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Management of Ductal Carcinoma in Situ of the Breast

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An assessment conducted in November 2025 deferred the review of Guideline 1-10 Version 4. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 1-10 Version 4 is comprised of 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/276

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Management of Ductal Carcinoma in Situ of the Breast

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

The objective of this guideline was to determine the most effective therapy options for patients with ductal carcinoma in situ (DCIS) of the breast.

TARGET POPULATION

These recommendations apply to women with DCIS, including women with DCIS with microinvasion (DCIS-M) (< 1 mm through the duct).

INTENDED USERS

Intended users of this guideline are clinicians and other healthcare professionals involved in the management of patients with DCIS.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

A) Primary Treatment of DCIS: Surgical Treatment

Recommendation 1

1.1. Women with DCIS of the breast (with or without microinvasion) who are candidates for BCS should be offered the choice of BCS or mastectomy with the option of reconstruction. The decision of whether to have one surgery over another should be made in consultation with the patient and should consider the balance of benefits and risks and patient preferences.

Qualifying Statements for Recommendations 1

- Benefits and harms may vary depending on patient and disease characteristics such as patient factors/comorbidities, patient's preferences, tumour characteristics, life expectancy, and any contraindication to or unwillingness to receive radiation therapy (RT).
- When BCS is performed, all mammographically suspicious calcifications should be removed and margins should be microscopically clear of DCIS. RT options after BCS are described in Recommendation 5 below.
- The option of immediate lumpectomy reconstruction in the case of BCS should be offered if a patient is deemed an appropriate candidate.
- Mastectomy, with the option of reconstruction (immediate or delayed), should be considered for those women who have an area of DCIS large enough that BCS would leave them with an unacceptable cosmetic result.
- Patients eligible for genetic testing should be referred so that results may be considered before a surgical treatment plan is finalized (this may include a bilateral risk-reducing mastectomy).
- Active surveillance is an area of ongoing investigation; it is not a standard option currently. This might be an area of consideration for certain patients.

- The use of imaging modalities to assess for residual disease in patients with positive markings post BCS is outsider the scope of this guideline. The Working Group consensus favours positive margins being treated surgically given perceived low sensitivity for detecting residual disease versus postoperative changes in patients having undergone recent surgery with all imaging modalities.

Recommendation 2
2.1. In patients undergoing BCS or mastectomy, a margin width of at least 2mm is optimal to minimize the risk of local recurrence (LR).

Qualifying Statements for Recommendations 2
- It remains entirely appropriate in pathology practice to report only DCIS at inked margin as "positive", and to provide distance to closest margin(s) when margins are negative.
- DCIS-M should be considered as DCIS when considering the optimal margin width and additional surgery.
- Patients who have close or positive margins are directed to the recommendation on the benefits of re-excision prior to receiving RT.

Recommendation 3
3.1. In patients with negative margins (at least 2 mm) undergoing BCS, routine additional surgery may not be warranted for patients if undergoing RT, but re-excision of wider excisions should be considered if the patients forego RT.
3.2. In patients with close margins (<2 mm) from BCS or mastectomy, a discussion should occur with the patient to weigh the risks of further surgery (re-excision or mastectomy) with the risk of recurrence for the individual patient. Patients with close margins where re-excision versus boost RT is being considered should be discussed in multidisciplinary discussions involving surgical and radiation oncologists to tailor the optimal treatment plan.
3.3. In patients with positive margins from BCS or mastectomy, re-excision should be considered as soon as information is available.

Qualifying Statements for Recommendation 3
- The potential risks of cancer recurrence versus additional surgical procedures should be discussed between the patient and surgeon.
- Benefits and harms of re-excision may vary depending on patient and disease characteristics such as patient factors/comorbidities, patient's preferences, tumour characteristics, life expectancy, and any contraindication to or unwillingness to receive RT.
- For patients whose close or positive margins are anterior or posterior, there may be no benefit for reexcision in areas where there is no remaining breast tissue. Multidisciplinary discussion is encouraged to discuss the benefit of boost RT.
- DCIS-M should be considered as DCIS when considering margin width and additional surgery.

B) Primary Treatment of DCIS: Surgical Treatment and/or RT

Recommendation 4
4.1. There are insufficient data to recommend or not recommend molecular profile testing as routine standard practice in women with DCIS. Molecular profile testing should only be performed as part of a research study.

