 years old with ER+ and PR+ tumours <21mm) also benefitted from radiotherapy, with a cumulative incidence of IBTR at 15 years of 5.3% (1.9 – 12.4%) compared to 25.9% (16.9 – 35.8%) for those who did not receive radiotherapy. Finally, Tinterri et al. (2014) showed that in patients aged 55 – 75 the cumulative incidence of in-breast recurrence after 108 months was 3.4% in the radiotherapy arm and 4.4% in the surgery only arm. There was no difference in distant disease-free survival (DFS) or OS between arms.

Recommendation 2.3.2.1

In patients who have undergone breast-conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations.

Grade of recommendation: A

Good practice point

- Radiotherapy omission may be considered for patients with breast cancer deemed to be at very low risk of recurrence (e.g. >70 years, G1 – 2, T1, luminal A disease) following discussion with the patient and at a multidisciplinary team meeting.

2025

2.3.3 Clinical question: In patients with early breast cancer who have undergone breast-conserving surgery does partial breast irradiation compared to whole breast irradiation provide equal oncological outcomes?

Evidence summary

Partial breast irradiation (PBI) is radiotherapy limited to the part of the breast around where the tumour was located. It can be delivered by different modalities: external beam radiotherapy (EBRT), brachytherapy, or intraoperative radiotherapy (IORT). It can also be accelerated (APBI), that is, delivered in a shorter timeframe using a higher dose per fraction. Within the body of evidence that compares PBI to whole breast irradiation (WBI), some individual studies include one or more PBI modalities and/or fractionation schedules in their analyses.

Notably, while some studies found slight differences in the risk of local recurrence between partial- and whole breast irradiation, local recurrence rates were generally low across all studies, regardless of whether WBI or PBI was delivered (range for 5-year absolute recurrence 0 – 4.2% (A)PBI; 0.5 – 3.3% WBI).

PBI delivered via multiple modalities

A Cochrane review (Hickey and Lehman, 2021), six meta-analyses (Ravani et al., 2024, Shumway et al., 2023a, Goldberg et al., 2023, Chua et al., 2023, Xiang et al., 2021, Haussmann et al., 2021), a comparative effectiveness review (Shumway et al., 2023b) and a randomised controlled trial (Vicini et al., 2019) compare the local recurrence outcomes of PBI (combining two or more modalities) to WBI. In general, studies that included all PBI modalities in their analyses concluded that WBI was better than PBI at controlling local recurrence. However, studies that excluded IORT as a modality found no difference in recurrence rates.

Hickey and Lehman (2021), Xiang et al. (2021), Goldberg et al. (2023), and Haussmann et al. (2021) include all PBI delivery modalities in their analyses. In their Cochrane review, Hickey and Lehman (2021) determined that the use of PBI probably slightly reduces local recurrence-free survival (HR 1.21 (95% CI 1.03 – 1.42)). Importantly, local recurrence rates were low in both groups (local recurrence-free survival 985 per 1000 in the WBI group compared to 982 per 1000 in the PBI group). These results are consistent with those of Xiang et al. (2021), Goldberg et al. (2023) and Haussmann et al. (2021).

Meta-analyses that included only EBRT and brachytherapy (i.e. excluded IORT) as PBI delivery modalities were consistent in finding no significant difference in ipsilateral breast tumour recurrence between PBI and WBI. For example, Shumway et al. (2023b) calculated a relative risk of recurrence at five- and ten years of 1.34

(95% CI 0.83 – 2.18), and 1.29 (95% CI 0.87 – 1.91), respectively. This was in agreement with findings by Ravani et al. (2024) (HR 1.20 (95% CI 0.95 – 1.52), p=0.12), and Chua et al. (2023) (OR 1.09 (95% CI 0.84 – 1.42)).

Hickey and Lehman (2021), Shumway et al. (2023a), Shumway et al. (2023b), Haussmann et al. (2023), and Chua et al. (2023) also compare the adverse effects of PBI to WBI. These studies were heterogeneous in terms of what adverse effects were measured (e.g. skin issues, breast pain, fat necrosis, or adverse effects overall), and largely did not distinguish between fractionation schedules or modality used in their analyses. Consequently, they are difficult to compare. However, their results showed that (A)PBI was favourable or there was no difference between (A)PBI and WBI. The exception was Hickey and Lehman (2021), who found that late adverse skin effects may increase with (A)PBI compared to WBI (OR 2.27 (95% CI 1.63 – 3.15), I^2=93%). Shumway et al. (2023a), (2023b) found no difference between PBI or WBI for either total late adverse events, or late adverse events ≥ grade 2 (incidence ratio rate 0.85 (95% CI 0.44 – 1.63), I^2=97% and 0.75 (95% CI 0.28 – 2.03), I^2=96%, respectively).

The NSABP B-39/RTOG trial randomised 4,216 patients aged ≥18 with stage 0 – II breast cancer to receive APBI or WBI after breast-conserving surgery. It was designed to test whether APBI (via either brachytherapy (34 Gy: 571 patients) or EBRT (38.5 Gy in 10 fractions delivered twice daily: 1,536 patients)) provides equivalent local control compared to WBI. The hazard ratio for ipsilateral breast tumour recurrence reported in the trial (HR 1.22 (90% CI 0.94 – 1.58)) did not meet the equivalence criteria prescribed by the trial (which required the 90% confidence intervals to lie between 0.66 and 1.5) (Vicini et al., 2019). Therefore, WBI was considered to provide better local control. However, the absolute difference in the 10-year cumulative incidence of ipsilateral breast tumour recurrence was less than 1% between the two groups (4.6% in the APBI group vs 3.9% in the WBI group). Ganz et al. (2024) reported quality of life outcomes for a subgroup of patients in this trial. Total treatment-related symptoms were worse for the WBI group of patients at the end-of-treatment and four weeks later; however, no significant difference was seen between the WBI or APBI arms at any time point thereafter. Radiotherapy-related breast skin changes were similarly worse in the WBI group at end-of-treatment, four weeks, and six months later, but no differences were seen after this. Conversely, while localised pain and breast symptoms were initially worse for the WBI group, the APBI group reported worse symptoms at two- and three years.

External beam radiotherapy (EBRT)

Six randomised trials compare PBI, delivered solely via EBRT, to whole breast radiotherapy: IMPORT-LOW (Coles et al., 2017), DBCG PBI (Offersen et al., 2022), Florence (Livi et al., 2015), HYPAB (Lo Faro et al., 2024), RAPID (Whelan et al., 2019), and IRMA (Meduri et al., 2023). Of note, there are some differences in patient eligibility criteria between trials, particularly regarding age and maximum tumour size

(see Table 1). While patients with tumours up to 3cm were eligible for some trials, in practice few patients with tumours >2cm were enrolled. With the exception of HYPAB (which was underpowered) all studies are consistent in showing no significant difference between WBI and PBI for local recurrence, despite the different fractionation schedules used to deliver PBI between the trials. Analysis of the adverse effects of treatment showed more inconsistent results. The guideline development group suggest this inconsistency may be due to the different fractionation schedules used.

- **Moderately hypofractionated partial breast irradiation**

IMPORT-LOW and the DBCG PBI trial both randomised patients with invasive breast cancer to either WBI or PBI delivered as 40 Gy in 15 fractions. These trials were consistent in finding no significant difference between local/locoregional recurrence between arms, while WBI was worse for breast induration.

IMPORT-LOW randomised 2,016 patients aged ≥50 years with pT1 – 2, pN0 – 1, M0 breast cancer to one of three arms: 40 Gy WBI, 36 Gy WBI and 40 Gy PBI (a reduced dose group), or 40 Gy PBI only (Coles et al., 2017). At five years, the cumulative incidence of local relapse was 0.5% (95% CI 0.2 – 1.4%) in the PBI arm and 1.1% (95% CI 0.5 – 2.3%) in the WBI arm (HR 0.65 (95% CI 0.23 – 1.84)), showing no significant difference between arms (p=0.42). The absolute difference between the arms was -0.38% (95% CI -0.84 – 0.90%), meeting the trial's non-inferiority criteria. While the trial showed no significant difference between the PBI or WBI arms for patient-reported moderate or marked adverse events at five years for most effects measured, significantly fewer patients reported changes in breast appearance (p<0.0001) or hardening/thickening of the breast (p=0.024) in the PBI arm. There was no significant difference in the clinical assessment of any late adverse events. Severe late effects were rare, and the proportion of patients reporting any arm or shoulder symptoms as moderate or marked at five years was low in all groups (Coles et al., 2017).

The DBCG PBI randomised trial analysed 865 patients, comparing grade 2 – 3 breast induration as the primary endpoint. The 3-year rate of induration was 9.7% (95% CI 7.0 – 12.9) in the WBI arm compared to 5.1% (95% CI 3.2 to 7.6) in the PBI arm, a risk difference of -4.6% (95% CI -8.2 – -0.9), p=0.014. The hazard ratio for grade 2 – 3 induration was 0.50 (95% CI 0.29 – 0.86), favouring PBI. Partial breast irradiation particularly reduced the risk of induration in women with large breasts (15% with WBI versus 8% with PBI (OR 0.49 (95% CI 0.33 – 0.74), p<0.0001)). There was no significant difference in locoregional recurrence risk between arms, with a 5-year cumulative incidence of 0.7% (95% CI 0.2 – 1.9) in the WBI arm, and 1.2% (95% CI 0.4 – 2.6) in the PBI arm (risk difference 0.5% (95% CI -0.8 – 1.7), p=0.47) (Offersen et al., 2022).

Table 1: Patient and tumour characteristics in randomised controlled trials comparing external beam partial breast irradiation to whole breast irradiation

Patient/ tumour characteristics	DBCG PBI (n=865)	IMPORT-LOW (n=2,016) [1]	NSABP B-39/ RTOG 0413 (n=4,216)	RAPID (n=2,135)	IRMA (n=3,225)	Florence (n=520)	HYPAB (n=172)
	40 Gy in 15 fractions	40 Gy in 15 fractions	38.5 Gy in 10 fractions twice daily	38.5 Gy in 10 fractions twice daily	38.5 Gy in 10 fractions twice daily	30 Gy in 5 fractions on alternate days	30 Gy in 5 fractions on alternate days
Age (years)	60 – 69: 80% ≥70: 20%	[Median 62, IQR 57 – 67]	<50: 38% 50 – 70: 49% >70: 13%	[Median 61, IQR 54 – 68]	49 – 60: 30% 60 – 70: 41% ≥70: 30%	<50: 17% 51 – 69: 61% ≥70: 23%	[Median 64, range 44 – 76]
Tumour stage • Tis • T1 • T2	 - 100% -	 - [Median 12 mm (IQR 8 – 16 mm)] [2]	 25% 58.1% 9.1%	 18% [<15 mm: 56.2%; ≥15 mm: 25.9%][3]	 - 92% 8%	 10.6% 83.8% 5.6%	 - 99% 1%
Nodal stage • pN0 • pNmi • pN1	 100% - -	 97% - 3%	 90% - 10%	 99% 1% -	 92% - 7%	 86% - 10%	 100% - -
Tumour grade • I • II • III	 52% 35% -	 43% 47% 10%	 28% 36% 27%	 43% 41% 16%	 28% 56% 14%	 44% 45% 11%	 12% 85% 3%
Subtype • ER positive • PR positive • HER2 positive	 100% NR 0%	 95% 81% 5%	 81%[4] NR	 90% NR 6%	 95% 85% 4%	 96% 90% 4%	 100% NR NR

[1]2,016 patients were analysed across three arms. Only the control (WBI) arm and the PBI arm are considered here (n=1,343).
[2]Only median tumour size and interquartile range reported. Patients with tumours up to 30 mm were eligible
[3]Tumour size reported only as </≥15 mm
[4]Reported as ER and/or PR positive
NR = not reported

- **Ultrahypofractionated Partial Breast Irradiation**

The Florence and HYPAB trials compared WBI to PBI delivered as 30 Gy in five fractions given on alternate days.

The Florence trial randomised 520 women aged >40 with early breast cancer. At five years, there were six incidences of ipsilateral breast tumour recurrence, three in each arm: with an IBTR rate of 1.5% in the APBI arm vs 1.4% in the PBI arm (HR 1.16 (95% CI 0.23 – 5.75)) (Livi et al., 2015). Patients in the HYPAB trial (n=172) similarly experienced very few local recurrences in either arm, with seven local recurrences after five years (Lo Faro et al., 2024). This trial was not sufficiently powered to show small differences in the recurrence rates between arms.

The Florence trial reported fewer adverse skin effects of any grade in the PBI arm during both the acute (19.9% vs 66.5%, p=0.0001) and late (4.5% vs 11.2%, p=0.004) periods. There was no significant difference in the incidence of grade 2 or higher late adverse effects between the arms (0.8% WBI vs 0% PBI, p=0.26) (Livi et al., 2015). The results from HYPAB were consistent with these findings, with fewer grade 1 – 2 acute and late adverse skin effects in the PBI arm (13% vs 62%, p<0.001; and 18% vs 41%, p<0.001, for the acute and late periods, respectively). Like the Florence trial, there was no significant difference in the incidence of grade 2 late adverse skin effects between the arms (4% WBI vs 1% APBI, p=0.34).

- **Accelerated Partial Breast Irradiation**

RAPID and IRMA are randomised trials that compare WBI to APBI delivered as 38.5 Gy in 10 fractions twice daily.

RAPID is a non-inferiority trial of 2,135 women aged ≥40 years who had DCIS or node-negative invasive breast cancer treated with breast-conserving surgery (Whelan et al., 2019). The 8-year cumulative incidence of ipsilateral breast tumour recurrence was 3.0% in the APBI group and 2.8% in the WBI group (HR 1.27 (90% CI 0.84 – 1.91)). The study concluded that APBI was non-inferior to WBI.

Regarding side effects of treatment, there were fewer grade 2 or higher acute adverse effects in the APBI group compared to the WBI group (28% vs 45%, p<0.001). There were very few grade 3 acute adverse effects in either group, with no significant difference between them (1.5% APBI vs 1.7% WBI, p=0.99). However, grade 2 or higher late adverse effects were significantly more frequent in the ABPI group (32% vs 13%, p<0.0001). This was also true for grade 3 events (4.5% APBI vs 1.0% WBI, p<0.0001) (Whelan et al., 2019).

The IRMA randomised trial analysed 3,225 patients aged ≥49 years with stage I – IIA breast cancer. Meduri et al. (2023) reported that while acute grade 3 – 4 side effects to the skin was higher in the WBI group (p<0.0001), there was no difference in the late skin side effects. Late side effects to the bone and the soft tissues of grade 3 or higher were significantly higher in the APBI arm. The primary outcome of ipsilateral breast tumour recurrence has yet to be reported for this trial.

While these trials (and the NSABP B-39/RTOG trial, which delivered the same fractionation schedule to patients receiving external beam APBI) are consistent in reporting that APBI is favourable in terms of acute side effects, there is some inconsistency in their findings for late side effects. IRMA and NSABP B-39/RTOG reported no difference between arms for adverse effects to the skin, while RAPID reported that late skin side effects were significantly worse with APBI, mostly due to an increase in skin telangiectasia and breast induration.

Brachytherapy

One randomised controlled trial compared WBI to brachytherapy-delivered PBI.

GEC-ESTRO (Strnad et al., 2016, Polgár et al., 2017, Strnad et al., 2023) randomised 1,184 patients aged ≥40 who had early breast cancer (≤3cm, pN0 – pN1mi, M0) to PBI via brachytherapy or WBI. After five years of follow-up there was no difference in ipsilateral breast tumour recurrence between both arms, with an incidence of 0.92% (95% CI 0.12 – 1.73) in the WBI arm versus 1.44% (95% CI 0.51 to 2.38) in the APBI arm (difference 0.52% (95% CI -0.72 – 1.75), p=0.42) (Strnad et al., 2016). After ten years, there were more recurrences in the APBI arm (1.58% (95% CI 0.37 – 2.78) WBI vs 3.51% (95% CI 1.99 – 5.03%) APBI), however this difference was non-significant (difference 1.95% (95% CI -0.018 – 3.87), p=0.074) (Strnad et al., 2023).

