National Cancer Control Programme

DRAFT Treatment of Patients with Breast Cancer: Radiation Oncology

Draft National Clinical Guideline

XXXXXXX 2022

Table of contents

1 Membership of the Guideline Development Group

1.1 Core members

Name	Title/Position	Role on guideline group
Chair of the Guideline Development Group		
Dr Eve O'Toole	Head of Evidence and Quality Hub, NCCP	Chair and writing member
Radiation Oncologists		
Prof. Fran Duane	Consultant Radiation Oncologist, SLRON	Writing member
Dr Aileen Flavin	Consultant Radiation Oncologist, CUH	Writing member
Dr Orla McArdle	Consultant Radiation Oncologist, SLRON	Writing member
Dr Carol McGibney	Consultant Radiation Oncologist, CUH	Writing member
Dr Kathy Rock	Consultant Radiation Oncologist, CUH	Writing member
Dr Orla Houlihan	Specialist Registrar, Radiation Oncology	Writing member
Dr Jana McHugh	Specialist Registrar, Radiation Oncology	Writing member
Dr Orla Monaghan	Specialist Registrar, Radiation Oncology	Writing member
Dr Killian Nugent	Specialist Registrar, Radiation Oncology	Writing member
Dr Hannah O'Driscoll	Specialist Registrar, Radiation Oncology	Writing member
Dr Neil Wallace	Specialist Registrar, Radiation Oncology	Writing member
Nursing		
Ms Fiona Liston	Clinical Nurse Specialist, SLRON	Writing member
Ms Elaine Richardson	Clinical Nurse Specialist, SJH	Writing member
Medical Physics		
Prof. Brendan McClean	Director of Physics, SLRON	Writing member
Radiation Therapy		
Mr Stephen Coyne	Radiotherapist, UHG	Writing member

Library		
Ms Marie Carrigan	HSE Librarian, SLRON	Information services
Ms Linda Halton	HSE Librarian	Information services
Mr Gethin White	HSE Librarian	Information services
NCCP		
Dr Niamh Kilgallen	Senior Research Officer	Project manager, senior researcher and writing member
Ms Ruth Ryan	Programme Manager, Radiation Oncology	Radiation Oncology Programme Manager

1.2 Additional guideline contributors

Name	Title/Position
Prof. Clare Faul	Consultant Radiation Oncologist, SLRON
Dr Guhan Rangaswamy	Clinical Tutor, Radiation Oncology, SLRON

2 Summary of changes from the 2015 Guideline

This Guideline retains clinical questions from the radiation oncology section of the 2015 National Clinical Guideline No. 7 (Diagnosis, staging and treatment of patients with breast cancer) (Department of Health, 2015) with an update to the evidence base which is clearly indicated throughout the text. Inclusion of the updated evidence has not resulted in any changes to the original recommendations, however some good practice points have been added or modified. This guideline also contains new clinical questions relating to areas of new or emerging evidence since the publication of the 2015 guideline. The numbering system for clinical questions and recommendations has been updated in this version of the guideline, with the original numbers indicated in parentheses throughout.

3 Clinical questions, evidence statements and recommendations

Clinical question 1 (2015: 2.5.3): 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 RCTs has shown significant reduction in breast cancer recurrence with RT given after 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 to 17.7, 2P<0.00001). Radiotherapy also reduced 15 year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, 95% CI 1.6 to 6.0, 2*P*=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 10.

Information regarding dose regimens has been removed from this section and is now addressed in more detail in Clinical question 3

2022 Updates to the Evidence Statement

No additional evidence was found to address this question in the update of this guideline.

Recommendation 1.1 (2015: 2.5.3.1)	**Grade**
Radiotherapy is recommended for all patients undergoing breast conserving surgery for early breast cancer.	**A**

Recommendation 2.5.3.2 (2015) regarding hypofractionation been removed in this update. This topic is now addressed in more detail in Clinical question 3

Good practice point (New 2022)
• 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.

Clinical question 2 (2015: 2.5.4): 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?

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, RT or both in reducing the incidence of ipsilateral breast tumour recurrence (IBTR) or contralateral breast cancer (CBC) in this low-risk group. Cumulative incidence of IBTR at eight years was 16.5% with tamoxifen, 9.3% with adjuvant RT 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 RT alone. The authors conclude that tumours <1cm recur with enough frequency after lumpectomy to justify considering RT, regardless of tumour 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 RT or tamoxifen alone. Median follow-up is now 12.6 years. At 10 years, freedom from locoregional recurrence was significantly improved in women receiving RT and tamoxifen compared to tamoxifen alone (98% versus 90%, 95% CI, 85% to 93%). There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer–specific survival, or overall survival between the two groups. Ten-year OS was 67% (95% CI, 62% to 72%) and 66% (95% CI, 61% to 71%) in the tamoxifen and RT and tamoxifen groups, respectively. Of the 636 women in this study, only 21 (3%) have died as a result of breast cancer, whereas 313 (49%) have 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 RT 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 RT reduces risk of recurrence in all subgroups; however in some cases the benefit may be small. There may be very low-risk patients in whom RT 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.

2022 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 RT reduced in-breast recurrence at 5 years compared to tamoxifen alone in elderly women (≥70 years old) with early stage breast cancer following breast conserving surgery (RR. 0.18, 95% CI 0.10-0.34, p<0.001). The benefit of RT remained significant at 10 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 5 years (RR0.98 (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 RT reduced the rate of IBTR in older patients when compared with patients who did not receive RT.

Kunkler et al. (2015) showed actuarial IBTR at 5 years in women aged >65 was 1.3% (95% CI 0.2 -2.3) in women allocated to RT compared with 4.1% (95% CI 2.4 -5.7) in those assigned no RT (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 RT, 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 RT. 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 RT arm and 4.4% in the surgery only arm. There was no difference in distant disease free survival or OS between arms.

Recommendation 3.1 (2015: 2.5.4.1)	**Grade**
In patients who have undergone breast conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations.	**A**

Good practice point (Modified 2022)

- 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.

Clinical question 3 (New 2022): In patients with breast cancer who have undergone breast conserving surgery does hypofractionation compared to conventional fractionation provide equivalent oncological outcomes?