Recommendation 5
5.1. Women with DCIS who have undergone BCS with negative margins should be offered adjuvant WBI (regardless of the grade of DCIS).
5.2. Women with DCIS who have undergone BCS with close margins (< 2mm) for whom re-excision surgery was not performed, multidisciplinary discussion regarding the option of radiation boost in addition to WBI to optimize local control should occur.
5.3. Post-mastectomy radiation therapy (PMRT) is not indicated for women with DCIS who have undergone mastectomy but may be considered if there are multiple positive margins (tumour on ink), that cannot be surgically excised.

Qualifying Statements for Recommendation 5

- The potential risks of cancer recurrence versus adjuvant irradiation should be discussed between the patient and clinicians post BCS and post-mastectomy. Fully informed patients with low-risk DCIS may prefer to avoid RT.
- Hypofractionated RT (HFRT) of 42.5 Gy in 16 fractions for 3.5 weeks or equivalent regimen (e.g., 40 Gy in 15 fractions in 3 weeks) should be offered. We acknowledge that even shorter regimens (e.g., 26 Gy in 5 fractions in 1 week) may also be offered (see recommendation justification below).
- Although there was a benefit for boost across all patients' subtypes, the dose of 16 Gy in eight fractions may be associated with increased toxicity over time and the risks and benefits of a boost need to be weighed, as well as other potential options using lower doses (10 Gy/4-5 fractions to 16 Gy/8 fractions).
- The risk of adverse effects associated with tumour bed boost following WBI should be discussed.
- For patients with low-risk DCIS patients with mammographically detected low or intermediate-grade DCIS measuring 2cm or less and who are 40 years old or older, partial breast irradiation (PBI) may be considered.
- It was the expert opinion of the Working Group that one could safely extrapolate the benefits of adjuvant radiation with more than 5cm of DCIS where complete excision is achieved. Patients were originally excluded from these studies [12,13] because advanced surgical breast conserving techniques did not exist at that time (e.g. oncoplastic reduction mammoplasty). In these cases, multidisciplinary discussion is encouraged for those presenting with more than 5 cm of disease.
- There is a lack of data around adding adjuvant chestwall irradiation after mastectomy as close or positive margin after mastectomy is quite rare. There are however studies showing higher risk of LR in patients with close or positive margins compared to negative margins [5,6]. It is not clear if PMRT is beneficial in this setting given there are few studies that specifically examine the LR risk post-mastectomy with positive margins with or without PMRT. Furthermore, while close or positive margins increase the risk of LR in this setting, overall, the LR risk is relatively low (5.3%) [6]. It was the expert opinion that PMRT is not indicated in this setting, but it is reasonable to consider chestwall irradiation in patients who have undergone mastectomy with multiple positive margins (tumour on ink) that cannot be surgically excised.

C) Management of DCIS after Primary Treatment

Recommendation 6

6.1. The risks and benefits of endocrine therapy, either tamoxifen or an aromatase inhibitor, after BCS should be discussed for women with estrogen receptor (ER)-positive DCIS.

Qualifying Statements for Recommendation 6

- This does not pertain for women with bilateral mastectomy for DCIS, but is relevant for unilateral mastectomy, whether they have had or not had RT.
- Possible risks could include increased toxicity and adverse events, with no survival benefit. There are higher reported rates of endometrial, ovarian, and non-melanoma skin cancer in tamoxifen use and higher rates of fractures, strokes and transient ischemic events with aromatase inhibitors use.
- Possible benefits include prevention of ipsilateral recurrences and contralateral events. This is true for pre-invasive and invasive disease.
- Tamoxifen or aromatase inhibitor for five years taken as once-daily tablet.
- For post-menopausal women younger than 60 years of age, there may be a greater benefit to anastrozole compared to tamoxifen.
- Shared decision-making process to discuss individual risk patient value, preference of agent, duration of agent, and cost.

Management of Ductal Carcinoma in Situ of the Breast

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

The objective of this guideline was to determine the most effective therapy options for patients with ductal carcinoma in situ (DCIS) of the breast.

TARGET POPULATION

These recommendations apply to women with DCIS, including women with DCIS with microinvasion (DCIS-M) (< 1 mm through the duct).

INTENDED USERS

Intended users of this guideline are clinicians and other healthcare professionals involved in the management of patients with DCIS.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

A) Primary Treatment of DCIS: Surgical Treatment

Research Question: What is the optimal surgical treatment (breast conserving surgery [BCS]; mastectomy; active surveillance) for patients with DCIS when considering disease-free survival (DFS), recurrence, and significant complications after surgery (i.e. bleeding or infection)?