There was no significant difference between the two arms in the cumulative incidence of any grade ≥2 side effect at five years (p=0.12), although grade 2 – 3 late skin toxicity was worse in the WBI group (difference at five years -3.8% (95% CI -7.2 – 0.4%), p=0.002) (Polgár et al., 2017). Neither was there any difference in any adverse events of any grade at ten years (p=0.70), although patients in the APBI group showed a significantly lower incidence of grade 3 late side effects (p=0.021). Grade 3 side effects were rare in both groups, however (Strnad et al., 2023).

Intraoperative radiotherapy (IORT)

Intraoperative radiotherapy is a type of PBI treatment that is delivered during surgery to remove the tumour. Three systematic reviews and meta-analyses (He et al., 2021, Ravani et al., 2024, Shumway et al., 2023a), a comparative effectiveness review (Shumway et al., 2023b), and three randomised controlled trials (ELIOT (Orecchia et

al. (2021), Veronesi et al. (2013)), TARGIT-A (Vaidya et al. (2020a), Vaidya et al. (2010)) and TARGIT-A delayed (Vaidya et al., 2020b) compare WBI to IORT.

The meta-analyses were consistent in showing that WBI was associated with more favourable recurrence outcomes. He et al. (2021) carried out a meta-analysis of 9 studies, containing 8,403 individuals, and the pooled result showed a significantly lower local recurrence-free survival rate for IORT compared to WBI (OR 2.36 (95% CI 1.66 – 3.36)). These findings were consistent with Shumway et al. (2023a) and Shumway et al. (2023b), who calculated a 5-year relative risk of 3.92 (95% CI 2.44 – 6.32) for ipsilateral breast tumour recurrence, favouring the WBI cohort (4,756 patients in two randomised controlled trials). Ravani et al. (2024) also showed a higher ipsilateral breast tumour recurrence risk for IORT compared to WBI (HR 1.46 (95% CI 1.23 – 1.72)) (9,562 patients, 3 studies).

The ELIOT trial randomised 1,305 patients aged 48 – 75 with a unicentric carcinoma ≤25 mm, cN0 to either IORT or WBI. Ipsilateral breast tumour recurrence was significantly worse with IORT (HR 4.62 (95% CI 2.68 – 7.95), p<0.0001) (Orecchia et al., 2021). After five years, the rate of ipsilateral breast tumour recurrence was 0.5% and 4.2% in the WBI and IORT groups, respectively. At 10 years, this increased to 1.1% and 8.1%, respectively.

TARGIT-A was a non-inferiority trial that randomised 2,298 women aged ≥45 years with invasive ductal carcinoma up to 3.5 cm, cN0 – 1 to either whole breast external beam irradiation or risk-adapted IORT. “Risk-adapted” IORT meant supplementing IORT with EBRT in patients who were found to have high risk factors postoperatively. A non-inferiority margin of 2.5% for the absolute difference between 5-year recurrences was set, and risk-adapted IORT was found to be non-inferior to EBRT (local recurrence risk at five years 2.11% for risk-adapted IORT and 0.95% for EBRT, difference 1.16% (90% CI 0.32 – 1.99)). After a median of 8.6 years of follow-up, there was no significant difference in local recurrence-free survival rates (HR 1.13 (95% CI 0.91 – 1.41), p=0.28) between the groups. Of note, of the 1,027 patients in the IORT arm 241 (23%) received external beam radiotherapy in addition to IORT (Vaidya et al., 2020a).

A parallel trial to TARGIT-A compared WBI to delayed IORT (i.e. IORT delivered during a second surgical procedure by reopening the initial incision). This study randomised 1,153 patients after their initial surgery. After five years of follow-up rates of local recurrence were 3.96% in the IORT group and 1.05% in the WBI group—a difference of 2.9%, and thus not considered non-inferior (Vaidya et al., 2020b).

All studies that report radiation-associated side effects consistently show that IORT is associated with fewer adverse effects than WBI or that there is no difference between the two treatments. Shumway et al. (2023a), (2023b) reported that IORT was associated with fewer total acute adverse effects (incidence rate ratio 0.16 (95%

CI 0.06 – 0.40), while there was no difference in total late effects. However, when only grade 2 or higher adverse effects are included, IORT was considered to be better (incidence rate ratio 0.26 (95% CI 0.11 – 0.64). Similarly, in the ELIOT trial, in patients for whom data were available, there were significantly fewer skin toxicities in the IORT group compared to the WBI group (2.7% vs 7.9%, p=0.0002) (Veronesi et al., 2013). In TARGIT-A, grade 3 radiation toxicity was lower in the risk-adapted IORT group compared to the EBRT group (0.5% vs 2.1%, p=0.002). No patient had grade 4 toxicities (Vaidya et al., 2010).

Benefits and harms

Most breast tumour recurrences occur near the original tumour location so the rationale for treating a patient with breast irradiation is to reduce the risk of local recurrence. Partial breast irradiation reduces radiation exposure to the rest of the breast. The potential benefits and harms of PBI differ depending on how it is delivered.

External beam radiotherapy

Partial breast irradiation delivered by external beam radiotherapy gives comparable local tumour control with less tissue exposure to radiation when compared with whole breast irradiation. Side effects to the skin and breast may be reduced when partial breast irradiation is delivered, though this may depend on the fractionation schedule used:

- **Moderately hypofractionated partial breast irradiation**

  Moderately hypofractionated partial breast irradiation (e.g. 40 Gy in 15 fractions) appears to be beneficial in reducing the risk of hardening or thickening of the breast compared to WBI (Coles et al., 2017, Offersen et al., 2022).

- **Ultrahypofractionated partial breast irradiation**

  Ultrahypofractionated partial breast irradiation (e.g. 30 Gy in five fractions) appears to be beneficial in reducing the incidence of acute and late side effects to the skin compared to WBI, although this benefit is apparent when only grade ≥2 side effects are considered (Livi et al., 2015, Lo Faro et al., 2024).

- **Accelerated partial breast irradiation**

  Accelerated partial breast irradiation (e.g. 38.5 Gy in 10 fractions delivered twice per day) reduces acute side effects compared to WBI but is more harmful for some late side effects, although there is some inconsistency across studies for this outcome (Whelan et al., 2019, Meduri et al., 2023, Ganz et al., 2024).

Brachytherapy

Partial breast irradiation delivered by brachytherapy also gives comparable local tumour control to whole breast irradiation and overall side effects are similar between groups, although APBI appears to be associated with fewer severe side effects after 10 years. Brachytherapy is an invasive treatment and its outcomes are highly operator-dependent, therefore it requires considerable operator expertise. Given that modern external beam radiotherapy may be delivered in five fractions, the number of visits for treatment would not be reduced by recommending brachytherapy.

Intraoperative radiotherapy

The benefit of IORT is that it can be delivered at the same time as the surgery to remove the tumour. However, IORT is associated with a higher ipsilateral breast tumour recurrence rate, as referenced in the ELIOT trial (Orecchia et al., 2021).

Regardless of whether WBI or PBI is delivered, patients should be reassured that recurrence rates are low and marked adverse effects to the skin and breast are rare. There is no difference in the follow-up of treatment with PBI compared to WBI.

Preferences and values

The guideline development group, including patient representatives, believe that any treatment that can achieve equivalent tumour control while resulting in fewer or less severe side effects is preferable to patients. Patients value the reassurance that partial breast irradiation is comparable to whole breast irradiation in controlling a recurrence of their tumour. They also value the reassurance that partial breast irradiation is more targeted.

Resources, capacity, equity and other considerations

External beam radiotherapy is available in all radiotherapy centres. Other techniques (i.e. brachytherapy and IORT) are not available in every institution. For staff performing interventional radiotherapy there is a need to do a minimum number of cases every year to maintain their skill.

Recommendation 2.3.3.1

For patients with early breast cancer who have undergone breast-conserving surgery external beam partial breast irradiation should be considered in those who meet the following criteria:

- Tumour size ≤2cm
- Age ≥50 years
- Unifocal tumour
- Invasive ductal carcinoma or other favourable subtypes
- pN0 – pNmi
- Grade 1 – 2
- ER-positive and likely to be compliant on hormonal therapy
- HER2-negative
- No known pathogenic variant in a very high-risk cancer predisposing gene

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.3.2

For patients with early breast cancer who have undergone breast-conserving surgery and are receiving partial breast irradiation, an accelerated twice-daily fractionation schedule is not recommended.

Moderately hypofractionated or ultrahypofractionated schedules, as would be indicated for whole breast irradiation, are recommended.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.3.3

For patients with early breast cancer who have undergone breast-conserving surgery intraoperative radiotherapy (with photons or electrons) is not recommended outside of a clinical trial or prospective registry.

Quality of evidence: High **Grade of recommendation: Strong**

Good practice point

- Comprehensive information on potential adverse effects, both short- and long-term, should be provided to patients

2023

2.3.4 Clinical question: In patients with breast cancer who have undergone breast-conserving surgery does hypofractionation compared to conventional fractionation provide equivalent oncological outcomes?

Evidence summary

Five meta-analyses (Andrade et al., 2019, Valle et al., 2017, Budach et al., 2015, Zhou et al., 2015, James et al., 2010) demonstrate equivalent recurrence rates in women with early breast cancer treated with breast-conserving surgery (BCS) and either conventional (range 45 – 50 Gy) or hypofractionated (range 23 – 43.5 Gy) radiotherapy. Two further phase III RCTs compare different fractionation schedules. FAST compared a 5-week schedule of 50 Gy in 25 fractions to 30 or 28.5 Gy in five once-weekly fractions of 6.0 or 5.7 Gy (Brunt et al., 2020a). FAST-Forward compared either 1-week hypofractionated radiotherapy (26 or 27 Gy in five fractions) to 3-week radiotherapy (40 Gy in 15 fractions) (Brunt et al., 2020b).

All of the meta-analyses included here show that hypofractionation has equivalent oncological outcomes to conventional fractionation (Andrade et al., 2019, Valle et al., 2017, Budach et al., 2015, Zhou et al., 2015, James et al., 2010). These studies combine data from three main RCTs (START-A and START-B (Haviland et al., 2013) and the Ontario (Canadian) trial (Whelan et al., 2010)). The meta-analysis by Valle et al. (2017) demonstrated that there was no difference in late cosmesis between hypo- and conventional fractionation, but hypofractionation was associated with significantly less acute toxicity. Similarly, Andrade et al. (2019) concluded from their study that there was a significant difference in outcomes of telangiectasia, breast oedema and acute skin toxicity, favouring hypofractionation. There was, however, a high degree of heterogeneity between the included studies examining these outcomes in their meta-analysis. Zhou et al. (2015) and Budach et al. (2015) both showed that hypofractionation lowered the risk of acute skin reactions, with Budach et al. (2015) specifically showing that a radiation dose of 40 Gy in 15 fractions proved to be significantly less toxic than conventional fractionation in terms of breast shrinkage, breast oedema and development of telangiectasia at ten years. James et al. (2010) in a Cochrane review included four trials on 7,095 women enrolled in trials comparing standard fractionation with doses per fraction >2 Gy. There was no difference in local recurrence risk with RR 0.97 (95% CI 0.76 – 1.22, p=0.78) or survival at five years (RR 0.89, 95% CI 0.77 – 1.04, p=0.16). Breast appearance was equivalent and acute skin toxicity was decreased with hypofractionation, RR 0.21 (95% CI 0.07 – 0.64, p=0.007).

The data on hypofractionated nodal radiation is limited, but a subset of these treatments was included in RCT. Fourteen percent of patients in START A and 7% in

START B received hypofractionated nodal irradiation and showed no increase in toxicity compared to standard fractionation nodal irradiation.

The FAST trial evaluated normal tissue effects and disease outcomes in 915 women ≥50 years with low-risk invasive disease (pT01 – 2, pN0) randomly assigned to either 50 Gy/25 fr (5 weeks) or 30 or 28.5 Gy in five once weekly fractions (Brunt et al., 2020a). Photographic breast appearance was the primary endpoint and photographs were available for 615 women after five years of follow-up. Of these, 489 women had no change in breast appearance, whereas 109 and 17 and mild and marked changes, respectively. Rates of mild/marked change in photographic breast appearance was statistically significantly higher for women treated with 30 Gy compared to 50 Gy (OR 1.64 (95% CI 1.08 – 2.49), p=0.019), but not significantly different for 28.5 Gy and 50 Gy (OR 1.10 (95% CI 0.70 – 1.71), p=0.686). Ipsilateral breast cancer events were reported for 11 of 915 patients at 10 years and as such numbers were too small to detect a difference between groups (Brunt et al., 2020a).

FAST-Forward is a phase III RCT that compares 1-week hypofractionated radiotherapy (26 or 27 Gy in five fractions) to 3-week hypofractionated radiotherapy (40 Gy in 15 fractions) (Brunt et al., 2020b). This trial is generalisable to patients who have had breast-only radiation (not having boost or nodal irradiation) and who are ≥40 years of age. The trial has reported 5-year efficacy and late normal tissue effects (Brunt et al., 2020b). It showed that a schedule of 26 Gy in 5 fractions is non-inferior to the 40 Gy hypofractionated regimen in terms of local tumour control and showed late tissue effects up to five years to be comparable. Patients who received concurrent chemotherapy (but not concurrent endocrine therapy or trastuzumab) were excluded from the FAST-Forward trial, as were the lowest risk patients (>65 years, pT1, grade 1 – 2, oestrogen receptor positive, HER2 negative, pN0, M0). Sequential boost (16 Gy in 8 fractions) was administered in approximately 25% of patients. Trials of 1-week hypofractionated nodal radiation are ongoing.

Benefits and harms

Oncological outcomes

Based on the clinical evidence, there is no significant difference in local recurrence rate, overall survival and cosmetic outcome between standard fractionation and hypofractionation schedules.

Toxicity and cosmetic outcomes — 40 Gy in 15 fractions

A meta-analysis by Valle et al. (2017) found that the risk of acute toxicity was more favourable in hypofractionated compared with conventionally fractioned treatment, and late breast cosmesis showed no significant difference between the two regimens, albeit this was based on heterogeneous results (I^2=56%) .

Toxicity and cosmetic outcomes — 26 Gy in 5 fractions

In a longitudinal analysis of all annual clinical assessments of normal tissue effects over follow-up, the FAST-Forward trial (Brunt et al., 2020b) reported no significant difference between the 40 Gy and 26 Gy schedules. The 5-year prevalence of patient-reported adverse effects did not differ significantly between the schedules, while there was also no significant difference between 26 Gy and 40 Gy schedules in a photographic assessment at 2- and 5-years when modelled together.

Other benefits

A hypofractionated radiotherapy schedule requires fewer hospital visits for the patient when compared with conventional fractionation.

Potential harms

On a hypofractionated regimen, any treatment error will affect a greater proportion of the treatment and would be reportable to HIQA. Additionally, because patients on a hypofractionated regimen are seen less often in clinic they may perceive that their care has been reduced.

Preferences and values

The guideline development group, including patient representatives, believe that, given the equivalent oncological outcomes, informed patients would choose hypofractionation as it is less burdensome for the patient. A reduced number of clinic visits for the patient resulting from the use of hypofractionation could also have a wider impact on the patient's family and/or carers. Patients and their families may value the treatment time saved.

Resources, capacity, equity and other considerations

Hypofractionation is likely to be cost-saving. In their meta-analysis comparing conventionally fractionated radiotherapy and hypofractionated radiotherapy, Zhou et al. (2015) record that in the US treatment costs for hypofractionated radiotherapy are lower than for conventionally fractionated radiotherapy.

Reducing the number of treatments will potentially give more equal access to all patients to this service.

A study undertaken in St. Luke's Radiation Oncology Network, Dublin, over six months from March to August 2020 showed that delivering a 1-week schedule (26 Gy in 5 fractions) to 135 patients over that time period led to a saving of 21,300 LINAC minutes and 1485 hospital visits when comparted to a 3-week schedule (Nugent et al., 2021).

No additional time is required for treatment planning, and the shorter schedule should free hospital capacity and facilitate more patients to be treated in the same timeframe as with conventional fractionation. No barriers are therefore envisaged to its implementation.

Recommendation 2.3.4.1

In patients with breast cancer who have undergone breast-conserving surgery and who require adjuvant radiotherapy to breast and nodal regions, a moderately hypofractionated regimen e.g. 40 Gy in 15 fractions is recommended.