Quality of evidence

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 randomised controlled trials compare different fractionation schedules. FAST compared a 5-week schedule of 50Gy in 25 fractions to 30 or 28.5Gy in five once-weekly fractions of 6.0 or 5.7Gy (Brunt et al., 2020a). FAST-forward compares either 1-week hypofractionated radiotherapy (26 or 27Gy in five fractions) to 3-week radiotherapy (40Gy 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 2010). These studies combine data from three main randomised controlled trials (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 to 1.22, P=0.78) or survival at five years (RR 0.89, 95% CI 0.77 to 1.04, p= 0.16). Breast appearance was equivalent and acute skin toxicity was decreased with hypofractionationation, 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 were included in RCT. 14% 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 50Gy/25fr (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 randomised controlled trial 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.

Benefit and harm

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 comsetic 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 heterogenous 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 patient s on a hypofractionated regimen are seen less often in clinic they may perceive that their care has been reduced.

Preferences and values

Hypofractionation should be more convenient for patients and reduce the burden of having to be away from home, particurly for those who have to travel a long distance for treatment.
Convenience is a driving factor given the equivalent oncological outcomes.

Resources, capacity 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 a 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 2.2:
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:
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 2.4:
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 hypofractionated 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 around patient care
• 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. • Patients should be reassured that hypofractionated radiotherapy schedules have equivalent oncological outcomes as conventional radiotherapy.

Clinical question 4 (2015: 2.5.5): 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 RT (50Gy in 25 fractions over five weeks). Participants were randomised to receive either no extra radiation or a boost dose of 16Gy 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 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 ≤3cm in size treated with local excision and whole breast RT (50Gy in 25 fractions over five weeks). Participants were randomised to receive either no additional radiation or a boost of 10Gy 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 is 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 RT 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.

2022 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 to 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 subanalysis 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 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 4.1 (2015: 2.5.5.1)	**Grade**
In patients who have breast conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis.	A

Recommendation 4.2 (2015: 2.5.5.2)	**Grade**
Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high grade invasive cancers).	A

Good practice points (New 2022)

- The benefits and risks of boost should be discussed separately to that 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 boost to the individual should be discussed taking the patient's individual risk into consideration.

Clinical question 5 (New 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?

Quality of evidence

Three randomised controlled trials address this question. All trials were found to have confounding factors and/or are underpowered to provide high-level evidence.

The IMRT-MC2 trial randomised 502 patients to receive either intensity modulated radiation therapy (IMRT) with simultaneous integrated boost (SIB) or 3D conformal radiotherapy (3DCRT) with a sequential boost (SeB). Hörner-Rieber et al. (2021) 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 was 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.

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 sequential boost or simultaneous integrated boost. 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.

Finally, the TomoBreast trial randomised 123 patients to receive either conventional radiotherapy with a sequential boost (CR-SeB), or tomotherapy with a simultaneous integrated boost (TT-SIB) (Van Parijs et al., 2021). After ten years of follow-up there was no difference in overall survival or disease free survival between the two arms, while dyspnea-free survival was higher in the TT-SIB arm compared with the CR-SeB arm, however this was non-significant (94.9% vs 85.9%, p = 0.098).

While small patient numbers and 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 non-inferior to a sequential boost.

The ongoing IMPORT HIGH phase III randomised controlled trial tests dose escalated simultaneous integrated boost against a sequential boost using IMRT and image guided radiotherapy. This trial directly addresses this clinical question, and when published, should add to the evidence base. IMPORT HIGH randomised women with pT1-3 pN0-3 M0 breast cancer to either 40Gy in 15 Fractions whole breast irradiation with a 16 Gy sequential boost in 8 fractions (control), or to 36Gy in 15 fractions to the whole breast, 40Gy to the partial breast and either 48Gy or 53Gy in 15 fractions SIB to the tumour bed (Coles et al., 2021).

Benefit and harm

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.

Consideration should be given to the possibility that SIB may be more toxic than SeB, however data available to date suggests this is not the case.

Preferences and values

A reduced number of clinic visits for the patient resulting from the use of SIB would also have a wider impact on the patient's family and/or carers. With no apparent increase in toxicity patients and their families may value the treatment time saved.

Resources, capacity and other considerations

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

In comparison with a sequential boost, the use of SIB has the potential to increase capacity within the system, reducing treatment time from four to three weeks.

Additional staff training and consultation with the Image-Guided Radiotherapy Group (IGRT) would be required for implementation. The NPRO 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 used in many tumour sites regularly across Ireland. Introducing the technique for 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 5.1:
In patients with early breast cancer receiving a radiotherapy tumour bed boost, a simultaneous integrated boost may 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:** Weak

Good practice points

- The placement of clips during surgery is critical for radiotherapy.
- Delineation and dosimetry guidelines for boost volume should be adhered to.

Clinical question 6 (2015: 2.5.2): 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 RT 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 RT reduced the absolute 10 year risk of an ipsilateral breast event (either recurrent DCIS or invasive cancer) by 15.2% (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 RT can be routinely omitted. However, while RT reduces the risk of recurrence, it has no impact on disease specific or overall survival. The individual risk/benefit of adjuvant RT should be discussed with all patients.

2022 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 years 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 to 3.7) and 7.1% (95% CI 4.0 to 11.5) with radiotherapy, and 9.2% (95% CI 6.2 to13.0) and 15.1% (95% CI 10.8 to 20.2) in the observation arm (HR=0.36 [95% CI 0.20 to 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 4 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 6.1 (2015: 2.5.2.1)	**Grade**
All patients with ductal carcinoma in situ having breast conserving surgery should be considered for adjuvant radiotherapy.	**A**

Clinical question 7 (New 2022): 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?

Quality of evidence

A meta-analysis (Nilsson and Valachis, 2015), a randomised controlled trial (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 ipsalateral 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.

Benefit and harm

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 malignance in the boost group. A substudy 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-repored 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. Use of boost also has an impact on hospital capacity.

Preferences and values

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 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 7.1:
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: Moderate **Grade of recommendation:** Strong

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 to that 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 around 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.

Clinical question 8 (2015: 2.5.1): 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 RT 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 RT 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, 2*P*=0.0002; overall mortality reduction 4.4%, SE 1.2, 2*P*=0.0009) with the addition of RT.

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 five 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 RT 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 five year local recurrence risk of 6% in the absence of RT. This was reduced to 2% with the addition of RT, 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 RT 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 RT (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 RT in women with 1–3 and ≥4 nodes positive. Although women with 1–3 positive nodes had lower absolute risks, RT 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 RT or not.