Recommendation 1

1.2. Women with DCIS of the breast (with or without microinvasion) who are candidates for BCS should be offered the choice of BCS or mastectomy with the option of reconstruction. The decision of whether to have one surgery over another should be made in consultation with the patient and should consider the balance of benefits and risks and patient preferences.

Qualifying Statements for Recommendations 1

- Benefits and harms may vary depending on patient and disease characteristics such as patient factors/comorbidities, patient's preferences, tumour characteristics, life expectancy, and any contraindication to or unwillingness to receive radiation therapy (RT).
- When BCS is performed, all mammographically suspicious calcifications should be removed and margins should be microscopically clear of DCIS. RT options after BCS are described in Recommendation 5 below.
- The option of immediate lumpectomy reconstruction in the case of BCS should be offered if a patient is deemed an appropriate candidate.
- Mastectomy, with the option of reconstruction (immediate or delayed), should be considered for those women who have an area of DCIS large enough that BCS would leave them with an unacceptable cosmetic result.
- Patients eligible for genetic testing should be referred so that results may be considered before a surgical treatment plan is finalized (this may include a bilateral risk-reducing mastectomy).

- Active surveillance is an area of ongoing investigation; it is not a standard option currently. This might be an area of consideration for certain patients.
- The use of imaging modalities to assess for residual disease in patients with positive markings post BCS is outsider the scope of this guideline. The Working Group consensus favours positive margins being treated surgically given perceived low sensitivity for detecting residual disease versus postoperative changes in patients having undergone recent surgery with all imaging modalities.

Key Evidence and Justification for Recommendation 1

There were no randomized controlled trials (RCTs) found comparing BCS versus mastectomy; therefore, no strong evidence for one treatment strategy over another is currently available. This recommendation with its Qualifying Statements was made through the consensus of the Working Group that patients and their health care provider team should discuss management strategies and the patient should be offered the choice of BCS or total mastectomy with the option of reconstruction. This is consistent with the recommendations from another consensus guideline [1]. Patients are eligible for BCS when, after removing disease tissue, there remains enough tissue to leave the patients with a cosmetically acceptable breast mound. The option of immediate lumpectomy reconstruction in the case of BCS should be offered if a patient is deemed an appropriate candidate. Recognizing that BCS can be offered in conjunction with RT, patients choosing not to receive RT may select mastectomy as their surgical treatment. The addition of adjuvant therapy to surgical treatment is covered in Recommendation 5 and 6. These recommendations place a high value in patients' individual preferences for surgery after reviewing the benefits and risks of either BCS and total mastectomy with or without immediate or delayed reconstruction. Active surveillance as an alternative to surgical treatment in DCIS patients has several ongoing RCTs comparing active surveillance and conventional surgical treatment, such as the LORIS trial (UK-LORIS), the LORD trial (NCT02492607) and the COMET trial (NCT02926911; see Appendix 7).

Research Question: What margin width minimizes the risk of recurrence, complications after surgery (i.e., bleeding, infection) and increases DFS in patients undergoing DCIS receiving BCS or mastectomy?

Recommendation 2

2.1. In patients undergoing BCS or mastectomy, a margin width of at least 2mm is optimal to minimize the risk of local recurrence (LR).

Qualifying Statements for Recommendations 2

- It remains entirely appropriate in pathology practice to report only DCIS at inked margin as "positive", and to provide distance to closest margin(s) when margins are negative.
- DCIS-M should be considered as DCIS when considering the optimal margin width and additional surgery.
- Patients who have close or positive margins are directed to the recommendation on the benefits of re-excision prior to receiving RT.

Key Evidence for Recommendation 2

- For BCS, one systematic review with meta-analysis [2] was retained. The risk of bias was low by using the ROBIS assessment tool. A total of 7883 women receiving whole-breast irradiation (WBI) from 20 studies (2 prospective, 17 retrospective) found that a margin width of 2 mm (odds ratio [OR], 0.51; 95% confidence interval [CI] 0.31 to 0.85), 3mm or 5mm (OR, 0.42; 95% CI, 0.18 to 0.97), and 10mm (OR, 0.60; 95% CI, 0.33 to 1.08)

had similar reductions in the odds of LR. A second analysis found similar odds of LR for >0 or 1 mm (OR, 0.45; 95% CI, 0.30 to 0.62), 2 mm (OR, 0.32; 95% CI, 0.21 to 0.48), 3 mm (OR, 0.30; 95% CI, 0.12 to 0.76) and 10 mm (OR, 0.32; 95% CI, 0.19 to 0.49). There was no difference in relative odds of LR between 10mm and 2 mm (relative OR, 0.99; 95% CI, 0.61 to 1.64).