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.4.2

In patients with breast cancer who have undergone breast-conserving surgery, and are having whole breast radiotherapy only (with no boost or nodal radiotherapy) an ultrahypofractionated regimen e.g. 26 Gy in 5 fractions should be considered.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.4.3

In patients with breast cancer who have undergone breast-conserving surgery, and are having whole breast radiotherapy with a boost (but no nodal radiotherapy) an ultrahypofractionated regimen e.g. 26 Gy in 5 fractions may be considered.

Quality of evidence: Low **Grade of recommendation: Weak**

Good practice points

- Daily Image Guided Radiotherapy should be performed for patients having an ultrahypofractionated regimen e.g. 26 Gy in 5 fractions.
- Dosimetric parameters as per the FAST-Forward trial should be adhered to.

Practical considerations for patient care

- Patients should be offered more than one opportunity to discuss their treatment and potential side effects and should be given the opportunity to ask any questions. This could be with a Radiation Oncologist, an ANP or CNS, or a Radiation Therapist.
- Patients should be reassured that hypofractionated radiotherapy schedules have equivalent oncological outcomes as conventional radiotherapy.
- Written information on radiotherapy and its potential side effects should be provided to the patient.
- It is important to counsel patients on the timing of adverse effects which may occur in the weeks after treatment completion if undergoing a 1-week schedule.
- It is important that patients are given skincare advice and are well informed on how to manage skin toxicity which may occur after treatment.
- It is important to consider offering follow-up appointments according to the likely timing of toxicity.

2023

2.3.5 Clinical question: In patients with breast cancer who have undergone breast-conserving surgery, what is the evidence that a radiotherapy boost improves outcome?

2015 Evidence statement

Current guidelines (SIGN, 2013) and two RCTs (Bartelink et al., 2007, Romestaing et al., 1997) addressed this question.

Bartelink et al. (2007) recruited 5,318 women undergoing BCS followed by adjuvant radiotherapy (50 Gy in 25 fractions over five weeks). Participants were randomised to receive either no extra radiation or a boost dose of 16 Gy in eight fractions to the original tumour bed. Addition of a boost significantly reduced risk of local recurrence (10.2% versus 6.2%, p<0.0001). The hazard ratio (HR) for local recurrence was consistent across all age groups at 0.59. The absolute risk reduction was greatest in younger women (i.e. 23.9% to 13.5% in women ≤40 years of age). Late radiation side effects were increased in the boost group, with severe fibrosis increasing from 1.6% to 4.4% (p<0.0001). Survival was equivalent in both arms.

The relative benefit in reducing risk exists in all age groups. Absolute benefit is highest in patients aged <50 years, with a reduction in local recurrence from 19.4% to 11.4% (p=0.0046; HR 0.51) (Jones et al., 2009). For all patients with high-grade invasive ductal carcinoma, boost reduced recurrence from 18.9% to 8.6% (p=0.01; HR 0.42) (Jones et al., 2009). (SIGN, 2013)

Romestaing et al. (1997) recruited 1,024 women in France with breast carcinoma ≤3 cm in size treated with local excision and whole breast radiotherapy (50 Gy in 25 fractions over five weeks). Participants were randomised to receive either no additional radiation or a boost of 10 Gy in five fractions to the tumour bed. Local recurrence was significantly reduced by the addition of the boost (3.6% versus 4.5%, p=0.04). The boost group had a higher rate of telangiectasia but no difference in self-reported cosmesis outcomes. However, the event rate in this trial was low and further follow-up is necessary to confirm these findings.

Vrieling et al. (1999) demonstrated that the higher radiation dose (boost) was associated with a limited but statistically significant worsening of the cosmetic result. However, the boost dose was not the sole factor that affected the cosmetic outcome negatively: the location of the primary tumour in the lower quadrants of the breast, the volume of the excision, breast infection and/or haematoma, and clinical T2 stage were all independent predictors of worse cosmetic results, in addition to the boost treatment (Bartelink et al., 2007).

A boost should be considered in women <50 years of age receiving whole breast radiotherapy after lumpectomy. For the patient group >50 years of age, a boost should be considered in the presence of other risk factors (e.g. high-grade). The risk for increase in long-term effects with this increased dose should be taken into account, and patients should be counselled, allowing them to judge the balance of benefits and harms in context.

2023 Updates to the evidence statement

A Cochrane Review (Kindts et al., 2017) and long-term follow-ups of the EORTC boost versus no-boost RCT (Vrieling et al., 2017, Bartelink et al., 2015) provide additional evidence to answer this question.

In a meta-analysis of five studies, Kindts et al. (2017) found that local control was better with the addition of tumour bed boost (HR 0.64, 95% CI 0.55 – 0.75, p<0.00001). This association remained significant when two studies were removed for sensitivity analysis: a tumour bed boost versus no-boost was associated with significantly better local control (HR 0.62 (95% CI 0.52 – 0.73), p<0.00001; 3 studies, 6963 women, high-quality evidence). No difference in overall survival or late toxicity was found between groups.

In a 20-year follow-up of the EORTC boost vs no boost trial (Bartelink et al., 2007), Bartelink et al. (2015) found that the relative reduction of risk of ipsilateral breast tumour recurrence (IBTR) was significant in younger age groups (≤40, p=0.003; and for 41 – 50 years, p=0.007), but not for older age groups. The absolute risk reduction was largest in the youngest age group (≤40). There continued to be no significant difference in survival between the boost and no-boost groups.

In a sub-analysis of the same trial (1616 patients with a microscopically complete resection included in central pathology review) Vrieling et al. (2017) found that for patients <50 years old the boost dose reduced the 20-year cumulative incidence of IBTR from 24% to 15 % (p=0.002), while in patients with additional ductal carcinoma in situ (DCIS) the boost dose reduced the 20-year cumulative incidence of IBTR from 22% to 14% (p<0.001). In patients with both of these risks combined the boost dose reduced the 20-year cumulative incidence of IBTR from 31% to 15% (p<0.001). The influence of boost dose in older patients with DCIS was not significant, with a 20-year cumulative incidence of IBTR of 15% without versus 14% with the boost (p=0.11). For the subgroup of patients with hormone receptor negative, high-grade tumours the boost dose reduced the 15-year cumulative incidence of IBTR from 31% to 5% (p=0.01).

In a meta-analysis of two studies with very high heterogeneity, Kindts et al. (2017) deemed cosmesis to be better in the no boost group (p=0.01), while similarly

Bartelink et al. (2015) found that the cumulative incidence of severe fibrosis at 20 years was significantly higher in the boost group.

Recommendation 2.3.5.1

In patients who have breast-conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis.

Grade of recommendation: A

Recommendation 2.3.5.2

Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high-grade invasive cancers).

Grade of recommendation: A

Good practice points

- The benefits and risks of boost should be discussed separately to those of whole breast radiotherapy. The patient should be well informed regarding the potential magnitude of benefit and the possible severity and duration of side effects when adding a boost to whole breast radiotherapy treatment.
- The placement of clips during surgery is critical for radiotherapy planning.
- With improving systemic therapies the absolute risk of recurrence for many patients is low and, therefore, the benefit of a boost to the individual should be discussed, taking the patient's individual risk into consideration.

2025

2.3.6 Clinical question: For patients with early breast cancer receiving a radiotherapy boost, how does simultaneous integrated boost compare with sequential boost in terms of toxicity and efficacy?

Evidence summary

IMPORT-HIGH is a non-inferiority trial that recruited 2,617 women with pT1 – 3, pN0 – 3a, M0 breast cancer to compare simultaneous integrated boost to sequential boost after breast-conserving surgery (Coles et al., 2023). Patients were randomised to a control group or one of two test groups. The control group received 40 Gy in 15 fractions whole breast irradiation with a 16 Gy sequential photon boost in eight fractions. The test groups received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast and either 48 Gy (test group 1) or 53 Gy (test group 2) in 15 fractions simultaneous integrated photon boost (SIB) to the tumour bed. The primary endpoint was ipsilateral breast tumour recurrence (IBTR). After five years of follow-up the IBTR rate was much lower than anticipated, with a cumulative incidence of 1.9% (95% CI 1.2 – 3.1) in the control group; 2.0% (95% CI 1.2 – 3.2) in test group 1; and 3.2% (95% CI 2.2 – 4.7) in test group 2. The estimated absolute differences in IBTR were 0.1% (95% CI -0.8 – 1.7) for test group 1, and 1.4% (95% CI 0.03 – 3.8) for test group 2. Non-inferiority was therefore claimed for test group 1 but not test group 2 (using a pre-specified inferiority margin of 3% for the absolute difference in IBTR) (Coles et al., 2023).

Clinically assessed adverse effects showed a low prevalence of moderate or marked effects across all groups. Cumulative incidence of moderate or marked breast induration was similar for the control group and test group 1 (HR 0.90 (95% CI 0.71 – 1.14), p=0.4), but higher for test group 2 compared to the control group (HR 1.31 (95% CI 1.05 – 1.63), p=0.015). For patient-reported adverse effects, moderate or marked breast hardness or firmness at five years was significantly lower for test group 1 compared to the control group (RR 0.54 (95% CI 0.38 – 0.78), p=0.001). Severe late adverse effects were rare across all groups (Coles et al., 2023).

Two other RCTs have also addressed this question. While small patient numbers or other confounding factors in these trials compromise the quality of the evidence, nevertheless, the body of data suggests that radiotherapy with a simultaneous integrated boost is a safe and effective treatment option.

The IMRT-MC2 trial randomised 502 patients to receive either intensity modulated radiotherapy (IMRT) with SIB or 3D conformal radiotherapy (3DCRT) with a sequential boost (SeB). After five years of follow-up, the local control rate in the IMRT-SIB arm was 98.7% compared to 98.3% in the 3DCRT-SeB arm, and was found to be non-inferior (HR 0.58 (95% CI 0.12 – 2.38), p=0.46) (Forster et al.,

2023). Hörner-Rieber et al. (2021) reported cosmetic outcomes at six weeks and two years, while Forster et al. (2021) reported quality of life (QoL) outcomes at the same time points in this trial. Results showed that both 6-week and 2-year cosmesis were non-inferior in the IMRT-SIB arm compared with the 3DCRT-SeB arm. No statistically significant differences were found using any scoring criteria. Neither was there any significant difference at any time point between arms for any measure of toxicity. The only significant difference between QoL scores in the two arms was seen at six weeks, where both pain (QLQ-C30: 22.3 points for IMRT-SIB vs. 27.0 points for 3DCRT-SeB, p=0.033, r=0.102) and arm symptoms (QLQ-BR23: 18.1 points for IMRT-SIB vs. 23.6 points for 3DCRT-SeB, p=0.013, r=0.118) were worse in the 3DCRT-SeB group. Neither was there a significant difference for any measure of toxicity between the arms after five years, with the exception of breast oedema which was worse in the 3DCRT-SeB arm (p=0.002) (Forster et al., 2023).

Paelinck et al. (2017) and Van Hulle et al. (2021) reported acute and late toxicity in a trial of 167 patients treated in the prone position with hypofractionated radiotherapy and randomised to either a SeB or SIB. Paelinck et al. (2017) reported that grade 2 – 3 acute dermatitis and pruritus were significantly more frequent in the SeB arm, while the incidence of oedema was also higher, although this was non-significant. For late (2-year) toxicity, the differences between the SIB and SeB arms were very small and none were statistically significant.

The ongoing NGR RTOG 1005 phase III trial compares hypofractionated whole breast radiotherapy with a simultaneous boost to conventional whole breast irradiation with a sequential boost in patients who have high-risk early breast cancer (Vicini et al., 2022). Results have not yet been reported.

Benefits and harms

Compared with a sequential boost, simultaneous integrated boost reduces the treatment time for patients from four to three weeks, resulting in significant time savings for the patient, and cost and time savings for the service.

Simultaneous boost has not been shown to be associated with increased toxicity compared with sequential boost and is therefore a safe and effective treatment option.

There are no identified harms associated with a simultaneous boost over a sequential boost.

Preferences and values

The guideline development group, including patient representatives, believe that, given the equivalent side effects and quality of life outcomes, informed patients

would choose simultaneous integrated boost as it is less burdensome. A reduced number of clinic visits for the patient resulting from the use of simultaneous integrated boost could also have a wider impact on the patient's family and/or carers. With no apparent increase in side effects, patients and their families may value the treatment time saved.

Resources, capacity, equity and other considerations

There is no envisaged barrier to SIB being delivered in all radiotherapy units across the country.

The use of SIB can reduce treatment time from four to three weeks compared to SeB, with the potential of increasing capacity within the system.

Additional staff training and consultation with the Image-Guided Radiotherapy Group (IGRT) would be required for implementation of SIB. The National Plan for Radiation Oncology is underway in Ireland in varying degrees of implementation. Introduction of all new techniques may be on a phased basis throughout the country.

SIB is regularly used in the treatment of many tumour sites across Ireland. Introducing the technique for the treatment of breast tumours will require new training for staff. Implementation of this new service is impacted by understaffing and evolving infrastructure in different departments (radiotherapists/planners) in some centres nationally and will have to be introduced at a rate acceptable to each centre.

Recommendation 2.3.6.1

In patients with early breast cancer receiving a radiotherapy tumour bed boost, a simultaneous integrated boost should be considered, e.g. 48 Gy in 15 fractions with 40 Gy in 15 fractions to the rest of the breast.

Quality of evidence: Moderate **Grade of recommendation: Conditional**

Good practice points

- The placement of clips during surgery is critical for radiotherapy.
- Delineation and dosimetry guidelines for boost volume should be adhered to. Practitioners should take into consideration the relatively small boost volumes that were attained in the relevant trials.
- It is important that the patient is informed that a boost is being prescribed so that they can provide fully informed consent.

2023

2.3.7 Clinical question: In patients with ductal carcinoma in situ who have undergone breast-conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome?

2015 Evidence statement

A meta-analysis (Correa et al., 2010), a systematic review (Goodwin et al., 2009) and five RCTs (Bijker et al., 2006, Emdin et al., 2006, Fisher et al., 1998, Holmberg et al., 2008, Houghton et al., 2003) addressed this question.

Four of these trials (Emdin et al., 2006, Fisher et al., 1998, Holmberg et al., 2008, Houghton et al., 2003) have been analysed both in a systematic review (Goodwin et al., 2009) and in a meta-analysis (Correa et al., 2010). Both analyses concluded that the addition of radiotherapy following BCS reduced the risk of recurrence in all patients with DCIS but had no impact on either breast cancer mortality or all-cause mortality.

The EBCTCG analysed individual patient data for 3,729 women and found that radiotherapy reduced the absolute 10-year risk of an ipsilateral breast event (either recurrent DCIS or invasive cancer) by 15.2% (standard error (SE) 1.6%, 12.9% vs. 28%, p<0.0001). Radiotherapy was effective regardless of age, focality, grade, comedo-necrosis or tumour size, among other factors. Women with negative margins and small low-grade tumours have an absolute reduction in 10-year risk of ipsilateral breast events of 18% (SE 5.5, 12.1% vs. 30.1%, p=0.002). (Correa et al., 2010)

Based on this data it is not yet possible to confidently identify a group of women with DCIS in whom radiotherapy can be routinely omitted. However, while radiotherapy reduces the risk of recurrence, it has no impact on disease-specific or overall survival. The individual risk/benefit of adjuvant radiotherapy should be discussed with all patients.

2023 Updates to the evidence statement

One meta-analysis (Garg et al., 2018) and two randomised trials (McCormick et al., 2015, McCormick et al., 2021, Wärnberg et al., 2014) contribute additional evidence to answer this question.

In a 20-year follow-up of the SweDCIS Trial (Emdin et al., 2006) that randomised 1067 patients to receive adjuvant radiotherapy or no radiotherapy, Warnberg et al.

(2014) showed a cumulative risk of IBTR after 20 years of 20% in the radiotherapy arm and 32% in the control arm, corresponding to a relative risk reduction of 37.5%.

Similarly, in a study of 636 patients randomly allocated to either adjuvant radiotherapy or observation, McCormick et al. (2015) found cumulative rates of local failure in the ipsilateral breast were significantly lower in the radiotherapy arm compared to the observation arm, with 5- and 7- year local failure rates of 0.4% and 0.7% versus 3.5% and 6.7%, respectively (log-rank and Gray's test, p<0.001; HR 0.11 (95% CI 0.03 – 0.47). In the follow-up paper reporting 15-year results of this trial, McCormick et al. (2021) calculated the cumulative incidence of ipsilateral breast recurrence at 10 and 15 years, respectively, to be 1.5% (95% CI 0.5 – 3.7) and 7.1% (95% CI 4.0 – 11.5) with radiotherapy, and 9.2% (95% CI 6.2 – 13.0) and 15.1% (95% CI 10.8 – 20.2) in the observation arm (HR=0.36 (95% CI 0.20 – 0.66), p=0.0007). There was no difference in rates of overall survival or disease-free survival between arms at any time point.