2022 Updates to the Evidence Statement

Two additional meta-analyses (McGale et al., 2014, Tseng et al., 2020) and a randomised controlled trial (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 number of positive lymph nodes. The analysis showed that in women with 1–3 positive nodes who had had an axillary dissection (n= 1314) 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, postmastectomy radiotherapy showed a benefit in both patients with 4+ positive node and 1–3 positive nodes.

Recommendation 8.1 (2015: 2.5.1.1)	**Grade**
Postmastectomy 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).	**A**

Recommendation 8.2 (2015: 2.5.1.2)	**Grade**
Postmastectomy radiotherapy should be considered in patients with intermediate risk of recurrence (1-3 nodes) and individual patients should be discussed at multidisciplinary team meeting.	**B**

Clinical question 9 (New 2022): In patients with breast cancer who have undergone mastectomy does radiotherapy boost improve rates of local recurrence compared with no radiotherapy boost?

Quality of evidence

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 4247 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.

Benefit and harm

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

These decisions are individualised as the benefit of a boost is unclear across the entire patient cohort. There are risks to be considered which may be unacceptable to some patients, as may the additional treatment time required.

Resources, capacity and other considerations

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

Recommendation 9.1:
In patients with breast cancer who have undergone mastectomy a boost is not routinely recommended.

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

Recommendation 9.2:
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.

Clinical question 10 (New 2022): 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?

Quality of evidence

There are four randomised controlled trials (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 recieve irradiation of the breast/chest wall and supraclavicular nodes with or without irradiation of the internal mammary chain, and 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 7 years was 10.2% without IMNI and 4.9% with IMNI (HR, 0.41; 95% CI, 0.17-0.99; log-rank P = .04), and the DMFS at 7 years was 82.3% without IMNI and 91.8% with IMNI (HR, 0.44; 95% CI, 0.23- 0.85; log-rank P = .01) among patients with mediocentrally located tumors. 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% to 78.0%) and 72.2% (95% CI, 69.9% to 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 to 0.94; P = 0.005). At 15 years the survival rates were 60.1% (95% CI 57.5 to 62.6) and 55.4% (95% CI 52.8 to 57.9) with and without internal mammary chain irradiation, respectively. The adjusted HR for death was 0.86 (95% CI 0.77 to 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 to 0.89; p=0.001), and the number of patients needed to treat to avoid one death at 8 years was 14.

Benefit and harm

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 recieved 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 lymphadema, subcutaneous fibrosis (hardening of the skin and soft tissues), and poor cosmetic outcomes such as telangectasia (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 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

Most patients have three main considerations when it comes to treatment. Firstly, they want to minimise the risk of recurrence of their cancer; secondly, they want to minimise the toxicity involved with treatment; and thirdly, they want to minimise the time and inconvenience involved in treatment. Individual patients may prioritise these concerns differently.

Resources, capacity and other considerations

Time to deliver radiation therapy is increased per patient when the internal mammary chain is irradiated. Radiation of the internal mammary chain cannot be delivered in all centres in the same way due to diffences in radiation techniques available.

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

Recommendation 10.1:
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 10.2:
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 point
• Consider deep inspiration breath hold and advanced planning techniques to optimise coverage, meet normal tissue constraints and minimise toxicity.

Clinical question 11 (New 2022): In patients with left-sided breast cancer does deep inspiration breath hold reduce predicted risk of cardio-toxicity?

Quality of evidence

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 generalisable 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 an 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 cadio-toxicity. The meta-analysis by Lai et al. (2020) included twleve studies and had 1019 patients. While the results of the studies are generalisable, 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.

Benefit and harm

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 late effects and toxicity of treatment.

Resources, capacity 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 11.1:
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

- 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.
- It is important to communicate to the patient that DIBH is just one technique to reduce cardiac dose and that an optimal radiotherapy plan can be done without using DIBH.

Practical considerations around patient care

- Try to minimise the number and length of each breath hold for each patient.

Clinical question 12 (2015: 2.5.6): 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 RT. 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 five year local recurrence rate was significantly higher in patients commencing adjuvant RT 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 to 2.16). Both authors conclude that delays in starting adjuvant RT should be as short as reasonably achievable.

In a retrospective Canadian study (Olivotto et al., 2009), women commencing RT more than 20 weeks after BCS had inferior distant recurrence free survival and breast cancer specific survival when compared to women commencing adjuvant RT 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 RT (Livi et al., 2009). For women treated with adjuvant RT alone (n=1,935) or with adjuvant RT and hormonal therapy (n=1,684), timing of RT had no impact on local recurrence rates. Only in the group of patients treated with adjuvant RT and chemotherapy (n=672) did multivariate analysis show RT timing as an independent prognostic factor (hazard ratio, 1.59; 95% confidence interval, 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 RT. (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 RT 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 RT 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 RT versus RT followed by chemotherapy, and five cohort studies

examining the effect of the sequencing of chemotherapy and RT were reviewed. Based on the available evidence, the maximum interval between surgery and commencement of RT was defined as 12 weeks. (Cancer Care Ontario, 2011)

2022 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 12.1 (2015: 2.5.6.1)	**Grade**
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.	C

Good practice points (New 2022)

- 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).

4 References

ALBERT, A., MANGANA, S., NITTALA, M. R., THOMAS, T. V., WEATHERALL, L. & VIJAYAKUMAR, S. 2019. The Impact of a Postmastectomy Chest Wall Scar Boost on Local Recurrence-free Survival in High-risk Patients. *Clin Breast Cancer,* 19**,** 363-369.

ANDRADE, T. R. M., FONSECA, M. C. M., SEGRETO, H. R. C., SEGRETO, R. A., MARTELLA, E. & NAZÁRIO, A. C. P. 2019. Meta-analysis of long-term efficacy and safety of hypofractionated radiotherapy in the treatment of early breast cancer. *Breast,* 48**,** 24-31.

BARTELINK, H., HORIOT, J. C., POORTMANS, P. M., STRUIKMANS, H., VAN DEN BOGAERT, W., FOURQUET, A., JAGER, J. J., HOOGENRAAD, W. J., OEI, S. B., WÁRLÁM-RODENHUIS, C. C., PIERART, M. & COLLETTE, L. 2007. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol,* 25**,** 3259-65.