- Three comparative studies of BCS (with or without RT) were retained [3,4]. The certainty of evidence was very low using the GRADE approach. In a multivariate analysis (adjusted for age, menopausal status, duration of endocrine therapy), there was a trend difference in margin width (>2 mm vs. <2 mm) and local regional recurrence (LRR) in patients receiving RT (hazard ratio [HR], 2.03; 95% CI, 0.89 to 4.64), p=0.09), but no difference when not receiving RT (HR, 2.08; 95% CI, 0.44 to 9.80), p=0.36). In another comparison study, patients who underwent adjuvant RT showed no significant difference in LRR between margin widths of <2 mm and ≥2 mm (HR, 0.77; 95% CI, 0.19 to 3.23, p=0.72) [4]. In a large multi-national pooled analysis of patient-level data of women undergoing BCS with or without RT, risks for both ipsilateral DCIS (HR 1.39, 95% CI, 1.04 to 1.87) and invasive ipsilateral breast cancer (IBC) (HR, 1.40; 95% CI, 1.07 to 1.83) were significantly higher with involved margins (< 2mm) when compared to clear margins (>2 mm) [5].
- For mastectomy, one systematic review with 12 retrospective studies [6] and a comparative study [5] were retained. The risk of bias was low according to the ROBIS assessment tool. Due to low heterogeneity, a fixed-effect model was used to analyze recurrence rate (RR). When comparing patients with positive or close margins to those with negative margins, there was a 3.72-fold higher risk of LR (RR, 3.72; 95% CI, 2.30 to 6.01). Patients with positive margins showed a 2.91-fold higher risk of LR when compared to patients with close margins (RR, 2.91; 95% CI, 1.14 to 7.41). Kim et al also conducted a subgroup meta-analysis based on the definition of close margins; studies that defined close margins as <1 mm had a LR of RR, 7.06 (95% CI, 2.81 to 17.71) and those defining as less than 2 mm had a LR of RR, 3.09 (95% CI, 1.75 to 5.46). In a large multi-national pooled analysis of patient level data, the risk of IBC was not significantly increased with involved margins (<2mm) [5].
- There was no evidence found for the outcomes of DFS or significant complications after surgery requiring reoperation within 30 days for BCS or mastectomy patients.

Justification for Recommendation 2

The Working Group members believed recurrence and DFS were critical outcomes. Significant complications after surgery requiring reoperation within 30 days were deemed important outcomes for recommendation development. The Working Group, including two patient representatives, were unanimous in their opinion that patients would value decrease recurrence and increase DFS in addition to acceptable adverse events. This recommendation places higher value on treating the cancer in a single surgery with optimal margins and minimized risk of recurrence than potential additional surgery and adverse events. The benefits are considered to be greater than the harms and the evidence is generalizable to the entire target population. The certainty of the evidence was from the two comparative studies and was considered very low; further, the risk of bias of the included systematic reviews was low. Positive and close margins after mastectomy are quite rare and evidence was limited. The available evidence suggests that a margin width of 2 mm minimizes the risk of recurrence, and a wider margin width is not indicative of a lower risk of LR. Therefore, the Working Group made the recommendation in favour of a margin width of a least 2 mm to minimize the risk of LR. It remains entirely appropriate in pathology practice to report only DCIS at inked margin as “positive”, and to provide distance to closest margin(s) when margins are negative.

Research Question: After initial surgery of BCS or mastectomy with suboptimal margin width (close or positive), should re-excision be considered to improve DFS, recurrence, and reduce complications after surgery requiring reoperation within 30 days (i.e. bleeding or infection)?

Recommendation 3

3.1. In patients with negative margins (at least 2 mm) undergoing BCS, routine additional surgery may not be warranted for patients if undergoing RT, but re-excision of wider excisions should be considered if the patients forego RT.

3.2. In patients with close margins (<2 mm) from BCS or mastectomy, a discussion should occur with the patient to weigh the risks of further surgery (re-excision or mastectomy) with the risk of recurrence for the individual patient. Patients with close margins where re-excision versus boost RT is being considered should be discussed in multidisciplinary discussions involving surgical and radiation oncologists to tailor the optimal treatment plan.

3.3. In patients with positive margins from BCS or mastectomy, re-excision should be considered as soon as information is available.