In a meta-analysis of four studies, Garg et al. (2018) showed that radiotherapy significantly reduced the relative risk of both ipsilateral breast tumour recurrence (RR 0.53 (95% CI 0.45 – 0.72)) and regional recurrence (RR 0.54 (95% CI 0.32 – 0.91)) compared with no radiotherapy. A significant effect was not shown for either distant recurrence or overall mortality.

Together this new evidence is consistent with the findings of previous studies, which showed that the addition of radiotherapy has a benefit on local recurrence but has no effect on overall survival.

Recommendation 2.3.7.1

All patients with ductal carcinoma in situ having breast-conserving surgery should be considered for adjuvant radiotherapy.

Grade of recommendation: A

2025

2.3.8 Clinical question: In patients with ductal carcinoma in situ (DCIS) does ultrahypofractionated radiotherapy compared to moderately hypofractionated radiotherapy provide equivalent oncological outcomes?

Evidence summary

No studies were identified that compared ultrahypofractionated radiotherapy to moderately hypofractionated radiotherapy in patients with ductal carcinoma in situ (DCIS) only, therefore, there is no direct evidence to answer this question.

Indirect evidence may be inferred from the FAST-Forward trial (Brunt et al., 2020b), which randomised patients with invasive breast cancer (pT1 – 3, pN0 – 1, M0) to moderately hypofractionated or ultrahypofractionated radiotherapy to the breast or chest wall. A one-week schedule of 26 Gy in five fractions was found to be non-inferior for local control and as safe in terms of normal tissue side effects to the moderately hypofractionated 3-week schedule of 40 Gy in 15 fractions.

Following the publication of the FAST-Forward trial, a number of expert groups internationally have made consensus statements regarding the use of ultrahypofractionated radiotherapy to treat patients with DCIS. A Royal College of Radiologists (RCR) multidisciplinary working group of breast cancer experts and patients were in strong agreement that patients with DCIS can be offered whole breast radiotherapy of 26 Gy in five fractions over one week (Royal College of Radiologists, 2021). A consensus statement by the European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice supported the use of ultrahypofractionated whole breast radiotherapy as standard of care or within an RCT or prospective registry regardless of invasive or pre-invasive (DCIS) tumour stage (Meattini et al., 2022). Similarly, an Ontario Health Working Group acknowledged that a regimen of 26 Gy in five fractions may be offered for patients with DCIS (Brackstone et al., 2024).

The guideline development group is in agreement with international consensus regarding the use of ultrahypofractionated radiotherapy for the treatment of DCIS.

Within randomised trials, radiotherapy for DCIS has approximately halved the risk of an ipsilateral recurrence (of both DCIS and invasive cancer). Radiotherapy has not been shown to have any survival advantage (Correa et al., 2010) (see section 2.3.8 of this guideline for further details).

Benefits and harms

The main benefit for patients who receive ultrahypofractionated radiotherapy is a much lower burden of treatment (compared to moderately hypofractionated radiotherapy), for example the number of visits or tolerability of treatment positioning. Patients who receive ultrahypofractionated radiotherapy for breast cancer complete their radiotherapy treatment in one week, whereas those who receive moderately hypofractionated radiotherapy are treated over three weeks.

Analysis by Nugent et al. (2023) calculated that the delivery of an ultrahypofractionated schedule to 135 consecutive patients across the St. Luke's Radiation Oncology Network, Ireland, over a six-month period saved 1,485 hospital visits when compared to a moderately hypofractionated schedule.

Long-term oncological outcome data directly related to patients with DCIS treated with ultrahypofractionated radiotherapy are lacking. Prospective studies are in development and ongoing. Clinical consensus is that this is an appropriate treatment to proceed with while we await the results of prospective studies providing direct data. With ultrahypofractionation, side effects to the skin may occur after completion of radiotherapy treatment when the patient is no longer attending the radiotherapy department daily.

Preferences and values

The guideline development group, including patient representatives, believe that informed patients and their families would value the treatment time saved when ultrahypofractionated radiotherapy is delivered. The reduced number of clinic visits resulting from the use of ultrahypofractionated radiotherapy could also have a wider impact on the patient's family and/or carers.

To be informed, patients must have the knowledge that ultrahypofractionated radiotherapy does not compromise oncological outcomes in invasive cancer compared to moderately hypofractionated radiotherapy. While explaining to patients that they can be treated over a week it is important to explain that receiving a larger fraction per day is not associated with any increased risk of side effects and it is an appropriate treatment.

Resources, capacity, equity and other considerations

The reduction in the number of treatment slots required to deliver ultrahypofractionated radiotherapy increases capacity throughout the radiotherapy network, improving equity of access to radiotherapy services for all patients.

No additional time is required for treatment planning and the shorter schedule should free hospital capacity and facilitate more patients to be treated in the same timeframe as with moderately hypofractionated radiotherapy.

Recommendation 2.3.8.1

In patients with ductal carcinoma in situ who have undergone breast-conserving surgery and are having whole breast radiotherapy not requiring a boost, an ultrahypofractionated regimen, e.g. 26 Gy in 5 fractions, may be considered.

Quality of evidence: Very low **Grade of recommendation: Conditional**

Good practice points

- The option of 40 Gy in 15 fractions versus 26 Gy in five fractions should be discussed with the patient (or their advocate)
- Consider enrolling the patient in an appropriate prospective study and/or registry
- While explaining to patients that they can be treated over a week it is important to explain that receiving a larger fraction per day is not associated with any increased risk of side effects.
- It is important for Radiation Oncologists to inform other members of the breast multidisciplinary team that ultrahypofractionated regimens can be used for DCIS so that the patient receives consistent information from their treating team members.

Practical considerations for patient care

- Patients should be informed of the peak timing of acute adverse effects
- It is important to consider offering follow-up appointments according to the likely timing of acute toxicity

2023

2.3.9 Clinical question: In patients with ductal carcinoma in situ (DCIS) who have undergone breast-conserving surgery does radiotherapy boost improve rates of local recurrence compared with no radiotherapy boost?

Evidence summary

A meta-analysis (Nilsson and Valachis, 2015), an RCT (Chua et al., 2022, King et al., 2020), and three retrospective cohort studies (Moran et al., 2017, Cambra et al., 2020, Jobsen et al., 2018) address this question.

Findings are not consistent across all studies in relation to the administration of a boost for patients with DCIS who have undergone breast-conserving surgery. Some studies do not find a benefit for a boost in the general cohort (Nilsson and Valachis, 2015, Cambra et al., 2020, Jobsen et al., 2018), while in a study of 4131 patients Moran et al. (2017) showed that boost radiotherapy was associated with a lower ipsilateral breast tumour recurrence compared with no boost. In a study on the use of a boost in patients with non-low-risk DCIS Chua et al. (2022) showed that administration of a boost resulted in more favourable free-from-local-recurrence.

The BIG 3-07/TROG 07.01 trial (Chua et al., 2022) randomised 1608 patients with non-low-risk DCIS to have no boost (n= 805) or a boost (n= 803). Patients had at least one marker for increased risk, including age <50 years, symptomatic presentation, palpable tumour, microscopic tumour size measuring ≥15mm, multifocal disease intermediate or high nuclear grade, central necrosis, comedo-histology, or a radial surgical margin of <10mm. After five years, the free-from-local-recurrence rate was significantly lower in the no-boost group compared to the boost group (92.7% (95% CI 90.6 – 94.4%) and 97.1% (95% CI 95.6 – 98.1%), respectively), HR 0.47 (0.31 – 0.72) p<0.001. This benefit was not reflected in the 5-year overall survival rates between the no-boost (98.2%) and boost (99%) groups, which were not significantly different (HR 0.81 (95% CI 0.45 – 1.45), p=0.47).

When accounting for additional risk factors, in a subanalysis of patients with positive margins Nilsson & Valachis (2015) showed that a boost reduced local recurrence compared with no boost. Jobson et al. (2018), showed that patients with a positive margin in the no-boost group had worse outcomes compared to those with negative margins, whereas patients with positive margins who were boosted did not do significantly worse than patients with a negative margin. The addition of a boost, therefore, seemed to eliminate the adverse effect of a positive margin. Moran et al. (2017), however, calculated that a boost was not significantly beneficial in patients with positive margins compared with no boost. However, those authors urge caution in the interpretation of this result given the small subsample size (168 patients) which was underpowered. In subanalyses of patients with a negative margin, Moran et al.

(2017) concluded that a boost is beneficial in patients with negative margins (irrespective of the definition of the margin). Cambra et al. (2020) found that the highest boost dose (>16 Gy) in the negative margin subgroup significantly reduced the likelihood of developing ipsilateral breast tumour recurrence. However, there is a potential for confounding factors in all these studies. Good clinical practice would indicate that patients should have a re-excision of positive margins if possible.

The benefit of a boost in women under 50 years of age was addressed by Nilsson & Valachis (2015) and Moran et al. (2017). Due to the smaller numbers in this age cohort, there is not sufficient power in these studies to determine if a boost is of benefit.

The above studies and their findings are generalisable to the Irish population. The absolute benefit of a boost is small.

Benefits and harms

Radiotherapy boost may reduce the risk of breast cancer recurrence, but has no impact on overall survival in women with DCIS.

The EORTC trial showed that women with invasive disease who were of younger age, or had a higher grade tumour, benefitted most from a boost (Bartelink et al., 2015, Jones et al., 2009), providing indirect evidence of likely benefit for patients with DCIS.

In the BIG 3-07/TROG 07.01 trial Chua et al. (2022) reported that the boost group had higher rates of grade 2 or higher breast pain ($p=0.003$) and induration ($p<0.001$) than the no-boost group. There was no significant increase in radiation pneumonitis, cardiac disease, or radiation-related second malignancy in the boost group. A sub-study of this trial examined the effect on the health-related quality of life of women being treated for non-low-risk DCIS (King et al., 2020). This sub-study randomised 1208 patients and measured the following patient-reported outcomes: fatigue, physical functioning, cosmetic status, arm- or shoulder-related functional status, breast-specific symptoms, body image and sexuality, and perceived risk of invasive breast cancer (assessed by the Cancer Worry Scale and a study-specific question). Cosmetic status and arm and shoulder functioning were both adversely affected by boost radiotherapy compared to no boost. The negative impact of boost on cosmetic status persisted at 24 months, however its effect on arm and shoulder function had resolved by this time. Boost was not associated with body image and sexuality or perceived risk of invasive breast cancer.

Boost significantly increases the risk of fibrosis. In a study of 5318 patients with stage I and II breast cancer who underwent breast-conserving treatment, Bartelink et al. (2015) showed that the cumulative incidence of severe fibrosis at 20 years was

5.2% (99% CI 3.9 – 6.4) in the boost versus 1.8% (99% CI 1.1 – 2.5) in the no boost group (p<0.0001). Boost is associated with increased skin reaction, acute and late toxicities. The use of boost also has an impact on hospital capacity.

Preferences and values

The guideline development group, including patient representatives, agree that the addition of a boost depends on individual preference based on the patient's understanding and perception of meaningful benefit. Boost incurs an extra week of treatment and may provide a small benefit overall and therefore may not be preferable for some patients.

Resources, capacity, equity and other considerations

Administration of a radiotherapy boost involves an additional 5 – 8 fractions and, therefore, has an impact on hospital capacity and resources. Boost treatment is commonly used in clinical practice for women with invasive cancer. Treatment capacity within radiotherapy departments may impact on ability to provide boost treatments for women with DCIS going forward.

Recommendation 2.3.9.1

In patients with ductal carcinoma in situ who have undergone breast-conserving surgery and have high-risk features, a radiotherapy boost may be considered.

Quality of evidence: High **Grade of recommendation: Weak**

Good practice points

- Radiotherapy boost is not a substitute for re-excision of margins where this is feasible.
- The benefits and risks of a boost should be discussed separately from those of whole breast radiotherapy. The patient should be well informed regarding the potential side effects of adding a boost to standard radiotherapy treatment.
- Tumour bed clips are standard of care and are required to define the boost target volume.

Practical considerations for patient care

- The patient should be informed of the recommendation for a boost at the time of the consultation.
- The patient should be given skin care advice.
- A shared decision-making approach should be adopted between the patient and their Consultant.
- Clear information about the absolute benefit of a boost on recurrence should be explained to the patient.

2023

2.3.10 Clinical question: In patients who have undergone a mastectomy for breast cancer, what is the evidence that radiotherapy to the chest wall improves outcomes?

2015 Evidence statement

Current guidelines (Scottish Intercollegiate Guidelines Network [SIGN], 2013), a meta-analysis (Clarke et al., 2005) and two RCTs (Ragaz et al., 2005, Overgaard et al., 2007) addressed this question.

A meta-analysis and randomised trials have shown that radiotherapy to the chest wall and regional lymph nodes reduced recurrence and mortality in women with node-positive breast cancer (Clarke et al., 2005, Ragaz et al., 2005, Overgaard et al., 2007).

The 2005 EBCTCG meta-analysis (Clarke et al., 2005) included 8,500 patients treated with mastectomy and axillary clearance with or without radiotherapy to the chest wall and regional lymph nodes. For women with node-positive breast cancer, five-year local recurrence risk was reduced from 23% to 6% and 15-year breast cancer mortality risk was reduced from 60.1% to 54.7% (SE 1.3, 2p=0.0002; overall mortality reduction 4.4%, SE 1.2, 2p=0.0009) with the addition of radiotherapy.

All patients with node-positive disease benefited from postmastectomy radiotherapy (PMRT), however the benefit was greater with those patients with ≥4 positive nodes compared with those with one to three positive nodes. In these two groups, the 5-year risk of local recurrence with the addition of PMRT was reduced from 26% to 12% and 16% to 4% respectively. There were also significant reductions in local recurrence in patients with tumours >50mm (T3 tumours) or those invading local structures (T4). Here, the local recurrence rate was reduced from 36% to 8% (Clarke et al., 2005). (Scottish Intercollegiate Guidelines Network [SIGN], 2013)

Radiotherapy produced similar proportional reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy). Large absolute reductions in local recurrence risk were seen only if the control risk was large. For example, women with node-negative disease had a 5-year local recurrence risk of 6% in the absence of radiotherapy. This was reduced to 2% with the addition of radiotherapy, an absolute benefit of only 4%. Radiotherapy had no impact on overall survival in women with node-negative disease. (Clarke et al., 2005)

Long-term data from individual trials have confirmed these benefits. In a 20 year follow-up of the British Colombia RCT of locoregional radiotherapy in patients with high-risk breast cancer receiving adjuvant chemotherapy, Ragaz et al. (2005) concluded that for patients with high-risk breast cancer treated with modified radical mastectomy, treatment with radiotherapy (schedule of 16 fractions) and adjuvant chemotherapy leads to better survival outcomes than chemotherapy alone, and it is well tolerated, with acceptable long-term toxicity. (Ragaz et al., 2005)

A subgroup analysis of the Danish trials 82 b and c was conducted comparing the recurrence and survival after radiotherapy in women with 1 – 3 and ≥4 nodes positive. Although women with 1 – 3 positive nodes had lower absolute risks, radiotherapy produced significant reductions in recurrence and overall survival at 15 years in both groups (overall survival 57% versus 48% with 1 – 3 nodes, 21% versus 12% with ≥4 positive nodes, p=0.03 in both cases). (Overgaard et al., 2007)

The ongoing SUPREMO (BIG 2-04) trial is further investigating this issue, randomising women with 1 – 3 positive nodes after mastectomy and axillary clearance to receive radiotherapy or not.

2023 Updates to the evidence statement

Two additional meta-analyses (McGale et al., 2014, Tseng et al., 2020) and an RCT (Overgaard et al., 2022) address this question.