BARTELINK, H., MAINGON, P., POORTMANS, P., WELTENS, C., FOURQUET, A., JAGER, J., SCHINAGL, D., OEI, B., RODENHUIS, C., HORIOT, J. C., STRUIKMANS, H., VAN LIMBERGEN, E., KIROVA, Y., ELKHUIZEN, P., BONGARTZ, R., MIRALBELL, R., MORGAN, D., DUBOIS, J. B., REMOUCHAMPS, V., MIRIMANOFF, R. O., COLLETTE, S. & COLLETTE, L. 2015. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol,* 16**,** 47-56.

BIJKER, N., MEIJNEN, P., PETERSE, J. L., BOGAERTS, J., VAN HOOREBEECK, I., JULIEN, J.-P., GENNARO, M., ROUANET, P., AVRIL, A., FENTIMAN, I. S., BARTELINK, H. & RUTGERS, E. J. T. 2006. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 24**,** 3381-3387.

BRUNT, A. M., HAVILAND, J. S., SYDENHAM, M., AGRAWAL, R. K., ALGURAFI, H., ALHASSO, A., BARRETT-LEE, P., BLISS, P., BLOOMFIELD, D., BOWEN, J., DONOVAN, E., GOODMAN, A., HARNETT, A., HOGG, M., KUMAR, S., PASSANT, H., QUIGLEY, M., SHERWIN, L., STEWART, A., SYNDIKUS, I., TREMLETT, J., TSANG, Y., VENABLES, K., WHEATLEY, D., BLISS, J. M. & YARNOLD, J. R. 2020a. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. *J Clin Oncol,* 38**,** 3261-3272.

BRUNT, A. M., HAVILAND, J. S., WHEATLEY, D. A., SYDENHAM, M. A., ALHASSO, A., BLOOMFIELD, D. J., CHAN, C., CHURN, M., CLEATOR, S., COLES, C. E., GOODMAN, A., HARNETT, A., HOPWOOD, P., KIRBY, A. M., KIRWAN, C. C., MORRIS, C., NABI, Z., SAWYER, E., SOMAIAH, N., STONES, L., SYNDIKUS, I., BLISS, J. M. & YARNOLD, J. R. 2020b. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet,* 395**,** 1613-1626.

BUDACH, W., BÖLKE, E. & MATUSCHEK, C. 2015. Hypofractionated Radiotherapy as Adjuvant Treatment in Early Breast Cancer. A Review and Meta-Analysis of Randomized Controlled Trials. *Breast Care (Basel),* 10**,** 240-5.

CAMBRA, M. J., MORENO, F., SANZ, X., ANGLADA, L., MOLLÀ, M., REYES, V., ARENAS, M., PEDRO, A., BALLESTER, R., GARCÍA, V., CASALS, J., CUSIDÓ, M., JIMENEZ, C., ESCRIBÀ, J. M., MACIÀ, M., SOLÉ, J. M., ARCUSA, A., SEGUÍ, M. A., GONZALEZ, S., FARRÚS, B. & BIETE, A. 2020. Role of boost radiotherapy for local control of pure ductal carcinoma in situ after breast-conserving surgery: a multicenter, retrospective study of 622 patients. *Clin Transl Oncol,* 22**,** 670-680.

CANCER CARE ONTARIO 2011. Members of the breast cancer disease site group. Breast irradiation in wome with early stage invasive breast cancer following breast conserving surgery. Toronto (Ontario): Cancer Care Ontario

CHEN, Z., KING, W., PEARCEY, R., KERBA, M. & MACKILLOP, W. J. 2008. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol,* 87**,** 3-16.

CHESNEY, T. R., YIN, J. X., RAJAEE, N., TRICCO, A. C., FYLES, A. W., ACUNA, S. A. & SCHEER, A. S. 2017. Tamoxifen with radiotherapy compared with Tamoxifen alone in elderly women with early-stage breast cancer treated with breast conserving surgery: A systematic review and meta-analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology,* 123**,** 1-9.

CHUA, B. H., LINK, E. K., KUNKLER, I. H., WHELAN, T. J., WESTENBERG, A. H., GRUBER, G., BRYANT, G., AHERN, V., PUROHIT, K., GRAHAM, P. H., AKRA, M., MCARDLE, O., O'BRIEN, P., HARVEY, J. A., KIRKOVE, C., MADURO, J. H., CAMPBELL, I. D., DELANEY, G. P., MARTIN, J. D., VU, T. T. T., MUANZA, T. M., NEAL, A. & OLIVOTTO, I. A. 2022. Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3-07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study. *Lancet,* 400**,** 431-440.

CLARK, R. M., MCCULLOCH, P. B., LEVINE, M. N., LIPA, M., WILKINSON, R. H., MAHONEY, L. J., BASRUR, V. R., NAIR, B. D., MCDERMOT, R. S. & WONG, C. S. 1992. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst,* 84**,** 683-9.

CLARKE, M., COLLINS, R., DARBY, S., DAVIES, C., ELPHINSTONE, P., EVANS, V., GODWIN, J., GRAY, R., HICKS, C., JAMES, S., MACKINNON, E., MCGALE, P., MCHUGH, T., PETO, R., TAYLOR, C. & WANG, Y. 2005. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet (London, England),* 366**,** 2087-2106.

COLES, C., LIGHTOWLERS, S., HAVILAND, J. S., GRIFFIN, C. L., HOPWOOD, P., RAJAPAKSE, C., STONES, L., TITLEY, J. C., BLISS, J. M., KIRBY, A. M., YARNOLD, J. R., BHATTACHARYA, I., TWYMAN, N. I., BRUNT, A. M., CHAN, C., DONOVAN, E. M., EATON, D. J., TSANG, Y., JEFFORD, M. L., SAWYER, E. & SYNDIKUS, I. 2021. IMPORT HIGH trial: Dose escalated simultaneous integrated boost radiotherapy in early breast cancer. *Radiotherapy and Oncology,* 161**,** S197-S199.

CORREA, C., MCGALE, P., TAYLOR, C., WANG, Y., CLARKE, M., DAVIES, C., PETO, R., BIJKER, N., SOLIN, L. & DARBY, S. 2010. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr,* 2010**,** 162-77.

DARBY, S., MCGALE, P., CORREA, C., TAYLOR, C., ARRIAGADA, R., CLARKE, M., CUTTER, D., DAVIES, C., EWERTZ, M., GODWIN, J., GRAY, R., PIERCE, L., WHELAN, T., WANG, Y. & PETO, R. 2011. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet,* 378**,** 1707-16.