Qualifying Statements for Recommendation 3

- The potential risks of cancer recurrence versus additional surgical procedures should be discussed between the patient and surgeon.
- Benefits and harms of re-excision may vary depending on patient and disease characteristics such as patient factors/comorbidities, patient's preferences, tumour characteristics, life expectancy, and any contraindication to or unwillingness to receive RT.
- For patients whose close or positive margins are anterior or posterior, there may be no benefit for reexcision in areas where there is no remaining breast tissue. Multidisciplinary discussion is encouraged to discuss the benefit of boost RT.
- DCIS-M should be considered as DCIS when considering margin width and additional surgery.

Key Evidence and Justification for Recommendation 3

There were no RCTs found comparing re-excision to no re-excision in patients with suboptimal margin (close or positive) after initial surgery of BCS or mastectomy; therefore, there is no strong evidence for one treatment strategy over another. It was the consensus of the Working Group that further surgery may be warranted in order to minimize the risk of recurrence, which is highest in patients with positive margins and less so in close margins, and even less with negative margins [2-4]. While such a procedure can be both physically and mentally challenging for the patient, the benefits of such a treatment plan outweigh the risks. Many factors such as comorbidity, patient's preferences, re-excision cosmetic impact, life expectancy, tumour characteristics and any contraindication to or unwillingness to receive RT should be considered before proceeding with re-excision.

B) Primary Treatment of DCIS: Surgical Treatment and/or RT

Research Question: Should molecular profile testing be added to clinical evaluation to guide the use of any adjuvant therapy in patients with DCIS?

Recommendation 4

4.1. There are insufficient data to recommend or not recommend molecular profile testing as routine standard practice in women with DCIS. Molecular profile testing should only be performed as part of a research study.

Key Evidence for Recommendation 4

- Two full-text publications reported on the outcome of recurrence on the molecular profile test Oncotype DX [7,8] and one abstract on DCISionRT [9]. The certainty of the evidence was downgraded to very low due to high risk of bias, indirectness, and imprecision using the GRADE approach.
- In a subgroup analysis, in patients with clinicopathological (CP) features (i.e., low or intermediate nuclear grade DCIS, wide clear margins and tumour size smaller than 2.5cm, majority 50 years or older at diagnosis), many of those cases also had a low-risk DCIS score where their treatment with BCS alone also had an expected low risk of LR (10.1% at 10 years). There was also a group of patients that had the same CP features during the same period and same treatment of BCS alone but were identified as having a high-risk DCIS score with a higher risk of LR (19.6% at 10 years) and a reduction in LR after RT.
- A retrospective exploratory analysis examined the association between 12-gene Oncotype DX and relevant CP factors with recurrence in a pooled cohort of women treated with local excision and accelerated partial breast irradiation (APBI). The study found that the DCIS score was significantly associated with local recurrence (p=0.01), but CP factors were not associated with LRR [8]. These results are highly variable due to the small number of LR events, the limited follow-up time and wide confidence intervals.
- In the abstract of four international cohorts of DCIS patients (n=926) treated with BCS (negative margins) with or without RT, tissues were analyzed according to the DCISionRT with Residual Risk subtype (RRt). Fifty one percent of patients with CP low-risk Radiation Therapy Oncology Group (RTOG) 9804-like features and 58% of favourable age/nuclear grade were re-classified as DCISionRT High Risk and showed significant RT benefit and absolute 10-year ipsilateral breast recurrence (IBR) reduction (see Table 4-3). Twenty-three percent of CP high risk group of no-9804 like features and 31% of non-favourable age/nuclear grade were re-classified as DCISionRT Low Risk, where RT did not significantly reduce IBR in these groups [9].

Justification for Recommendation 4

The Working Group members believed that the critical outcomes for recommendation development were recurrence or RT benefit. The research question aimed to determine if molecular profile testing could be added to clinical evaluation to guide the use of any adjuvant therapy in patients with DCIS. The certainty of the evidence was considered very low, and the results are very highly variable due to the small number of LR events, limited follow-up time and wide confidence intervals. In addition, one study included only patients with negative margins. It was the consensus of the Working Group that due to the lack of mature data, molecular profile testing could not be recommended or not recommended as a routine standard practice in women with DCIS. The Working Group recognizes that ongoing trials may provide further information in this area in the next several years (See Appendix 7 for a list of ongoing trials).

Research Question: In DCIS patients who have undergone BCS or mastectomy, should breast irradiation be offered to improve DFS and reduce recurrence with acceptable adverse events of irradiation?

Recommendation 5

5.1. Women with DCIS who have undergone BCS with negative margins should be offered adjuvant WBI (regardless of the grade of DCIS).