The EBCTCG meta-analysis (McGale et al., 2014) examined the benefit of post-mastectomy radiotherapy in terms of the number of positive lymph nodes. The analysis showed that in women with 1 – 3 positive nodes who had had an axillary dissection (n=1,314) adjuvant radiotherapy significantly reduced the 10-year risk of locoregional recurrence from 20.3% to 3.8%. Ten-year overall recurrence was also significantly reduced in these women (RR 0.68 (95% CI 0.57 – 0.82), 2p=0.00006) as was breast cancer mortality at 20 years (RR 0.80 (95% CI 0.67 – 0.95), 2p=0.01). Death from any cause after 20 years was higher in women who did not have radiotherapy compared to those who had (56.5% vs 53.5%, respectively), though this was non-significant (RR 0.89 (95% CI 0.77 – 1.04), 2p>0.1). This study therefore showed that women with just one nodal metastasis experienced a significant benefit from the addition of post-mastectomy radiotherapy with regard to any first recurrence and breast cancer mortality. The same study found that for women ≥4 positive lymph nodes who had had an axillary dissection (n=1772) adjuvant radiotherapy significantly reduced the 10-year risk of locoregional recurrence from 32.1% to 13%. Ten-year overall recurrence was also reduced (RR 0.79 (95% CI 0.69 – 0.90), 2p=0.0003), as was 20-year breast cancer mortality (RR 0.87 (95% CI 0.77 – 0.99), 2p=0.04). Death from any cause after 20 years was higher in women who did not have radiotherapy compared to those who did (82.7% vs 75.1%, respectively, (RR

0.89 (95% CI 0.78 – 1.00), 2p=0.05)). No advantage in terms of overall recurrence (RR 1.06 (95% CI 0.76 – 1.48), 2p>0.1) or breast cancer mortality (RR 1.18 (95% CI 0.89 – 1.55), 2p>0.1) was seen for radiotherapy for patients who were node-negative after axillary dissection.

The DBCG 82bc trial compared outcomes between patients with stage II and III breast cancer who underwent mastectomy and adjuvant systemic therapy with or without postoperative radiation. After 30 years of follow-up the locoregional recurrence was 9% in patients who received radiotherapy and 37% in those who did not (HR 0.21 (95% CI 0.18 – 0.26)), p<0.0001) Overgaard et al. (2022). Overall mortality in the same period was 81% in the radiotherapy cohort, and 86% in the patients who did not receive radiotherapy (HR 0.83 (0.77 – 0.90), p<0.0001). Other causes of death not related to breast cancer were not significantly different among the two treatment groups (Overgaard et al., 2022). In subgroup analysis, post-mastectomy radiotherapy showed a benefit in both patients with ≥4 positive nodes and 1 – 3 positive nodes.

Recommendation 2.3.10.1

Post-mastectomy radiotherapy should be recommended in patients with lymph node-positive breast cancer if they have high risk of recurrence (≥4 positive lymph nodes and/ or T3/T4 primary tumour).

Grade of recommendation: A

Recommendation 2.3.10.2

Post-mastectomy radiotherapy should be considered in patients with intermediate risk of recurrence (1 – 3 nodes) and individual patients should be discussed at a multidisciplinary team meeting.

Grade of recommendation: B

2023

2.3.11 Clinical question: In patients with breast cancer who have undergone mastectomy does radiotherapy boost improve rates of local recurrence compared with no radiotherapy boost?

Evidence summary

There are four retrospective studies that address this question (Panoff et al., 2012, Mayadev et al., 2014, Naoum et al., 2019, Albert et al., 2019), of which only Mayadev et al. (2014) had a large sample size of 4,247 patients. The quality of evidence is therefore low.

Some of the studies would not be expected to show a difference in locoregional recurrence and breast cancer specific survival rates between the boost and no-boost groups given low patient numbers and the short follow-up time, which ranged from a median of 43.6 months to 5.2 years across studies. These studies are potentially underpowered as the baseline locoregional recurrence rates are lower than may have been anticipated.

Albert et al. (2019) and Naoum et al. (2019) investigated whether a boost delivered a benefit to local/locoregional recurrence rates, however both failed to show a statistically significant benefit. Furthermore, Naoum et al. (2019) demonstrated what the addition of a boost was associated with increased reconstruction complications.

Mayadev et al. (2014) looked at the effect of delivering a boost on breast cancer survival and overall survival. This study did not show a benefit to chest wall boost apart from in patients who did not receive chemotherapy, where patients who received a chest wall boost had improved breast cancer survival (HR 1.77, 95% CI 1.11 – 2.83).

Finally, Panoff et al. (2012) showed a statistically significant benefit to locoregional control and progression free- and overall survival with the addition of a chest wall boost.

Based on these studies, there is no strong evidence to support the routine use of chest wall boost. However, there may be a cohort of patients considered to be at high risk for local recurrence whom chest wall boost may be considered.

The study by Naoum et al. (2019), which consisted of a chart review of 746 patients with a median follow-up time of 5.2 years, showed that boost increased the risk of complications in reconstruction.

Benefits and harms

As it has been shown that boost increases the risk of complications in patients who have undergone reconstruction (Naoum et al., 2019) it is important that patients are properly informed of the risks in order to give informed consent.

Boost prolongs the overall treatment time and number of visits to the radiation oncology department by 1 – 2 weeks.

Boost may reduce locoregional recurrence in patients who are at high risk for local recurrence.

Preferences and values

The guideline development group, including patient representatives, feel that due to the uncertainty regarding the benefit of a boost in this patient cohort, these decisions should be individualised and a shared decision-making approach should be adopted There are risks to be considered, for example the increased risk of fibrosis or the risk of complications to a reconstruction, which may be unacceptable to some patients, as may the additional treatment time required.

Resources, capacity, equity and other considerations

The addition of a boost will incur increased use of radiotherapy capacity and resources within the system but is of uncertain benefit to the patient.

Recommendation 2.3.11.1

In patients with breast cancer who have undergone mastectomy a boost is not routinely recommended.

Quality of evidence: Low **Grade of recommendation: Weak**

Recommendation 2.3.11.2

In patients with breast cancer who have undergone mastectomy and are considered to be at high risk for local recurrence a boost may be considered on a case-by-case basis.

Quality of evidence: Low **Grade of recommendation: Weak**

Good practice points

- Shared decision-making should take place if a boost is being considered, taking patient preferences into account.
- It is important to have the patient's pre-operative imaging and examination findings to plan the boost as accurately as possible.

2025

2.3.12 Clinical question: In patients with early stage breast cancer who have had a positive sentinel lymph node biopsy, how does regional nodal radiotherapy compare with axillary lymph node dissection in terms of local recurrence, overall survival, lymphoedema, and quality of life?

Evidence summary

Two randomised controlled trials directly answer this question, while further trials provide indirect supporting evidence. The characteristics of the patient populations in all trials are summarised in Table 2.

The AMAROS (Donker et al., 2014, Bartels et al., 2023) and OTOASOR (Sávolt et al., 2017) trials randomised patients who had a positive sentinel node biopsy to either completion axillary lymph node dissection (ALND) or axillary radiotherapy, to determine whether axillary radiotherapy was non-inferior to ALND with respect to axillary recurrence. Secondary endpoints included disease-free survival, overall survival, lymphoedema and quality of life.

Both trials had methodological flaws. Due to a lower than anticipated axillary recurrence rate, AMAROS was under-powered to show non-inferiority. Additionally, there was increasingly poor compliance with the follow-up of morbidity and quality of life assessments in this trial after baseline, such that a 10-year analysis of these outcomes could not be performed. In the OTOASOR trial the randomisation and concealment processes were poorly described, and only patients in the axillary radiotherapy arm were consented (as ALND was considered standard of care). Patients in the ALND arm had larger tumours compared to those in the axillary radiotherapy arm, which may bias the results in favour of radiotherapy being non-inferior. Data on lymphoedema and quality of life in this trial are insufficiently reported.

The recurrence rates in both trials were low (≤2%). AMAROS reported no significant difference in the 10-year cumulative incidence of axillary recurrence between the two arms: 1.82% (95% CI 0.74 – 2.94) in the axillary radiotherapy arm, and 0.93% (95% CI 0.18 – 1.68) in the ALND arm; HR 1.71 (95% CI 0.67 – 4.39) (Bartels et al., 2023). After eight years of follow-up in the OTOASOR trial, there were only 5 (2%) and 4 (1.7%) axillary recurrences in the axillary radiotherapy and the ALND arms, respectively (Sávolt et al., 2017). Neither was there a significant difference in overall survival rates. Overall survival reported by AMAROS was 92.5% (95% CI 90 – 94.4) and 93.3% (95% CI 91 – 95) in the axillary radiotherapy and ALND arms, respectively, at five years (Donker et al., 2014); and 81.4% (95% CI 77.9 – 84.4) and 84.6% (95% CI 81.5 – 87.1) in the axillary radiotherapy and ALND arms, respectively, at ten years (Bartels et al., 2023). Overall survival in the OTOASOR

trial was 77.9% and 84.8% in the axillary radiotherapy and ALND arms, respectively, at eight years (p=0.06) (Sávolt et al., 2017).

The quality of evidence to address lymphoedema and quality of life outcomes in these trials is low. In the AMAROS trial, rates of clinically significant lymphoedema (defined as an arm circumference increase of ≥10% compared to the contralateral arm) were worse in the ALND group. However, this reached statistical significance only at five years (axillary radiotherapy vs ALND groups at year 1 5.9% vs 7.8%, p=0.333; year 3, 6.3% vs 10.4%, p=0.05; year 5, 5.3% vs 12.6%, p<0.001) (Bartels et al., 2023). No clinically significant difference in any quality of life measure was observed in either trial (Bartels et al., 2023, Sávolt et al., 2017).

SENOMAC is a randomised controlled non-inferiority trial designed to compare the omission of ALND to its use in patients who had one or two sentinel nodes positive for macrometastases (de Boniface et al., 2024). It provides additional indirect evidence to answer this question as most (88.6%) patients across both arms received nodal radiotherapy. The primary endpoint is overall survival, with recurrence-free survival, breast cancer-specific survival and patient reported outcomes as secondary endpoints. The median follow-up for results reported for this trial by de Boniface et al. (2024) is less than four years (46.8 months). Data are therefore not mature, and long-term results are not yet available. Nonetheless, the estimated 5-year recurrence-free survival was similar in both groups, at 89.7% (95% CI 87.5 – 91.9) in the Sentinel Node Biopsy-only arm and 88.7% (95% CI 86.3 – 91.1) in the ALND arm. The omission of ALND was considered to be non-inferior to its use.

Additional indirect evidence is provided by the ACOSOG Z0011 trial, which accrued 891 women with cT1 – 2, N0, M0 breast cancer between 1999 and 2004. It was designed to determine whether the 10-year overall survival patients with sentinel node metastases treated with breast-conserving surgery and sentinel lymph node dissection alone is non-inferior to that of women treated with ALND. No difference in overall survival was seen after ten years (86.3% in the SLND arm and 83.6% in the ALND arm, HR 0.85 (0 – 1.16)) (Giuliano et al., 2017). All women underwent opposing tangential whole-breast irradiation and third-field irradiation was prohibited, however 18.9% of patients (for whom data were available) received regional radiotherapy outside of protocol, and approximately an additional 51% received high tangents (Jagsi et al., 2014). Therefore, it is difficult to conclude what effect radiotherapy had on the outcomes in this trial.

Table 2: Characteristics of the patient populations addressed by relevant trials

Patient/tumour characteristics		AMAROS (n=1425)	OTOASOR (n=474)	SENOMAC[1] (n=2540)	Z0011 (n=856)
Surgery type	Mastectomy	17.4%	15.6%	36.2%	0%
	BCS	81.8%	84.4%	63.8%	100%
Grade	I – II	70.2%	68.4%	77.0%	53.5%
	III	27.5%	31.6%	22.1%	21.1%
	Unknown	2.3%	-	0.9%	25.6%
Lymphovascular invasion	Present	NR	NR	28.2%	28.3%
Menopausal status	Premenopausal	40.1%	30.6%	NR	34.5%[2]
	Postmenopausal	59.9%	69.4%	NR	63.6%[2]
Age	Mean (range)	NR	55 (26 – 74)	61	
	Median (*IQR/^range)	ALND 56 (*48 – 64); aRT 55 (48 – 63)	NR	61 (^20 – 94)	ALND 56 (^24 – 92); SLND 54 (^25 – 90)
cT stage	T1	80.4%	65.2%	53.6%	68.6%
	T2	19.2%	34.8%	40.6%	30.4%
	T3	<1%	-	5.8%	-
No. sentinel nodes removed	≤2	73.2%	[ALND arm mean 1.83, range 1 – 5; RNI arm mean 1.95, range 1 – 5]	70.5%	[Median 2 (IQR 1 – 4)][4]
	>2	26.8%		29.5%	
No. positive sentinel nodes	1 – 2	95%	[ALND arm mean 1.36, range 1 – 4; RNI arm mean 1.17, range 1 – 4]	100%	89.4%[4]
	≥3	5%		-	3.6%
Extracapsular extension	Present	NR	NR	34.3%	NR
Subtype	ER-positive	NR	83.8%	93.4%	77%
	PR-positive	NR	73%	NR	62.4%
	HER2-positive	NR	14.3%	9%	NR
Size of largest sentinel node metastasis	Macrometastasis	60.4%	60.4%[3]	100%	50.2%
	Micrometastasis	28.8%	33.5%[3]	-	35.1%
	Isolated tumour cells	10.8%	6.1%[3]	-	-
	Unknown	-	-	-	14.6%

[1] Data reported for the per-protocol population
[2] Characteristics reported as ≤50 or >50 years rather than menopausal status
[3] Data from Axillary Radiotherapy arm. Not reported for Axillary Lymph Node Dissection arm.
[4] Data for SLND arm only, as trial reports total number of lymph nodes removed/total positive nodes rather than sentinel nodes.
NR = not reported; IQR = interquartile range

Benefits and harms

The purpose of treating the axilla with either axillary lymph node dissection (surgery to remove the lymph nodes) or axillary radiotherapy is to reduce the risk of recurrence. There are potential benefits and harms associated with both.

Benefit of axillary radiotherapy

The benefit of axillary radiotherapy when compared to axillary lymph node dissection (ALND) is the avoidance of a second surgery to remove the lymph nodes and the harms associated with ALND. The overall treatment time is also reduced when ALND is avoided.

Harms of axillary radiotherapy

There are also potential harms associated with axillary radiotherapy. These specifically relate to the larger target volume and the acute toxicity associated with this. The late effects of axillary radiotherapy may include lymphoedema, shoulder stiffness, pneumonitis (inflammation of the lung tissue) due to the increased dose to the lung, and dermatological issues.

Lymphoedema can occur following both axillary radiotherapy and ALND, however the rates are significantly lower with radiotherapy.

These potential harms can be mitigated by precision radiotherapy with volume delineation. The inclusion of the axilla should not require additional treatment appointments as axillary radiotherapy is given in conjunction with radiotherapy to the rest of the breast and regional nodes. The increased field of radiotherapy should not impact the patient's experience of attending for radiotherapy.

Benefit of axillary lymph node dissection

As the lymph nodes have been removed the radiotherapy field does not need to extend to the axilla. Some patients may be reassured by having their cancer surgically removed rather than treated in situ.

Harms of axillary lymph node dissection

Axillary lymph node dissection requires the patient to be admitted into hospital for an additional surgery (after the initial tumour excision). In the short-term, it therefore is associated with the potential harms of undergoing general anaesthetic and possible post-operative complications such as bleeding, infection, thrombosis (blood clots), or seroma (fluid collection in the surgical site). It prolongs the overall treatment time by several weeks as patients must wait through the second surgical procedure and a second recovery period before starting their systemic therapy and/or radiotherapy. In the long term, ALND may cause lymphoedema, parasthesis (pins and needles), swelling, and arm pain and/or shoulder mobility issues in some patients.

Preferences and values

The guideline development group, including patient representatives, recognise knowledge and understanding as important patient values. Very clear communication on the benefits and harms of both axillary lymph node dissection and axillary radiotherapy in the management of their cancer will facilitate this. It is important to communicate why further axillary management is being considered. This should include information on why a patient may not need any further surgery, as patients may perceive a benefit of ALND is that their cancer is physically removed. It should be emphasised that the axillary lymph nodes will be treated with either modality.