DARBY, S. C., EWERTZ, M., MCGALE, P., BENNET, A. M., BLOM-GOLDMAN, U., BRØNNUM, D., CORREA, C., CUTTER, D., GAGLIARDI, G., GIGANTE, B., JENSEN, M. B., NISBET, A., PETO, R., RAHIMI, K., TAYLOR, C. & HALL, P. 2013. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med,* 368**,** 987-98.

DEPARTMENT OF HEALTH 2015. Diagnosis, staging and treatment of patients with breast cancer. National Clinical Guideline No. 7.

EMDIN, S. O., GRANSTRAND, B., RINGBERG, A., SANDELIN, K., ARNESSON, L.-G., NORDGREN, H., ANDERSON, H., GARMO, H., HOLMBERG, L. & WALLGREN, A. 2006. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. *Acta oncologica (Stockholm, Sweden),* 45**,** 536-543.

FISHER, B., ANDERSON, S., REDMOND, C. K., WOLMARK, N., WICKERHAM, D. L. & CRONIN, W. M. 1995. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med,* 333**,** 1456-61.

FISHER, B., BRYANT, J., DIGNAM, J. J., WICKERHAM, D. L., MAMOUNAS, E. P., FISHER, E. R., MARGOLESE, R. G., NESBITT, L., PAIK, S., PISANSKY, T. M. & WOLMARK, N. 2002. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol,* 20**,** 4141-9.

FISHER, B., DIGNAM, J., WOLMARK, N., MAMOUNAS, E., COSTANTINO, J., POLLER, W., FISHER, E. R., WICKERHAM, D. L., DEUTSCH, M., MARGOLESE, R., DIMITROV, N. & KAVANAH, M. 1998. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 16**,** 441-452.

FORSTER, T., HOMMERTGEN, A., ARIANS, N., LAILA, K., SCHLAMPP, I., KOHLER, C., DEBUS, J., HOERNER-RIEBER, J., HAFNER, M. F., HARRABI, S., HEINRICH, V., WEIDNER, N., HUSING, J., GOLATTA, M., HEIL, J., SOHN, C., HOF, H. & KRUG, D. 2021. Quality of Life After Simultaneously Integrated Boost With Intensity-Modulated vs. Conventional Radiotherapy Followed by Sequential Boost for Adjuvant Treatment of Breast Cancer: 2-Year Results of the Multicenter Randomized IMRT-MC2 Trial. *International journal of radiation oncology, biology, physics,* 111**,** S35.

FYLES, A. W., MCCREADY, D. R., MANCHUL, L. A., TRUDEAU, M. E., MERANTE, P., PINTILIE, M., WEIR, L. M. & OLIVOTTO, I. A. 2004. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med,* 351**,** 963-70.

GARG, P. K., JAKHETIYA, A., PANDEY, R., CHISHI, N. & PANDEY, D. 2018. Adjuvant radiotherapy versus observation following lumpectomy in ductal carcinoma in-situ: A meta-analysis of randomized controlled trials. *The breast journal,* 24**,** 233-239.

GOODWIN, A., PARKER, S., GHERSI, D. & WILCKEN, N. 2009. Post-operative radiotherapy for ductal carcinoma in situ of the breast. *Cochrane Database Syst Rev***,** CD000563.

HAVILAND, J. S., OWEN, J. R., DEWAR, J. A., AGRAWAL, R. K., BARRETT, J., BARRETT-LEE, P. J., DOBBS, H. J., HOPWOOD, P., LAWTON, P. A., MAGEE, B. J., MILLS, J., SIMMONS, S., SYDENHAM, M. A., VENABLES, K., BLISS, J. M. & YARNOLD, J. R. 2013. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol,* 14**,** 1086-1094.

HENNEQUIN, C., BOSSARD, N., SERVAGI-VERNAT, S., MAINGON, P., DUBOIS, J. B., DATCHARY, J., CARRIE, C., ROULLET, B., SUCHAUD, J. P., TEISSIER, E., LUCARDI, A., GERARD, J. P., BELOT, A., IWAZ, J., ECOCHARD, R. & ROMESTAING, P. 2013. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys,* 86**,** 860-6.

HERSHMAN, D. L., WANG, X., MCBRIDE, R., JACOBSON, J. S., GRANN, V. R. & NEUGUT, A. I. 2006. Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. *Int J Radiat Oncol Biol Phys,* 65**,** 1353-60.

HOLMBERG, L., GARMO, H., GRANSTRAND, B., RINGBERG, A., ARNESSON, L. G., SANDELIN, K., KARLSSON, P., ANDERSON, H. & EMDIN, S. 2008. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. *J Clin Oncol,* 26**,** 1247-52.

HÖRNER-RIEBER, J., FORSTER, T., HOMMERTGEN, A., HAEFNER, M. F., ARIANS, N., KÖNIG, L., HARRABI, S. B., SCHLAMPP, I., WEYKAMP, F., LISCHALK, J. W. & ET AL. 2021. Intensity Modulated Radiation Therapy (IMRT) With Simultaneously Integrated Boost Shortens Treatment Time and Is Noninferior to Conventional Radiation Therapy Followed by Sequential Boost in Adjuvant Breast Cancer Treatment: results of a Large Randomized Phase III Trial (IMRT-MC2 Trial). *International journal of radiation oncology, biology, physics,* 109**,** 1311-1324.

HOUGHTON, J., GEORGE, W. D., CUZICK, J., DUGGAN, C., FENTIMAN, I. S. & SPITTLE, M. 2003. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of

the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet (London, England),* 362**,** 95-102.

HUANG, J., BARBERA, L., BROUWERS, M., BROWMAN, G. & MACKILLOP, W. J. 2003. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *J Clin Oncol,* 21**,** 555-63.

HUGHES, K. S., SCHNAPER, L. A., BELLON, J. R., CIRRINCIONE, C. T., BERRY, D. A., MCCORMICK, B., MUSS, H. B., SMITH, B. L., HUDIS, C. A., WINER, E. P. & WOOD, W. C. 2013. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 31**,** 2382-2387.

JAMES, M. L., LEHMAN, M., HIDER, P. N., JEFFERY, M., HICKEY, B. E. & FRANCIS, D. P. 2010. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database of Systematic Reviews*.