5.2. Women with DCIS who have undergone BCS with close margins (< 2mm) for whom re-excision surgery was not performed, multidisciplinary discussion regarding the option of radiation boost in addition to WBI to optimize local control should occur.
5.3. Post-mastectomy radiation therapy (PMRT) is not indicated for women with DCIS who have undergone mastectomy but may be considered if there are multiple positive margins (tumour on ink), that cannot be surgically excised.

Qualifying Statements for Recommendation 5

- The potential risks of cancer recurrence versus adjuvant irradiation should be discussed between the patient and clinicians post BCS and post-mastectomy. Fully informed patients with low-risk DCIS may prefer to avoid RT.
- Hypofractionated RT (HFRT) of 42.5 Gy in 16 fractions for 3.5 weeks or equivalent regimen (e.g., 40 Gy in 15 fractions in 3 weeks) should be offered. We acknowledge that even shorter regimens (e.g., 26 Gy in 5 fractions in 1 week) may also be offered (see recommendation justification below).
- Although there was a benefit for boost across all patients' subtypes, the dose of 16 Gy in eight fractions may be associated with increased toxicity over time and the risks and benefits of a boost need to be weighed, as well as other potential options using lower doses (10 Gy/4-5 fractions to 16 Gy/8 fractions).
- The risk of adverse effects associated with tumour bed boost following WBI should be discussed.
- For patients with low-risk DCIS patients with mammographically detected low or intermediate-grade DCIS measuring 2cm or less and who are 40 years old or older, partial breast irradiation (PBI) may be considered.
- It was the expert opinion of the Working Group that one could safely extrapolate the benefits of adjuvant radiation with more than 5cm of DCIS where complete excision is achieved. Patients were originally excluded from these studies [12,13] because advanced surgical breast conserving techniques did not exist at that time (e.g. oncoplastic reduction mammoplasty). In these cases, multidisciplinary discussion is encouraged for those presenting with more than 5 cm of disease.
- There is a lack of data around adding adjuvant chestwall irradiation after mastectomy as close or positive margin after mastectomy is quite rare. There are however studies showing higher risk of LR in patients with close or positive margins compared to negative margins [5,6]. It is not clear if PMRT is beneficial in this setting given there are few studies that specifically examine the LR risk post-mastectomy with positive margins with or without PMRT. Furthermore, while close or positive margins increase the risk of LR in this setting, overall, the LR risk is relatively low (5.3%) [6]. It was the expert opinion that PMRT is not indicated in this setting, but it is reasonable to consider chestwall irradiation in patients who have undergone mastectomy with multiple positive margins (tumour on ink) that cannot be surgically excised.

Key evidence for Recommendation 5

A. BCS

a. RT vs. none

- Four RCTs with multiple different follow-up times suggests that the addition of RT after BCS could reduce recurrence rates and have a long-term beneficial effect of RT [10-14].
- The SweDCIS trial showed a significant reduction in the risk of IBR in patients undergoing RT [10]. At 20 years' follow-up, the RT arm showed an absolute risk reduction of 12.0% and relative risk reduction of 37.5% [11].

- The European Organization for Research and Treatment of Cancer Randomized Phase II Trial 10853 (EORTC 10853) 10-year follow-up found that RT after BCS reduced LR, DCIS recurrence and invasive recurrence risk when compared to BCS alone [12]. At 15 years, treatment with adjuvant RT approximately halved LR risk [13]. RT also reduced the risk of pure DCIS and invasive LR at 15 years.
- The Radiation Therapy Oncology Group (RTOG 9804) trial randomized women with 'good risk' to RT or none after BCS and found at a median follow-up time of seven years, IBR was significantly less with the addition of RT versus no RT (0.9% vs. 6.7%; p<0.001) [14]. At 15-year cumulative IBR, rates remained significantly lower for patients in the RT group (7.1% vs 15.1%; p=0.007) [15]. Similarly, the rates of invasive LR were lower in the RT group (5.4% vs 9.5%, p=0.027).
- Moderate certainty in the evidence from six full-text publications on three trials with multiple different follow-up times suggests that the addition of RT after BCS does not alter survival rates [10-15]. The SweDCIS trial at five years showed far fewer event-free survivals in the RT group compared to no RT (p<0.001 log-rank test; [10]); however at 20 years' follow up, the lower risk in the RT arm was nonsignificant [11]. In the EORTC 10853 study, results at 10 years [12] and 15 years [13] results showed no differences in overall survival (OS) and the RTOG 9804 trial found no difference DFS and OS at seven years' [14] or 15 years [15] follow-up.
- Moderate level of certainty of evidence from two full-text publications on one trial with multiple follow-up times to suggest that with the addition of RT increases, the number of adverse events experiences increases [14,15]. The RTOG 9804 trial RT group had higher rates of grade 1 and 2 acute toxicities than no RT (76% vs. 30%, p<0.001), but grade 3 or greater toxicities were similar (4%) in each group [14]. For late toxicities, there was a slightly higher rate of grade 1 toxicities (30%) than grade 2 (4.6%) or 3 (0.7%) [14]. At 13.9 years' follow-up, grade 3 late RT toxicities was 1.0% and there were no grade 4 or 5 toxicities [15].