The timing of such conversations are important and should take place when the patient is able to understand and process the information given to them. While the conversation may be with either a surgeon or a radiation oncologist, clinical nurse specialists and advanced nurse practitioners are particularly important as they have valuable experience in ensuring the patient is hearing and understanding the information that they are given. Many patients also feel more comfortable and confident in speaking with a clinical nurse specialist or advanced nurse practitioner.

The concept of multi-disciplinary team meetings should be explained to the patient to reassure them that their specific case has been discussed by the surgeon and the radiation oncologist, amongst others, at such a meeting. Reassurance that the best plan has been made for them on an individual basis fosters trust between the patient and their treating team.

The guideline development group, including patient representatives, believe that informed patients may prefer axillary radiotherapy to ALND based on the balance of benefits and harms, particularly in terms of the side effects of treatment. Logistical considerations are also important to patients, and the shorter treatment time and fewer appointments and surgeries associated with axillary radiotherapy (in comparison to ALND) may be preferable to many.

Resources, capacity, equity and other considerations

In comparison to axillary lymph node dissection, axillary radiotherapy should be resource saving. The resources required for ALND, such as hospital admittance, theatre time, etc. are saved when it is omitted in favour of axillary radiotherapy. While radiotherapy to the axilla may increase the complexity of radiotherapy planning for the radiotherapy team, the time slot required for radiotherapy treatment delivery and number of treatment sessions is the same whether the axilla is included in the target volume or not. Patients will already be undergoing radiotherapy to the breast or chest wall and regional nodes.

Recommendation 2.3.12.1

In patients with:

- early breast cancer (cT1 – 2)
- who have undergone upfront breast-conserving surgery or mastectomy
- and have had a positive sentinel lymph node biopsy (≤2 sentinel lymph nodes positive for macrometastases ± extracapsular extension)

axillary radiotherapy (as part of regional nodal irradiation) should be considered, avoiding axillary lymph node dissection.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.3.12.2

In patients with

- early breast cancer
- who have had a positive sentinel lymph node biopsy
- and do not meet the criteria listed in Recommendation 2.3.12.1

and are not proceeding to axillary lymph node dissection for a documented reason, axillary radiotherapy (as part of regional nodal irradiation) should be considered.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Good practice points

- Patients should be given sufficient time with a member of their medical team so the rationale for their treatment can be explained
- A physiotherapy referral should be considered for all patients
- Patients should be seen in appropriate survivorship clinics (dietetics, physiotherapy, etc.)

2023

2.3.13 Clinical question: In patients with node-positive breast cancer does the addition of radiation to the internal mammary chain improve oncological outcomes compared to breast/chest wall radiotherapy (+/- regional axilla) alone?

Evidence summary

There are four RCTs (Poortmans et al., 2015, 2020, Hennequin et al., 2013, Whelan et al., 2015, Kim et al., 2022) and one prospective cohort study (Thorsen et al., 2016, 2022) to address this question. Kim et al. (2022) and Hennequin et al. (2013) randomised patients to receive irradiation of the breast/chest wall and supraclavicular nodes with or without irradiation of the internal mammary chain. Thorsen et al. (2016) compared patients who had radiotherapy to the breast/chest wall, undissected axilla and supraclavicular fossa plus irradiation of the internal mammary chain to radiotherapy to breast/chest wall, undissected axilla and supraclavicular fossa alone. However, the study groups in Poortmans et al. (2015, 2020) received either irradiation of the whole breast/chest wall and the internal mammary chain plus the medial supraclavicular nodes or whole breast/chest wall irradiation alone, while Whelan et al. (2015) compared whole breast irradiation alone to irradiation of the whole breast plus the internal mammary, supraclavicular and axillary nodes.

Kim et al. (2022) showed a 3.4% improvement in 7-year disease-free survival rates in the internal mammary node irradiation (IMNI) group compared to those who did not receive IMNI, however this difference was not statistically significant (81.9% vs 85.3%; HR 0.80 (95% CI 0.57 – 1.14), log-rank p=0.22). Similarly, the group who received IMNI trended towards better outcomes for breast cancer mortality, distant metastasis-free survival and overall survival, however none were statistically significant. In a post hoc subgroup analysis by tumour location, 7-year disease-free survival was 91.8% in the IMNI group and 81.6% in the without IMNI group among patients with mediocentrally located tumours (HR 0.42 (95% CI 0.22 – 0.82), log-rank p=0.008). Breast cancer mortality at seven years was 10.2% without IMNI and 4.9% with IMNI (HR 0.41 (95% CI 0.17 – 0.99), log-rank p=0.04), and the distant metastasis-free survival (DMFS) at seven years was 82.3% without IMNI and 91.8% with IMNI (HR 0.44 (95% CI 0.23 – 0.85), log-rank p=0.01) among patients with mediocentrally located tumours. The insufficient patient numbers in this study limit the ability to detect small differences in outcomes between the study arms. Hennequin et al. (2013) did not show a benefit of internal mammary node irradiation to disease-free survival at ten years, though the authors of that study concede that it was underpowered to detect a slight increase in survival. Hennequin et al. (2013) showed a benefit to internal mammary chain irradiation on 10-year overall survival in

the group of patients who were node-positive and had centrally located tumours, however this was non-significant (although the study was underpowered).

Poortmans et al. (2015) and Whelan et al. (2015) both show that irradiation of the regional nodes confers a statistically significant benefit to disease-free survival at ten years. In a follow-up paper, reporting on outcomes at 15 years, Poortmans (2020) did not find a significant difference in disease-free survival between groups, however patients treated with internal mammary- and medial supraclavicular irradiation had a significantly lower mortality from breast cancer and lower rates of any breast cancer recurrence. Thorsen et al. (2016) reported 8-year overall survival rates of 75.9% (95% CI 73.6% – 78.0%) and 72.2% (95% CI 69.9% – 74.4%) for patients with or without internal mammary chain irradiation, respectively. The adjusted HR for death with versus without irradiation of the internal mammary chain was 0.82 (95% CI 0.72 – 0.94, p=0.005). At 15 years the survival rates were 60.1% (95% CI 57.5 – 62.6) and 55.4% (95% CI 52.8 – 57.9) with and without internal mammary chain irradiation, respectively. The adjusted HR for death was 0.86 (95% CI 0.77 – 0.96), p=0.007 in favour of internal mammary chain irradiation (Thorsen et al., 2022).

In an exploratory subgroup analysis, Thorsen et al. (2016) demonstrated that irradiation of the internal mammary chain reduced mortality in patients who had centrally/medially located tumours and/or had four or more positive nodes. When these subgroups (patients with centrally/medially located tumours, patients with 4 – 9 positive nodes, or patients with ≥10 positive nodes) were combined the adjusted HR for death with versus without irradiation of the internal mammary chain was 0.76 (95% CI 0.66 – 0.89, p=0.001), and the number of patients needed to treat to avoid one death at eight years was 14.

Benefits and harms

Based on the five studies included, and acknowledging their limitations and study design, the addition of internal mammary chain irradiation appears to improve disease-free survival.

Internal mammary chain irradiation increases the radiation dose to normal tissues, including the heart and lungs, which may result in increased toxicity. Poortmans et al. (2015) showed that the group who received regional nodal irradiation (internal mammary and medial supraclavicular nodes) had significantly more pulmonary fibrosis and cardiac fibrosis after 10 years than the group who received whole breast/chest wall irradiation alone. In the same trial, after 15 years, the group who received regional nodal irradiation continued to have a higher incidence of pulmonary and cardiac fibrosis (Poortmans et al., 2020). Whelan et al. (2015) showed that grade 4 adverse events were rare, and no grade 5 events occurred. In their study, nodal irradiation was associated with increased rates of radiation

dermatitis, and pneumonitis, while late effects were increased rates of lymphoedema, subcutaneous fibrosis (hardening of the skin and soft tissues), and poor cosmetic outcomes such as telangiectasia (prominent blood vessels on the skin). Kim et al. (2022) found no difference in the toxic effects between groups treated with or without internal mammary chain irradiation (though the authors note that their study population size is insufficient to detect small differences).

These trials were carried out at a time before current techniques (such as Deep Inspiration Breath Hold (DIBH) and IMRT) were employed. These techniques reduce the dose to the heart and lungs which may reduce the risk of late cardiac complications.

Preferences and values

Due to the greater survival benefit associated with internal mammary chain irradiation for some patients, this treatment may be preferable. The main considerations most patients have as regards their treatment are: to maximise survival and minimise the risk of recurrence of their cancer; to minimise the side effects involved; and to minimise the time and burden of treatment.
Individual patients may prioritise these concerns differently.

Resources, capacity, equity and other considerations

Time to deliver radiotherapy may increase per patient when the internal mammary chain is irradiated depending on the technique used. Radiation of the internal mammary chain cannot be delivered in all centres in the same way due to differences in radiation techniques available.

Geography and travel may be a barrier to delivery of internal mammary chain irradiation. Advanced technologies and the national plan for radiation oncology will facilitate delivery at all sites.

Recommendation 2.3.13.1

In patients with N2 – 3 breast cancer at diagnosis radiation of the internal mammary chain is recommended.

Quality of evidence: High **Grade of recommendation: Strong**

Recommendation 2.3.13.2

In patients with N1 breast cancer at diagnosis and a central or medial tumour or multiple adverse factors, internal mammary chain irradiation should be considered.

Quality of evidence: Moderate **Grade of recommendation: Strong**

Good practice points

- Consider deep inspiration breath hold and advanced planning techniques to optimise coverage, meet normal tissue constraints and minimise toxicity.

2023

2.3.14 Clinical question: In patients with left-sided breast cancer does deep inspiration breath hold reduce predicted risk of cardio-toxicity?

Evidence summary

The evidence to address this questions is based on retrospective studies (Lin et al., 2019, Simonetto et al., 2019, Swanson et al., 2013) , and a meta-analysis of retrospective data (Lai et al., 2020). The patient population is generalizable to the population of relevance to this guideline.

In a study of the risk of ischemic heart disease following radiotherapy for breast cancer, Darby et al. (2013) revealed that with each increase of 1 Gy there is a corresponding increase of 7.4% in the risk of cardiotoxicity. The results of the studies examined here showed that Deep Inspiration Breath Hold (DIBH) consistently reduced the mean heart dose to less than 2 Gy.

All of the studies were consistent in their findings that DIBH reduced the mean heart dose and cardio-toxicity. The meta-analysis by Lai et al. (2020) included twelve studies and had 1019 patients. While the results of the studies are generalizable, the earlier studies may have underestimated the effect of the technique as the technology and techniques for DIBH have improved over recent years.

There is an absence of long-term studies available to show the clinical outcomes of using DIBH.

Benefits and harms

Any radiation exposure to the heart may be harmful and should be avoided if possible with cardiac sparing techniques such as DIBH. DIBH is an effective lung sparing technique, particularly when irradiating the internal mammary chain.

Not every patient with left-sided breast cancer will benefit from DIBH.

Patients may struggle with the technique which can cause additional stress and anxiety. Patients who cannot hold their breath during coaching are excluded from DIBH, causing anxiety as they perceive this as negatively affecting their treatment.

Treatment may need to be converted from DIBH to free breathing due to patient factors mid-way through treatment, which may cause anxiety and other psychological impacts.

Preferences and values

Patient preference around choosing DIBH is driven by peace of mind around side effects of treatment.

Resources, capacity, equity and other considerations

Capacity may not allow use of DIBH on every patient. Using a DIBH technique impacts on capacity in radiation oncology treatment as it takes longer to complete the treatment (20 minutes for DIBH vs 15 minutes free breathing techniques). Treatment planning also requires an additional coaching session with the patient.

Training for radiation therapists, in scanning, coaching and treating patients, is required to ensure the skill mix to carry out the technique.

Recommendation 2.3.14.1

In patients with left-sided breast cancer deep inspiration breath hold should be considered as a cardiac-sparing technique.

Quality of evidence: Low **Grade of recommendation: Strong**

Good practice points

- It is important to communicate to the patient that DIBH is just one technique to reduce the cardiac dose and that an optimal radiotherapy plan can be done without using DIBH.
- In patients with left-sided breast cancer not undergoing DIBH other cardiac-sparing techniques are recommended.
- Coaching in DIBH is essential and it is important that a patient can hold their breath for approximately 20 seconds before commencing DIBH.

Practical considerations for patient care

- Try to minimise the number and length of each breath hold for each patient.
- Reassure the patient that if they have difficulty maintaining a breath hold in their radiotherapy session that the machine will be switched off.

2023

2.3.15 Clinical question: In patients who have undergone surgery for breast cancer, what evidence is there that time from final surgery to starting a first adjuvant radiotherapy influences outcomes?

2015 Evidence statement

There were no randomised trials identified comparing different time intervals between surgery and commencement of radiotherapy. Current guidelines (Cancer Care Ontario, 2011), two systematic reviews (Huang et al., 2003, Chen et al., 2008) and three retrospective studies (Livi et al., 2009, Olivotto et al., 2009, Hershman et al., 2006) addressed this question. However, none of these produced strong evidence to support the recommendation.

A systematic review by Chen et al. (2008) identified 44 relevant studies of which 24 were for breast cancer. A meta-analysis of 11 high quality studies of local control in breast cancer demonstrated a significant increase in the risk of local failure with increasing waiting time ($RR_{\text{local recurrence/month}}$=1.11, 95% CI 1.04 – 1.19). There was little evidence of any association between waiting time and risk of distant metastasis or survival. (Chen et al., 2008)

In a second systematic review, Huang et al. (2003) showed that the 5-year local recurrence rate was significantly higher in patients commencing adjuvant radiotherapy more than eight weeks after surgery when compared with those treated within eight weeks of surgery (odds ratio (OR)=1.62, 95% CI 1.21 – 2.16). Both authors conclude that delays in starting adjuvant radiotherapy should be as short as reasonably achievable.

In a retrospective Canadian study (Olivotto et al., 2009), women commencing radiotherapy more than 20 weeks after BCS had inferior distant recurrence free survival and breast cancer specific survival when compared to women commencing adjuvant radiotherapy within four to eight weeks of surgery. Outcomes were statistically similar for surgery-to-RT intervals up to 20 weeks, but there were inferior for intervals beyond 20 weeks.

Multivariate analysis of retrospective data has demonstrated that local recurrence is mainly related to prognostic factors such as age at presentation, surgical margin status and the use of a radiotherapy boost, rather than the timing of radiotherapy (Livi et al., 2009). For women treated with adjuvant radiotherapy alone (n=1,935) or with adjuvant radiotherapy and hormonal therapy (n=1,684), timing of radiotherapy had no impact on local recurrence rates. Only in the group of patients treated with adjuvant radiotherapy and chemotherapy (n=672) did multivariate analysis show

radiotherapy timing as an independent prognostic factor (HR 1.59 (95% CI 1.01 – 2.52), p=0.045). Analysing this group of patients, the authors found that most patients included had worse prognostic factors and had received chemotherapy consisting of cyclophosphamide, methotrexate, and 5-fluorouracil before undergoing radiotherapy. (Livi et al., 2009)

Hershman et al. (2006) conducted a retrospective study using Surveillance, Epidemiology, and End Results (SEER) data for women over 65 years of age not receiving chemotherapy. Early initiation of radiotherapy was not associated with survival. Although delays of more than 3 months were uncommon, they were associated with poor survival. It was not possible to say whether this association is causal or due to confounding factors, such as poor health behaviours and the authors suggest initiating radiotherapy in a timely fashion until further data becomes available.

Data from the four randomised trials comparing radiation versus no radiation following BCS (Fisher et al., 1995, Liljegren et al., 1994, Clark et al., 1992, Veronesi et al., 1993), six randomised trials comparing lumpectomy plus radiation versus mastectomy, two large cohort studies, an ongoing randomised trial of chemotherapy followed by radiotherapy versus radiotherapy followed by chemotherapy, and five cohort studies examining the effect of the sequencing of chemotherapy and radiotherapy were reviewed. Based on the available evidence, the maximum interval between surgery and commencement of radiotherapy was defined as 12 weeks. (Cancer Care Ontario, 2011)

2023 Updates to the evidence statement

Three additional retrospective cohort studies address this question (Ma et al., 2021, Raphael et al., 2020, Vujovic et al., 2015). None of these additional studies provides any high level evidence regarding the optimal time interval between final surgery to starting radiotherapy. All studies had multiple confounding factors and small patient numbers.