JOBSEN, J. J., SCHEIJMANS, L., SMIT, W., STENFERT KROESE, M. C., STRUIKMANS, H. & VAN DER PALEN, J. 2018. Breast-conserving therapy for primary Ductal Carcinoma in Situ in The Netherlands: A multi-center study and population-based analysis. *Breast,* 42**,** 3-9.

JONES, H. A., ANTONINI, N., HART, A. A., PETERSE, J. L., HORIOT, J. C., COLLIN, F., POORTMANS, P. M., OEI, S. B., COLLETTE, L., STRUIKMANS, H., VAN DEN BOGAERT, W. F., FOURQUET, A., JAGER, J. J., SCHINAGL, D. A., WARLAM-RODENHUIS, C. C. & BARTELINK, H. 2009. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol,* 27**,** 4939-47.

KILLANDER, F., MALMSTROM, P., KARLSSON, P., LUNDSTEDT, D., ANDERSON, H., MATTSSON, J., HOLMBERG, E. & HOLMBERG, L. 2016. No breast cancer subgroup can be spared postoperative radiotherapy after breast-conserving surgery. Fifteen-year results from the Swedish Breast Cancer Group randomised trial, SweBCG 91 RT. *European Journal of Cancer,* 67**,** 57-65.

KIM, Y. B., BYUN, H. K., KIM, D. Y., AHN, S.-J., LEE, H.-S., PARK, W., KIM, S. S., KIM, J. H., LEE, K. C., LEE, I. J., KIM, W. T., SHIN, H. S., KIM, K., SHIN, K. H., NAM, C. M. & SUH, C.-O. 2022. Effect of Elective Internal Mammary Node Irradiation on Disease-Free Survival in Women With Node-Positive Breast Cancer: A Randomized Phase 3 Clinical Trial. *JAMA Oncology,* 8**,** 96-105.

KINDTS, I., LAENEN, A., DEPUYDT, T. & WELTENS, C. 2017. Tumour bed boost radiotherapy for women after breast-conserving surgery. *Cochrane Database of Systematic Reviews*.

KING, M. T., LINK, E. K., WHELAN, T. J., OLIVOTTO, I. A., KUNKLER, I., WESTENBERG, A. H., GRUBER, G., SCHOFIELD, P. & CHUA, B. H. 2020. Quality of life after breast-conserving therapy and adjuvant radiotherapy for non-low-risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol,* 21**,** 685-698.

KUNKLER, I. H., CAMERON, D. A., DIXON, J. M., WILLIAMS, L. J. & JACK, W. J. L. 2015. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): A randomised controlled trial. *The Lancet Oncology,* 16**,** 266-273.

LAI, J., HU, S., LUO, Y., ZHENG, R., ZHU, Q., CHEN, P., CHI, B., ZHANG, Y., ZHONG, F. & LONG, X. 2020. Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer. *Breast Cancer,* 27**,** 299-307.

LILJEGREN, G., HOLMBERG, L., ADAMI, H. O., WESTMAN, G., GRAFFMAN, S. & BERGH, J. 1994. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. *J Natl Cancer Inst,* 86**,** 717-22.

LIN, C. H., LIN, L. C., QUE, J. & HO, C. H. 2019. A seven-year experience of using moderate deep inspiration breath-hold for patients with early-stage breast cancer and dosimetric comparison. *Medicine (Baltimore),* 98**,** e15510.

LIVI, L., BORGHESI, S., SAIEVA, C., MEATTINI, I., RAMPINI, A., PETRUCCI, A., DETTI, B., BRUNI, A., PAIAR, F., MANGONI, M., MARRAZZO, L., AGRESTI, B., CATALIOTTI, L., BIANCHI, S. & BITI, G. 2009.

Radiotherapy timing in 4,820 patients with breast cancer: University of Florence experience. *Int J Radiat Oncol Biol Phys,* 73**,** 365-9.

MA, X., CHEN, J., MA, D., JIANG, Y., LIU, Z., CHEN, S., ZHANG, Y., SHEN, Y., YU, X., YANG, Z., LI, S., MO, M., QIAN, Y., LIU, G., WU, J., SHAO, Z., YU, K. & DI, G. 2021. Delayed initiation of radiation therapy is associated with inferior outomes for breast cancer patients with hormone receptor-negative tumors after breast-conserving surgery *Gland Surgery,* 10**,** 2631 -2543.

MAYADEV, J., FISH, K., VALICENTI, R., WEST, D., CHEN, A., MARTINEZ, S. & PHILLIPS, T. 2014. Utilization and impact of a postmastectomy radiation boost for invasive breast cancer. *Pract Radiat Oncol,* 4**,** e269-78.

MCCORMICK, B., WINTER, K., HUDIS, C., KUERER, H. M., RAKOVITCH, E., SMITH, B. L., SNEIGE, N., MOUGHAN, J., SHAH, A., GERMAIN, I., HARTFORD, A. C., RASHTIAN, A., WALKER, E. M., YUEN, A., STROM, E. A., WILCOX, J. L., VALLOW, L. A., SMALL, W., JR, PU, A. T., KERLIN, K. & WHITE, J. 2015. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 33**,** 709-715.

MCCORMICK, B., WINTER, K. A., WOODWARD, W., KUERER, H. M., SNEIGE, N., RAKOVITCH, E., SMITH, B. L., GERMAIN, I., HARTFORD, A. C., O'ROURKE, M. A., WALKER, E. M., STROM, E. A., HOPKINS, J. O., PIERCE, L. J., PU, A. T., SUMIDA, K. N. M., VESPRINI, D., MOUGHAN, J. & WHITE, J. R. 2021. Randomized Phase III Trial Evaluating Radiation Following Surgical Excision for Good-Risk Ductal Carcinoma In Situ: Long-Term Report From NRG Oncology/RTOG 9804. *Journal of Clinical Oncology,* 39**,** 3574-3582.

MCGALE, P., TAYLOR, C., CORREA, C., CUTTER, D., DUANE, F., EWERTZ, M., GRAY, R., MANNU, G., PETO, R., WHELAN, T., WANG, Y., WANG, Z. & DARBY, S. 2014. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet (London, England),* 383**,** 2127-2135.

MORAN, M. S., ZHAO, Y., MA, S., KIROVA, Y., FOURQUET, A., CHEN, P., HOFFMAN, K., HUNT, K., WONG, J., HALASZ, L. M., FREEDMAN, G., PROSNITZ, R., JR., YASSA, M., NGUYEN, D. H. A., HIJAL, T., HAFFTY, B. G., WAI, E. S. & TRUONG, P. T. 2017. Association of Radiotherapy Boost for Ductal Carcinoma In Situ With Local Control After Whole-Breast Radiotherapy. *JAMA Oncol,* 3**,** 1060-1068.