b. Tumour Boost vs. none

- High level of certainty of evidence to suggests that the addition of RT tumour bed boost following WBI could reduce recurrence rates. An international, RCT phase 3 study from 11 countries randomized non-low-risk DCIS patients treated with BCS (at least 1 mm clear resection) to tumour boost or no boost after postoperative WBI and found that boost had significantly decreased LR. The five-year free from LR rates for the boost group was 97.1% and for the no-boost group was 92.7%, an absolute gain in local control of 4.4% at five years with boost radiation. Almost one-half of the LR were invasive in both groups. When looking at 5-year disease free recurrence rate, the boost group was 93.7% and the no boost group was 89.6% [16]. There was potentially greater benefit for patients with larger tumour size on multivariate analysis (MVA). Although other risk factors such as high grade and younger age were only associated with a trend for boost benefit, they were not statistically significant on multivariate analysis.
- Moderate certainty of evidence to suggests no difference in survival with the addition of tumour bed boost. BIG 3-07/TROG 07.01 found that there were no significant differences in five-year OS between patients randomized in the tumour bed boost group (99.0%) versus the no tumour bed boost (98.2%) after WBI (p=0.47; [16]).
- High certainty of evidence from two full-text publications on two trials to suggests that the addition of boost to the tumour bed is associated with an increase in treatment adverse events [16,17]. BIG 3-07/TROG 07.01 found the addition of tumour bed boost was associated with significantly higher rates of grade 2 or higher breast pain and induration, however there was no significant increase in RT pneumonitis, cardiac

disease, or RT-related malignancy. There also were no grade 5 events and grade 4 events were rare [16]. The BONBIS phase III trial evaluated the role of a localized RT boost (16-Gy) in patients with DCIS patients. It reported acute toxicities (during and up to 3 months after RT completion) as part of their quality assurance program and found that localized boost significantly increases the rate of grade 2 or higher breast erythema, dermatitis, and grade 2 hyperpigmentation. Cardiac or lung toxicities were not reported.

c) Conventional RT vs. HFRT

- There is high level of certainty to suggest that moderately HFRT is as effective as conventional RT (CRT) in patients with non-low-risk DCIS after BCS. BIG 3-07/TROG 07.01 found no statistically significant differences in five-year free from LR between CRT (50 Gy/25 fractions/5 weeks) versus HFRT (42.5 Gy/16 fractions/3.5 weeks). An analysis involving all patients found that the five-year free from LR rate was 94.9% in both groups (p=0.85). The five-year free from disease recurrence rate for all patients was 91.0% in the CRT group and 92.4% in the HFRT group (p=0.46). The literature review did not find any trials meeting our inclusion criteria of outcomes of DFS or treatment adverse events.

d. PBI RT (PBI) vs WBI

- There is moderate level of certainty to suggest that PBI is as effective as WBI in terms of recurrence rates among patients with DCIS. A high-level systematic review with meta-analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP)-39 [18] and RAPID [19] studies did not observe a significant difference in 10-year recurrence rates among patients treated with PBI compared with WBI (HR, 1.26; 95% CI, 0.004 to 45.14, I2 = 35.10) [20]. There was no further information on which DCIS patients may or may not be favourable candidates for PBI.

B. Mastectomy

There was no RCT evidence found for DCIS patients who have undergone mastectomy and whether breast irradiation should be offered to improve DFS and reduce recurrence and treatment adverse events.

Justification for Recommendation 5

The Working Group members believed recurrence and DFS were critical outcomes. Adverse events were deemed important outcomes for recommendation development. These recommendations place higher value on avoiding cancer recurrence than the risk of higher adverse events. The certainty of evidence ranges from moderate to high. With the addition of RT versus no RT, the desirable effects were moderate (i.e., significant differences in recurrence rates, but no significant differences in survival rates) and the undesirable effects were moderate (i.e., there was clinically meaningful differences in adverse events). It was the consensus of the Working Group that the significant reduction in recurrence rates outweighed the adverse effects of the adjuvant breast irradiation. The potential risks of cancer recurrence versus with the potentially adverse effects of breast irradiation should be discussed between the patient and surgeon.