Ma et al. (2021) showed that for patients who did not receive chemotherapy (n = 402), disease-free survival was significantly worse in the group with delayed initiation of radiotherapy after surgery (>69 days) (p=0.003), but there was no difference in ipsilateral breast tumour recurrence, locoregional failure or overall survival. Of these 402 patients, only 50 patients had a delayed initiation of radiotherapy, therefore this study may be underpowered to show a difference in outcomes between the two groups if there is one.

After seven years follow-up, in a retrospective analysis of 599 women who received radiotherapy alone after breast-conserving surgery, on multivariable analysis Raphael et al. (2020) found that a waiting time of 12 weeks or more was associated

with worse event-free survival, though this was non-significant (HR 1.44, 95% CI 0.98 – 2.11, p=0.07), a fact that the authors attributed to the study being under-powered.

In a study of 566 patients, where timing of surgery to radiotherapy was analysed in four time-interval categories ranging from 0 to >16 weeks, Vujovic et al. (2015) found no statistically significant differences between the four time interval categories with respect to either local recurrence or disease-free survival despite a median follow-up time of more than 17 years.

Recommendation 2.3.15.1

Women who have undergone surgery for breast cancer should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of surgery.

Grade of recommendation: C

Good practice points

- This recommendation should not be applied to women who have undergone neoadjuvant chemotherapy.
- For high-risk patients, such as those who have undergone neoadjuvant chemotherapy, a timeframe of less than eight weeks may be considered (see KATHERINE study protocol NCT01772472).

2.4 Plain language summary

Summary of National Clinical Guideline

This National Clinical Guideline gives evidence-based recommendations on using radiotherapy to treat people with breast cancer. Radiotherapy reduces the risk of cancer coming back.

This guideline helps healthcare professionals decide how to use radiotherapy to treat people with breast cancer based on each person's specific case. It aims to optimise patient outcomes and ensure care is based on the best evidence available. The guideline covers:

- Who may benefit from radiotherapy
- What parts of the breast and nearby areas should be treated with radiotherapy
- How much radiotherapy to give and how many treatment sessions are needed
- How to reduce the risk of side effects from radiotherapy
- When to start radiotherapy

This guideline does not cover other breast cancer treatments like surgery or chemotherapy.

What does this guideline mean for you?

Questions you may want to ask your healthcare professionals?

- What are the benefits and risks of the treatment you are advising me to have?
- What are the risks if I decide to do nothing for the time being?
- How long will I have to wait before starting treatment?
- If there is a delay in starting my treatment, how will this affect my outcome?
- What will the treatment be like and how long will it take?
- Will I need to have someone with me?
- What are the side effects, when will they appear, and how long will they last?
- Will I need to take any special precautions, for example with my skincare?
- How can I expect to feel after treatment?
- Will radiotherapy affect my regular activities, for example work, exercise or driving?
- Who should I contact if I have questions or concerns either during my treatment or after it has finished?
- Will I be able to have reconstructive surgery after my radiotherapy (if applicable)?

Understanding the language

Medical Term	Plain language explanation
Adverse effect	An undesired effect of radiotherapy or a drug or other type of treatment, such as surgery. Adverse effects can range from mild to severe and can be life-threatening. Also called adverse event and adverse reaction.
Axillary lymph node dissection	Surgery to remove the lymph nodes found in the armpit region, also called axillary dissection.
Breast-conserving surgery	Surgery to remove cancer or other abnormal tissue from part of the breast and some normal tissue around it, but not whole breast.
Ductal carcinoma in situ (DCIS)	A condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, ductal carcinoma in situ may become invasive breast cancer and spread to other tissues. At this time, there is no way to know which abnormal cells could become invasive.
Fractionation	A way of dividing the total dose of radiation into separate doses.
Mastectomy	Surgery to remove the breast.
Radiotherapy	The use of high-energy radiation to kill cancer cells. Also called irradiation and radiation therapy.
Radiotherapy boost	An extra amount of radiotherapy targeted at the area in the breast where the cancer was removed.
Sentinel lymph node	The first lymph node to which cancer is likely to spread from the primary tumour. When cancer spreads, the cancer cells may appear first in the sentinel node before spreading to other lymph nodes.

3 Methodology

3.1 Establishment of a guideline development group

A guideline development group was responsible for the development and delivery of this National Clinical Guideline and included representatives from relevant medical professionals and stakeholders (see Appendix I for a list of the members of the guideline development group).

3.2 List of clinical questions

Br_RO_253_2015

In breast cancer patients who have undergone breast-conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome?

Population	Patients with invasive breast cancer who have undergone breast conservation surgery
Intervention	Radiotherapy
Control	No radiotherapy
Outcome	Locoregional recurrence; Overall survival; Disease-free survival; Cosmesis; Toxicity; Cost effectiveness

Br_RO_254_2015

In otherwise healthy breast cancer patients who have undergone breast-conserving surgery, are there any sub populations in terms of age, tumour size and nodal involvement where radiotherapy is not necessary?

Population	Otherwise healthy breast cancer patients who have undergone breast-conserving treatment
Intervention	Radiotherapy (any dose/cycle)
Control	No radiotherapy
Outcome	Locoregional recurrence; Disease-free survival; Overall Survival; Cosmesis; Toxicity; Number of mastectomies

Br_RO_PBI_2024

In patients with early breast cancer who have undergone breast-conserving surgery does partial breast irradiation compared to whole breast irradiation provide equal oncological outcomes?

Population	Patients with early breast cancer who have undergone breast-conserving surgery
Intervention	Partial breast irradiation
Control	Whole breast irradiation
Outcome	Local recurrence

Br_RO3_2019

In patients with breast cancer who have undergone breast-conserving surgery does hypofractionation compared to standard fractionation provide equivalent oncological outcomes?

Population	Patients who have undergone breast-conserving surgery
Intervention	Adjuvant hypofractionated radiotherapy
Control	Adjuvant conventionally fractionated radiotherapy
Outcome	Breast cancer recurrence, acute and late radiotherapy related effects

Br_RO_255_2015

In patients with breast cancer who have undergone breast-conserving surgery, what is the evidence that a radiotherapy boost improves outcome?

Population	Patients with invasive breast cancer who have undergone breast conservation surgery
Intervention	Radiotherapy boost (aimed at tumour bed with or without the use of clips)
Control	No radiotherapy boost
Outcome	Locoregional recurrence; Overall survival; Disease-free survival; Cosmesis; Toxicity; Cost effectiveness

Br_RO6_2022

For patients with early breast cancer receiving a radiotherapy boost, how does simultaneous integrated boost compare with sequential boost in terms of toxicity and efficacy?

Population	Patients with early breast cancer
Intervention	Simultaneous integrated boost
Control	Sequential boost
Outcome	Toxicity, Ipsilateral breast tumour recurrence

Br_RO_252_2015

In patients with DCIS who have undergone breast-conserving surgery, what is the evidence that adjuvant radiotherapy improves outcome?

Population	Patients with DCIS treated with breast-conserving surgery
Intervention	Radiotherapy (any dose/cycle)
Control	No radiotherapy
Outcome	Locoregional recurrence; Overall survival; Toxicity; Quality of life; Cost effectiveness

Br_RO_DCIS_2024

In patients with ductal carcinoma in situ (DCIS) does ultrahypofractionated radiotherapy compared to moderately hypofractionated radiotherapy provide equivalent oncological outcomes?

Population	Patients with ductal carcinoma in situ (DCIS)
Intervention	Ultrahypofractionated radiotherapy
Control	Moderately hypofractionated radiotherapy
Outcome	Locoregional recurrence

Br_RO5_2019

In patients with ductal carcinoma in situ (DCIS) who have undergone breast-conserving surgery does radiotherapy boost improve rates of local recurrence compared with no radiotherapy boost?

Population	Patients with ductal carcinoma in situ (DCIS) who have undergone breast-conserving surgery
Intervention	Boost
Control	No boost
Outcome	Local recurrence, overall survival, toxicity

Br_RO_251_2015

In patients who have undergone a mastectomy for breast cancer, what is the evidence that radiotherapy to the chest wall improves outcome?

Population	Patients with breast cancer treated surgically with mastectomy and axillary staging
Intervention	Chest wall radiotherapy +/- regional nodal radiotherapy (any dose/cycle)
Control	No radiotherapy
Outcome	Locoregional recurrence >2 months; Breast cancer specific survival 5 yrs, 10 yrs; Disease-free survival 5 yrs, 10 yrs; Non breast cancer survival 5 yrs, 10 yrs; Overall survival 5 yrs, 10 yrs; Toxicity; Cost effectiveness

Br_RO4_2019

In patients with breast cancer who have undergone mastectomy does radiotherapy boost improve rates of local recurrence compared with no radiotherapy boost?

Population	Patients with breast cancer who have undergone mastectomy
Intervention	Boost
Control	No boost
Outcome	Rate of local recurrence, survival, morbidity, quality of life

Br_RO_RNI_2024

In patients with early stage breast cancer who have had a positive sentinel lymph node biopsy, how does regional nodal radiotherapy compare with axillary lymph node dissection in terms of local recurrence, overall survival, lymphoedema, and quality of life?

Population	Women with early stage breast cancer who have had a positive sentinel lymph node biopsy
Intervention	Regional nodal radiotherapy
Control	Axillary lymph node dissection
Outcome	Locoregional recurrence, overall survival, lymphoedema, quality of life

Br_RO1_2019

In patients with node-positive breast cancer does the addition of radiation to the internal mammary chain improve oncological outcomes compared to breast wall radiotherapy (+/- regional axilla) alone?

Population	Patients with node-positive breast cancer (subpopulations?)
Intervention	Additional radiation of the internal mammary chain
Control	No radiation
Outcome	Oncological outcomes, overall survival, local recurrence, distal recurrence

Br_RO2_2019

In patients with left-sided breast cancer does deep inspiration breath hold reduce predicted risk of cardio-toxicity?

Population	Patients with left sided breast cancer
Intervention	Deep inspiration breath hold (DIBH)
Control	No deep inspiration breath hold
Outcome	Reduced predicted risk of cardio-toxicity

Br_RO_256_2015

In patients who have undergone surgery for breast cancer, what evidence is there that time from final surgery to starting a first adjuvant radiation therapy influences outcome?

Population	Patients who have undergone surgery for breast cancer
Intervention	Time to adjuvant radiation therapy (any accepted regimen)
Control	
Outcome	Local recurrence; Overall survival; Disease-free survival; Regional recurrence; Cost effectiveness

3.3 Describe and document the evidence search

Clinical questions and their corresponding recommendations are marked to indicate the year of the last evidence review.

All (twelve) clinical questions were retained from the 2023 guideline. An updated evidence search was carried out for one of these (see section 2.3.6). Three additional clinical questions were developed and a separate evidence search conducted for each one (see sections 2.3.3, 2.3.8, 2.3.12).

A systematic literature review protocol, developed for the guideline development process by the HSE librarians in conjunction with the NCCP, was used and is available upon request. The literature search strategies for each clinical question are also available upon request.

3.4 Describe the method of screening and evidence appraisal

An NCCP senior research officer and at least one other researcher and/or Specialist Registrar screened the literature searches independently to identify relevant primary papers. Any disagreements on primary paper inclusion were agreed through discussion.

All primary papers deemed suitable for inclusion were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

There were three main points considered when appraising the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of the guideline? (external validity)

3.5 Formulation and grading of recommendations

The evidence to address the clinical questions, both from primary literature and international guidelines, was extracted into evidence tables for review by the guideline development group.

Recommendations were formulated through a formal structured process. An 'Evidence to Decision Framework' was completed for each clinical question. The following domains were discussed by the guideline development group for new and updated clinical questions:

Evidence summary

The body of evidence was reviewed and discussed taking into account the types of studies available, the quality of those studies and their degree of bias, the precision of the results, and whether all studies were consistent in their findings. The directness of the evidence and generalisability to the target population were also considered.

Benefit and harm

The balance of potential benefits versus potential harms of the proposed recommendations were considered.

Preferences and values

The preferences and values of the patient were discussed and considered, noting particularly the acceptability of the proposed recommendations to patients and their carers' in the context of the balance of benefits and harms.

Resources, capacity, equity and other considerations
Any factors which may affect the implementation of the proposed recommendations were discussed and documented. Potential issues around equity was explicitly considered.

Recommendation

Following discussion on the four domains above the recommendations were agreed by the guideline development group. The following terms were considered for use in recommendations:

- is recommended
- should be considered
- may be considered
- is not recommended.

The use of these terms are dependent on all four domains outlined above. Each recommendation was assigned a quality of evidence and a grade of recommendation by the guideline development group. Good practice points and practical considerations for patient care were also agreed by the guideline development group. Further information on the grading systems used are documented in Appendix III. Note that the original grading system has been maintained for all clinical questions retained from the 2015 guideline.

3.6 Consultation

National review

The draft guideline was signed-off by the guideline development group before going to national stakeholder review.

It was placed on the NCCP website and circulated to relevant organisations and individuals for comment between [date month] and [date month year].

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided along with a completed conflict of interest form.

International review

The draft guideline was also submitted for international expert review. The guideline development nominated the following experts to provide feedback on the draft guideline:

- [insert name, title, and location of all international reviewers]

The reviewers were chosen by the guideline development group based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the National Review.

All feedback received was reviewed by the guideline development group. Suggested amendments and supporting evidence were reviewed and consensus reached to accept or reject the amendments. All modifications were documented and the report is available upon request.

3.7 National implementation plan

An implementation plan was developed based on the NCEC Implementation Guide (DoH, 2018). It outlines the actions required to implement this guideline, who has lead responsibility for delivering the action, the timeframe for completion and the expected outcomes of implementation (see Appendix IV).

This National Clinical Guideline including the implementation plan should be reviewed by the multidisciplinary team and senior management in each cancer centre/hospital as it outlines the actions required to implement the recommendations.

The CEO, General Manager and Clinical Lead of each cancer centre/hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline.

The National Clinical Guideline has been circulated and disseminated through the professional networks who participated in developing and reviewing this document.

3.8 Governance and approval

The final draft of the guideline was Quality Assured internally by a member of the NCCP Evidence and Quality Team to confirm adherence to the National Standards for Clinical Practice Guidance (Department of Health, 2015b).

The guideline, along with confirmation of the outcome of the Quality Assurance process, was then submitted to the NCCP National Executive on [date month year] for approval. A full list of the members can be found in Appendix II.

3.9 Communication and dissemination plan

This National Clinical Guideline is available on the HSE National Central Repository.

A Communication and Dissemination Plan was developed by the guideline development group to raise awareness of the development of this guideline, to ensure effective communication and collaboration with all key stakeholders

throughout the various stages of guideline development process and to maintain momentum for the widespread adoption of the guideline.

In conjunction with the HSE Communications Division, key stakeholders were identified and a list of strategies was developed to inform them of the new guideline. The implementation of the guideline will also be supported by communication and dissemination. Details of the Communication and Dissemination Plan are available in Appendix V.

3.10 Plan for national monitoring, evaluation and audit

Monitoring and evaluation

Each cancer centre/hospital should implement a systematic process of gathering information and tracking over time to achieve the objectives of this guideline.

The Breast Cancer Tumour Conference in each cancer centre/hospital should monitor the implementation of recommendations specific to their practice.

Audit

It is important that implementation of this National Clinical Guideline is audited to ensure that this guideline positively impacts patient care. Each cancer centre/hospital should audit implementation of this guideline at least annually.

A number of metrics were discussed by the guideline development group which could be used by cancer centres/hospitals to audit their compliance with the recommendations and assess any discrepancies between the guideline and clinical practice. Details available upon request by contacting guidelines@cancercontrol.ie.

3.11 Review/update

This guideline was issued on [date month year] and will be considered for review by the NCCP in three years.

Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period where new evidence emerges or as a result of three year review will be noted in the guidelines section of the NCCP websites.