NAOUM, G. E., SALAMA, L., HO, A., HORICK, N. K., OLADERU, O., ABOUEGYLAH, M., DANIELL, K., MACDONALD, S., ARAFAT, W. O., SMITH, B. L., COLWELL, A. S. & TAGHIAN, A. G. 2019. The Impact of Chest Wall Boost on Reconstruction Complications and Local Control in Patients Treated for Breast Cancer. *Int J Radiat Oncol Biol Phys,* 105**,** 155-164.

NILSSON, C. & VALACHIS, A. 2015. The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: a meta-analysis of observational studies. *Radiother Oncol,* 114**,** 50-5.

NUGENT, K., QUINLAN, E., CLEARY, S., O'DRISCOLL, H., TROUSDELL, J., WILLIAMS, J., DUNNE, M., MCARDLE, O. & DUANE, F. K. 2021. Implementation of FAST-Forward during COVID19: Report of acute skin toxicity /resource implications. *Radiotherapy and Oncology,* 161**,** S915-S916.

OLIVOTTO, I. A., LESPERANCE, M. L., TRUONG, P. T., NICHOL, A., BERRANG, T., TYLDESLEY, S., GERMAIN, F., SPEERS, C., WAI, E., HOLLOWAY, C., KWAN, W. & KENNECKE, H. 2009. Intervals longer than 20 weeks from breast-conserving surgery to radiation therapy are associated with inferior outcome for women with early-stage breast cancer who are not receiving chemotherapy. *J Clin Oncol,* 27**,** 16-23.

OVERGAARD, M., NIELSEN, H. M. & OVERGAARD, J. 2007. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol,* 82**,** 247-53.

OVERGAARD, M., NIELSEN, H. M., TRAMM, T., HØJRIS, I., GRANTZAU, T. L., ALSNER, J., OFFERSEN, B. V. & OVERGAARD, J. 2022. Postmastectomy radiotherapy in high-risk breast cancer patients

given adjuvant systemic therapy. A 30-year long-term report from the Danish breast cancer cooperative group DBCG 82bc trial. *Radiotherapy and Oncology,* 170**,** 4 -13.

PAELINCK, L., GULYBAN, A., LAKOSI, F., VERCAUTEREN, T., DE GERSEM, W., SPELEERS, B., MONTEN, C., MULLIEZ, T., BERKOVIC, P., VAN GREVELING, A. & ET AL. 2017. Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation? A randomized controlled trial. *Radiotherapy and oncology,* 122**,** 30-36.

PANOFF, J. E., TAKITA, C., HURLEY, J., REIS, I. M., ZHAO, W., RODGERS, S. E., GUNASEELAN, V. & WRIGHT, J. L. 2012. Higher chest wall dose results in improved locoregional outcome in patients receiving postmastectomy radiation. *Int J Radiat Oncol Biol Phys,* 82**,** 1192-9.

POORTMANS, P. M., COLLETTE, S., KIRKOVE, C., VAN LIMBERGEN, E., BUDACH, E., STRUIKMANS, H., COLLETTE, L., FOURQUET, A., MAINGON, P., VAILLI, M., DE WINTER, K., MARNITZ, S., BARILLOT, I., SCANDOLARO, L., VONK, E., RODENHUIS, C., MARSIGLIA, H., WEIDNER, N., VAN TIENHOVEN, G., GLANZMANN, C., KUTEN, A., ARRIAGADA, R., BARTELINK, H. & VAN DEN BOGAERT, W. 2015. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer *The New England Journal of Medicine,* 373**,** 317-327.

POORTMANS, P. M., WELTENS, C., FORTPIED, C., KIRKOVE, C., PEIGNAUX-CASASNOVAS, K., BUDACH, V., VAN DER LEIJ, F., VONK, E., WEIDNER, N., RIVERA, S., VAN TIENHOVEN, G., FOURQUET, A., NOEL, G., VALLI, M., GUCKENBERGER, M., KOITER, E., RACADOT, S., ABDAH-BORTNYAK, R., VAN LIMBERGEN, E. F., ENGELEN, A., DE BROUWER, P., STRUIKMANS, H. & BARTELINK, H. 2020. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I–III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. *The Lancet Oncology,* 21**,** 1602-1610.

RAGAZ, J., OLIVOTTO, I. A., SPINELLI, J. J., PHILLIPS, N., JACKSON, S. M., WILSON, K. S., KNOWLING, M. A., COPPIN, C. M., WEIR, L., GELMON, K., LE, N., DURAND, R., COLDMAN, A. J. & MANJI, M. 2005. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst,* 97**,** 116-26.

RAPHAEL, M. J., SASKIN, R. & SINGH, S. 2020. Association between waiting time for radiotherapy after surgery for early-stage breast cancer and survival outcomes in Ontario: a population-based outcomes study. *Current oncology (Toronto, Ont.),* 27**,** e216-e221.

ROMESTAING, P., LEHINGUE, Y., CARRIE, C., COQUARD, R., MONTBARBON, X., ARDIET, J. M., MAMELLE, N. & GERARD, J. P. 1997. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol,* 15**,** 963-8.

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK [SIGN] 2013. Treatment of primary breast cancer - a national clinical guideline. Edinburgh: SIGN.

SIGN 2013. Treatment of primary breast cancer - a national clinical guideline. [Sign publicatoin number 134]. Edinburgh: SIGN.

SIMONETTO, C., EIDEMÜLLER, M., GAASCH, A., PAZOS, M., SCHÖNECKER, S., REITZ, D., KÄÄB, S., BRAUN, M., HARBECK, N., NIYAZI, M., BELKA, C. & CORRADINI, S. 2019. Does deep inspiration breath-hold prolong life? Individual risk estimates of ischaemic heart disease after breast cancer radiotherapy. *Radiother Oncol,* 131**,** 202-207.

SWANSON, T., GRILLS, I. S., YE, H., ENTWISTLE, A., TEAHAN, M., LETTS, N., YAN, D., DUQUETTE, J. & VICINI, F. A. 2013. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. *Am J Clin Oncol,* 36**,** 24-30.