4 Abbreviations

APBI	Accelerated partial breast irradiation
ANP	Advanced nurse practitioner
BCS	Breast-conserving surgery
CBC	Contralateral breast cancer
CI	Confidence interval
CNS	Clinical nurse specialist
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DIBH	Deep inspiration breath hold
DMFS	Distant metastasis-free survival
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
Gy	Gray
HIQA	Health Information and Quality Authority
HR	Hazard ratio
HSE	Health Service Executive
IBTR	Ipsilateral breast tumour recurrence
IGRT	Image guided radiotherapy
IORT	Intraoperative radiotherapy
IMNI	Internal mammary node irradiation
IMRT	Intensity modulated radiotherapy
LINAC	Linear accelerator
NCCP	National Cancer Control Programme
NCEC	National Clinical Effectiveness Committee
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Odds radio
OS	Overall survival
PMRT	Post-mastectomy radiotherapy
PBI	Partial breast irradiation

QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
RT	Radiotherapy/Radiation therapy
SE	Standard error
SeB	Sequential boost
SEER	Surveillance, epidemiology and end result
SIB	Simultaneous integrated boost
WBI	Whole breast irradiation

5 Glossary of Terms

Adjuvant therapy
Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiotherapy, hormone therapy, targeted therapy, or biological therapy.

Adverse effect
An undesired effect of a drug or other type of treatment, such as surgery. Adverse effects can range from mild to severe and can be life-threatening. Also called adverse event and adverse reaction

Axillary lymph node dissection
Surgery to remove the lymph nodes found in the armpit region. Also called axillary dissection.

Benefits and harms
Benefits refer to improved quality of life and reductions in mortality and morbidity. There are physical risks of harm such as exposure to radiation and there are also emotional and psychological risks of harm such as anxiety and depression.

Biopsy
The removal of cells or tissues for examination by a pathologist.

Brachytherapy
A type of radiotherapy in which radioactive implants, such as pellets, seeds, ribbons, wires, needles, balloons, or capsules, are placed in the body, directly into or near the tumour. The radiation is delivered through a flexible tube called a catheter or a larger device called an applicator. Brachytherapy is often used to treat cancers of the head and neck, breast, cervix, prostate, and eye. Depending on the type of cancer and treatment plan, the implant may be kept in place for a few minutes, many days, or permanently. Also called implant radiotherapy and radiation brachytherapy.

Breast-conserving surgery
Surgery to remove cancer or other abnormal tissue from the breast and some normal tissue around it, but not the breast itself. Some lymph nodes under the arm may be removed for biopsy. Part of the chest wall lining may also be removed if the cancer is near it. Also called breast-sparing surgery, lumpectomy, partial mastectomy, quadrantectomy, and segmental mastectomy.

Cohort study
The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed,

or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels.

Confidence intervals
Confidence intervals indicate the consistency, or variability of a result. If a study has 95% confidence interval calculated, this means that if the study was repeated multiple times with samples from the whole population and the confidence intervals were calculated for each of those repeated studies, then the true value would lie within the calculated confidence intervals 95% of the time.

Deep inspiration breath hold (DIBH)
Deep inspiration breath hold radiotherapy is external beam radiotherapy that is delivered while the breath is held in comfortable inspiration. It is mainly used where there is need to reduce the amount of normal tissue that receives radiation.

Ductal carcinoma in situ (DCIS)
A condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, ductal carcinoma in situ may become invasive breast cancer and spread to other tissues. At this time, there is no way to know which abnormal cells could become invasive. Also called DCIS and intraductal breast carcinoma.

External beam radiotherapy
A type of radiotherapy that uses a machine outside the body to send high-energy radiation beams toward the area of the body with cancer. It is used to treat many types of cancer. It may also be used to shrink tumours to treat pain and other problems caused by the tumour, such as trouble breathing or loss of bowel and bladder control. Also called external radiotherapy.

Fractionation
A way of dividing the total dose of radiation into separate doses.

Hazard ratio
A measure of how often a particular event happens in one group compared to how often it happens in another group, over time.

Induration
Hardening or thickening of the skin.

Intraoperative radiotherapy (IORT)
Radiation treatment aimed directly at a tumour during surgery.

Ipsilateral
On the same side of the body as another structure or a given point.

Locoregional
An occurrence that is limited to a certain part of the body or a narrowly-defined body region.

Mastectomy
Surgery to remove part or all of the breast. There are different types of mastectomy that differ in the amount of tissue and lymph nodes removed.

Meta-analysis
A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself.

Multidisciplinary meetings (MDM)/ Multidisciplinary team (MDT)
Multidisciplinary meetings (MDMs) play an essential part in the management of many diseases, including cancer. At a cancer MDM, the relevant specialists discuss each patient's clinical presentation, radiological (scans/ imaging), histopathological (examination of tissue or surgical specimen) and other relevant findings, to draw up an appropriate individual treatment plan based on current best practices. To ensure that the MDM process is safe and effective, the patient and all their relevant data need to be discussed by the appropriate professionals. An agreed care plan must then be recorded, communicated and put in place. This requires the allocation of clearly defined roles and responsibilities to key members of the multidisciplinary team (MDT).

Non-inferiority trial
A study that tests whether a new treatment is not worse than an active treatment it is being compared to. Non-inferiority trials are sometimes done when a placebo (an inactive treatment) cannot be used. These trials may show that a new treatment (such as a drug) is not worse than the active treatment being compared, and it may be safer and easier to take or cause fewer side effects.

Quality of evidence
The extent to which one can be confident that an estimate of effect is correct.

Randomised trial
An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups.

Sentinel lymph node biopsy
A sentinel lymph node biopsy (SLNB) is a procedure in which the sentinel lymph node is identified, removed, and examined to determine whether cancer cells are present.

Strength of a recommendation
The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

Telangiectasia
Small, widened blood vessels near the surface of the skin. Also known as spider veins.

Toxicity
The extent to which something is poisonous or harmful.

Tumour conference
Also known as multidisciplinary team (MDT) meetings. A tumour conference involves a group of people from different healthcare disciplines, who meet together at a given time (whether physically in one place or by video or teleconferencing) to discuss a given patient and who are each able to contribute independently to the discussion on diagnosis and to make recommendations on patient management. It provides a forum for multidisciplinary teams to regularly convene and discuss the diagnosis and management of cancer patients.

6 Appendices

Appendix I Members of the guideline development group

A conflict of interest form was signed by all members of the guideline development group. No conflicts of interest were declared.

Members of the 2025 guideline development group

Name	Title/position	Role
Co-chairs of the guideline development group		
Prof. Frances Duane	Consultant Radiation Oncologist, St Luke's Radiation Oncology Network	Clinical chair and writing member
Dr Eve O'Toole	Head of Evidence and Quality Hub, National Cancer Control Programme	Evidence chair and writing member
Patient/Service user partners		
Dr Claire O'Brien	Patient and public partner	Writing member
Ms Kathleen O'Connor	Patient and public partner	Writing member
Radiation oncology		
Prof. Aisling Barry	Consultant Radiation Oncologist, Cork University Hospital	Writing member
Dr Joseph Martin	Consultant Radiation Oncologist, Galway University Hospital	Writing member
Prof. Orla McArdle	Consultant Radiation Oncologist, St Luke's Radiation Oncology Network	Writing member
Dr Kathy Rock	Consultant Radiation Oncologist, Bons Secours Cork	Writing member
Dr Sinéad Cleary	Specialist Registrar	Writing member
Dr Elaine Quinlan	Specialist Registrar	Writing member
Dr Eva Ruane	Specialist Registrar	Writing member
Surgery		
Ms Shona Tormey	Consultant Surgeon, University Hospital Limerick	Writing member
Radiation therapy		
Mr Stephen Coyne	Radiation Therapy Services Manager, Galway University Hospital	Writing member
Ms Sarah Downey	Radiation Therapist, University of Pittsburgh Medical Centre, Waterford	Writing member
Ms Claire Harman	Radiation Therapist, Cork University Hospital	Writing member
Ms Ruth Woods	Radiation Therapy Services Manager, St Luke's Radiation Oncology Network	Writing member
Medical physics		
Mr Conor Heeney	Chief Physicist, MWROC	Writing member
Mr Aodh MacGairbhith	Medical Physicist, St Luke's Radiation Oncology Network	Writing member
Nursing		
Ms Leonie Brady	Clinical Nurse Specialist, St Luke's Radiation Oncology Network	Writing member

Ms Fiona Liston	Clinical Nurse Specialist, St Luke's Radiation Oncology Network	Writing member
Ms Elaine Richardson	Clinical Nurse Specialist, St James's Hospital	
Evidence		
Mr Paul Flood	Research Officer, National Cancer Control Programme	Writing member
Ms Linda Halton	HSE Librarian	Information services
Dr Niamh Kilgallen	Senior Research Officer, National Cancer Control Programme	Researcher, project manager and writing member
Mr Gethin White	HSE Librarian	Information services
Other/NCCP		
Ms Evelyn O'Shea	Programme Manager, Radiation Oncology, National Cancer Control Programme	Programme manager and writing member

Members of the 2023 guideline development group

Name	Title/position	Role
Chair of the guideline development group		
Dr Eve O'Toole	Head of Evidence and Quality Hub, National Cancer Control Programme	Chair and writing member
Radiation oncology		
Prof. Frances Duane	Consultant Radiation Oncologist, St Luke's Radiation Oncology Network	Writing member
Dr Aileen Flavin	Consultant Radiation Oncologist, Cork University Hospital	Writing member
Prof. Orla McArdle	Consultant Radiation Oncologist, St Luke's Radiation Oncology Network	Writing member
Dr Carol McGibney	Consultant Radiation Oncologist, Cork University Hospital	Writing member
Dr Kathy Rock	Consultant Radiation Oncologist, Cork University Hospital	Writing member
Dr Orla Houlihan	Specialist Registrar	Writing member
Dr Jana McHugh	Specialist Registrar	Writing member
Dr Orla Monaghan	Specialist Registrar	Writing member
Dr Killian Nugent	Specialist Registrar	Writing member
Dr Hannah O'Driscoll	Specialist Registrar	Writing member
Dr Neil Wallace	Specialist Registrar	Writing member
Radiation therapy		
Mr Stephen Coyne	Radiation Therapy Services Manager, Galway University Hospital	Writing member
Medical physics		
Prof. Brendan McClean	Director of Physics, St Luke's Radiation Oncology Network	Writing member
Nursing		
Ms Fiona Liston	Clinical Nurse Specialist, St Luke's Radiation Oncology Network	Writing member
Ms Elaine Richardson	Clinical Nurse Specialist, St James's Hospital	Writing member

Evidence		
Ms Marie Carrigan	HSE Librarian, St Luke's Radiation Oncology Network	Information services
Ms Linda Halton	HSE Librarian	Information services
Dr Niamh Kilgallen	Senior Research Officer, National Cancer Control Programme	Researcher, project manager and writing member
Ms Julia Reynolds	HSE Librarian	Information services
Me Gethin White	HSE Librarian	Information services
Other/NCCP		
Ms Ruth Ryan	Programme Manager, Radiation Oncology, National Cancer Control Programme	Programme manager and writing member

The following people participated in the Patient Focus Group (October 2022):

Name	Role
Ms Aisling Downey	Patient and public partner
Ms Fiona McEntee	Patient and public partner
Ms Kathleen O'Connor	Patient and public partner
Ms Doris O'Toole	Patient and public partner
Prof. Fran Duane	Clinical Facilitator
Dr Orla McArdle	Clinical Facilitator
Dr Niamh Kilgallen	Evidence Facilitator
Ms Deirdre Love	Evidence Facilitator
Dr Eve O'Toole	Moderator

The following people also contributed to the development of this guideline:

- Prof. Clare Faul, Consultant Radiation Oncologist, St Luke's Radiation Oncology Network
- Prof. Colm Power, Consultant Surgeon, Beaumont Hospital
- Dr Guhan Rangaswamy, Clinical Tutor, Radiation Oncology, St Luke's Radiation Oncology Network

The NCCP would like to acknowledge the guideline development group responsible for the development of 'National Clinical Guideline No. 7 Diagnosis, staging and treatment of patients with breast cancer' in 2015, on which this guideline is based. A list of members of the guideline development group for that guideline is available upon request.

Appendix II Membership of NCCP National Executive

Name	Role and position

Sign-off by Chair of Approval Governance Group

National Clinical Guideline: [insert title] was formally ratified and recorded in the minutes of the Approval Governance Group on [date month year].

Name:	
Title:	
Signature:	

Appendix III Grading the recommendations in this guideline

2023/2025 levels of evidence and grading system

The guideline development group assigned each recommendation a quality of evidence and grade of recommendation. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides an explicit system for rating the quality of evidence and whether the recommendation is strong or weak/conditional (Guyatt et al., 2008).

Quality of evidence

It is recognised in guideline development that just assessing the level of evidence does not take into account the methodological quality of each individual study or the quality of the body of evidence as a whole (Harbour and Miller, 2001). The guideline development group used an amended GRADE system which considers the following factors when classifying the quality of evidence; high, moderate or low (Guyatt et al., 2008):

- Study design
- Study design limitations
- Consistency of results
- Directness of the evidence
- Imprecision of results
- Reporting bias

Table i: Quality of evidence adapted from GRADE working group 2013

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Grade of recommendation

There are two grades of recommendation: strong or weak/conditional. These reflects the balance of the following items:

- The quality of the body of evidence
- The balance between benefit and harm to patient
- Patient preferences and values
- Resources/cost

Table ii: Grade of recommendation adapted from GRADE working group 2013

Strong	A strong recommendation is one for which the guideline development group is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). Strong recommendations are not necessarily high priority recommendations. A strong recommendation implies that most or all individuals will be best served by the recommended course of action.
Weak/Conditional	A weak or conditional recommendation is one for which the desirable effects probably outweighs the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak or conditional recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's circumstances, preferences, and values. When there are weak or conditional recommendations caregivers need to allocate more time to shared decision-making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.

Good practice points

Good practice points were based on the clinical expertise of the guideline development group.

Practical considerations for patient care

Practical considerations for patient care are statements developed with the patients that were involved in the development of the guideline on issues that were important to them in relation to their own experience of the diagnosis and staging of their breast cancer.

2015 grade of recommendations

For clinical questions and recommendations that have been retained from the 2015 guideline the following grades of recommendation apply:

Table iii: Levels of evidence for interventional studies for recommendations that have been retained from the 2015 guideline (Scottish Intercollegiate Guideline Network [SIGN], 2011)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias .
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

Table iv: Grades of recommendations for interventional studies for recommendations that have been retained from the 2015 guideline (Scottish Intercollegiate Guideline Network [SIGN], 2011)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as2++.
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

Appendix IV National Implementation Plan

National Clinical Guideline	[insert title]
Date National Clinical Guideline approved	[date month year]
Expected date of full implementation	[year]

Implementation action	Implementation barriers / enablers	List of tasks to implement the action	Lead responsibility for delivery of the action	Expected completion date	Expected outcomes
	Enabler: Barrier:				

Appendix V Communication & Dissemination Plan

Key stakeholders were identified by the guideline development group and in conjunction with the HSE Communications Division, a list of strategies was developed to inform these stakeholders of the new guideline. Some strategies will include:

- Official publication and launch of the guideline.
- Direct communication from NCCP Director to hospital and cancer network managers raising awareness and setting out expectations/actions.
- Circulation to the networks who participated in developing and reviewing the guideline.
- Circulation to NCCP staff.
- Liaison with HSE Clinical Programmes, academic faculties and professional bodies for dissemination to their members.
- Inform the relevant voluntary organisations and patient advocacy groups that the guideline has been updated and is available for representation in their patient and public information.
- Promotion through the HSE/NCCP website, internal HSE media, social and print media.
- NCCP to include details of the guideline in presentations by clinical leads, sub-group chairs, NCCP Director.
- NCCP to promote the guideline at conferences, workshops, and CPD sessions.

A plain language summary of the guideline is included as a key element of the Communication and Dissemination Plan - for patients, their families and other non-specialists who may be interested in the potential implications of the recommendations within the guideline and what it may mean for them.

Description of stakeholder communications	Communication method	Owner	Timeline
Patients			
Plain language summary	Guideline	Project team	Pre 'go live'
Guideline development group			
New guideline alert	Email	Project team	Pre 'go live'
National stakeholders			
New guideline to Hospital Managers/Cancer Network Managers	Email	National Director, NCCP	Pre 'go live'
New guideline to relevant stakeholders (incl. National groups, organisations,	Email	Project team	Pre 'go live'

faculties, patient support & advocacy groups, international reviewers)			
New guideline to NCCP staff	Email	Project team	Pre ‘go live’
Press Release (HSE website)	Article	Project team/HSE Comms	Official launch
Social media coverage (Irish & English)	“X” posts	Project team	‘go live’ & official launch
News articles	Article	Project team/HSE Comms	Within 2 months of 'go live'

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