THORSEN, L. B., OFFERSEN, B. V., DANØ, H., BERG, M., JENSEN, I., PEDERSEN, A. N., ZIMMERMANN, S. J., BRODERSEN, H. J., OVERGAARD, M. & OVERGAARD, J. 2016. DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer. *Journal of Clinical Oncology,* 34**,** 314-20.

THORSEN, L. B. J., OVERGAARD, J., MATTHIESSEN, L. W., BERG, M., STENBYGAARD, L., PEDERSEN, A. N., NIELSEN, M. H., OVERGAARD, M. & OFFERSEN, B. V. 2022. Internal Mammary Node Irradiation in Patients With Node-Positive Early Breast Cancer: Fifteen-Year Results From the Danish Breast Cancer Group Internal Mammary Node Study. *Journal of Clinical Oncology,* 0**,** JCO.22.00044.

TINTERRI, C., GATZEMEIER, W., COSTA, A., GENTILINI, M. A., ZANINI, V., REGOLO, L., PEDRAZZOLI, C., RONDINI, E., AMANTI, C., GENTILE, G., TAFFURELLI, M., FENAROLI, P., TONDINI, C., SACCHETTO, G., SISMONDI, P., MURGO, R., ORLANDI, M., CIANCHETTI, E. & ANDREOLI, C. 2014. Breast-conservative surgery with and without radiotherapy in patients aged 55-75 years with early-stage breast cancer: a prospective, randomized, multicenter trial analysis after 108 months of median follow-up. *Annals of surgical oncology,* 21**,** 408-415.

TSENG, M., VELLAYAPPAN, B., SOON, Y. Y., CHOONG, R. & APPALANAIDO, G. K. 2020. Post mastectomy radiotherapy for elderly patients with intermediate risk (T1-2N1 OR T3N0) breast cancer: A systematic review and meta-analysis. *Translational Cancer Research,* 9**,** S23-S28.

VALLE, L. F., AGARWAL, S., BICKEL, K. E., HERCHEK, H. A., NALEPINSKI, D. C. & KAPADIA, N. S. 2017. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat,* 162**,** 409-417.

VAN HULLE, H., DESAUNOIS, E., VAKAET, V., PAELINCK, L., SCHOEPEN, M., POST, G., VAN GREVELING, A., SPELEERS, B., MAREEL, M., DE NEVE, W. & ET AL. 2021. Two-year toxicity of simultaneous integrated boost in hypofractionated prone breast cancer irradiation: comparison with sequential boost in a randomized trial. *Radiotherapy and oncology,* 158**,** 62-66.

VAN PARIJS, H., FONTAINE, C., STORME, G., ADRIAENSSENS, N., DE RIDDER, M., VINH-HUNG, V., VERSCHRAEGEN, C., NGUYEN, D. M., NGUYEN, N. P. & GOROBETS, O. 2021. Cardiopulmonary-related patient-reported outcomes in a randomized clinical trial of radiation therapy for breast cancer. *BMC Cancer,* 21**,** 1177.

VERONESI, U., LUINI, A., DEL VECCHIO, M., GRECO, M., GALIMBERTI, V., MERSON, M., RILKE, F., SACCHINI, V., SACCOZZI, R. & SAVIO, T. 1993. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med,* 328**,** 1587-91.

VRIELING, C., COLLETTE, L., FOURQUET, A., HOOGENRAAD, W. J., HORIOT, J. C., JAGER, J. J., PIERART, M., POORTMANS, P. M., STRUIKMANS, H., VAN DER HULST, M., VAN DER SCHUEREN, E. & BARTELINK, H. 1999. The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC "boost versus no boost" trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol Biol Phys,* 45**,** 677-85.

VRIELING, C., VAN WERKHOVEN, E., MAINGON, P., POORTMANS, P., WELTENS, C., FOURQUET, A., SCHINAGL, D., OEI, B., RODENHUIS, C. C., HORIOT, J.-C., STRUIKMANS, H., VAN LIMBERGEN, E., KIROVA, Y., ELKHUIZEN, P., BONGARTZ, R., MIRALBELL, R., MORGAN, D. A. L., DUBOIS, J.-B., REMOUCHAMPS, V., MIRIMANOFF, R.-O., HART, G., COLLETTE, S., COLLETTE, L. & BARTELINK, H. 2017. Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial. *JAMA oncology,* 3**,** 42-48.

VUJOVIC, O., YU, E., CHERIAN, A., DAR, A. R., STITT, L. & PERERA, F. 2015. Time interval from breast-conserving surgery to breast irradiation in early stage node-negative breast cancer: 17-year follow-up results and patterns of recurrence. *International journal of radiation oncology, biology, physics,* 91**,** 319-324.

WÄRNBERG, F., GARMO, H., EMDIN, S., HEDBERG, V., ADWALL, L., SANDELIN, K., RINGBERG, A., KARLSSON, P., ARNESSON, L.-G., ANDERSON, H., JIRSTRÖM, K. & HOLMBERG, L. 2014. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 32**,** 3613-3618.

WHELAN, T. J., OLIVOTTO, I. A., PARULEKAR, W. R., ACKERMAN, I., CHUA, B. H., NABID, A., VALLIS, K. A., WHITE, J. R., ROUSSEAU, P., FORTIN, A., PIERCE, L. J., MANCHUL, L., CHAFE, S., NOLAN, M. C., CRAIGHEAD, P., BOWEN, J., MCCREADY, D. R., PRITCHARD, K. I., GELMON, K., MURRAY, Y., CHAPMAN, J. A., CHEN, B. E. & LEVINE, M. N. 2015. Regional Nodal Irradiation in Early-Stage Breast Cancer. *The New England Journal of Medicine,* 373**,** 307-16.

WHELAN, T. J., PIGNOL, J.-P., LEVINE, M. N., JULIAN, J. A., MACKENZIE, R., PARPIA, S., SHELLEY, W., GRIMARD, L., BOWEN, J., LUKKA, H., PERERA, F., FYLES, A., SCHNEIDER, K., GULAVITA, S. & FREEMAN, C. 2010. Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer. *New England Journal of Medicine,* 362**,** 513-520.

ZHOU, Z. R., MEI, X., CHEN, X. X., YANG, Z. Z., HOU, J., ZHANG, L., YU, X. L. & GUO, X. M. 2015. Systematic review and meta-analysis comparing hypofractionated with conventional fraction radiotherapy in treatment of early breast cancer. *Surg Oncol,* 24**,** 200-11.