There is high certainty in the evidence to suggest that the additional RT boost following WBI could reduce recurrence rates but at the additional risk of increased a treatment-related adverse events in patients undergoing BCS. A dose of 16 Gy in eight fractions was used in the BIG 3-07/TROG 07.01. There was potentially greater benefit for patients with larger tumor size and other risk factors such as high grade and younger age were associated with a trend for

boost benefit. There was some evidence to suggest no difference in survival with the additional tumour boost; however, there is no long-term evidence yet of survival data (only 5 years follow-up).

There is high level of certainty to suggest that moderately HFRT is as effective as CRT in women with non-low-risk DCIS after BCS. Evidence from a large international study suggests that fewer, larger radiation doses over a shorter period was safe and as effective as CRT. It was the consensus of the Working Group that HFRT of 42.5 Gy in 16 fractions or equivalent regimen (e.g., 40 Gy in 15 fractions in 3 weeks) should be offered to patients. The Working Group acknowledged that shorter regimens (e.g., 26 Gy in 5 fractions) may also be offered, such as those used in the FAST-Forward randomized trial for invasive breast cancer which showed that 26 Gy in five fractions over one week was non-inferior to moderate HFRT both for local control and normal tissue toxicity at five years [21].

There is moderate level of certainty to suggest that PBI is as effective as WBI in terms of recurrence rates among patients with DCIS. Data from a systematic review of two trials support the use of PBI among patients with DCIS; however, the systematic review was unable to provide additional details of which DCIS patients would be suitable for PBI. It was the expert opinion of the Working Group that adjuvant PBI after BCS may be considered in carefully selected patients with good risk or low-risk DCIS meeting all aspects of, as defined by the RTOG 9804 criteria of mammographically detected low or intermediate-grade DCIS, measuring less than 2.5 cm with margins $\geq$3 mm. This is consistent with the ASTRO guideline [22,23]. There were two other RCTs on PBI after BCS for early-stage breast cancer that did not meet prespecified criteria of separating DCIS and invasive disease (University of Florence and GEC-ESTRO) that show that PBI has similar recurrence rates as WBI.

C) Management of DCIS after Primary Treatment

Research Question: In DCIS patients who have undergone BCS or mastectomy, what is the role of endocrine therapy in the management of DCIS to improve DFS and reduce recurrence (invasive or non-invasive) and contralateral events with acceptable treatment adverse events?

Recommendation 6
6.1. The risks and benefits of endocrine therapy, either tamoxifen or an aromatase inhibitor, after BCS should be discussed for women with estrogen receptor (ER)-positive DCIS.

Qualifying Statements for Recommendation 6

- This does not pertain for women with bilateral mastectomy for DCIS, but is relevant for unilateral mastectomy, whether they have had or not had RT.
- Possible risks could include increased toxicity and adverse events, with no survival benefit. There are higher reported rates of endometrial, ovarian, and non-melanoma skin cancer in tamoxifen use and higher rates of fractures, strokes and transient ischemic events with aromatase inhibitors use.
- Possible benefits include prevention of ipsilateral recurrences and contralateral events. This is true for pre-invasive and invasive disease.
- Tamoxifen or aromatase inhibitor for five years taken as once-daily tablet.
- For post-menopausal women younger than 60 years of age, there may be a greater benefit to anastrozole compared to tamoxifen.
- Shared decision-making process to discuss individual risk patient value, preference of agent, duration of agent, and cost.

Key Evidence for Recommendation 6

A. BCS

a. Tamoxifen vs. none

- Moderate certainty evidence from one full publication of a trial to suggests a benefit with the addition of tamoxifen in reducing recurrence in women with DCIS treated with BCS [24]. In the UK/ANZ DCIS trial at 12 years' follow-up, when looking at all patients randomized to tamoxifen vs. none, patients in the tamoxifen group had significantly fewer new breast events compared to those not receiving tamoxifen (18.1% vs 24.6%, p=0.002); specifically, tamoxifen reduced the rate of recurrence of ipsilateral DCIS events, but not ipsilateral invasive events. When patients were analyzed based on who received RT or not, it was found that in patients not receiving RT, tamoxifen significantly reduced the rate of recurrence of ipsilateral DCIS events, but not ipsilateral invasive events [24]. In patients receiving RT, there was no significant reduction in either ipsilateral DCIS or invasive events between tamoxifen versus none [24].
- Moderate level of certainty evidence suggests that there is a benefit to tamoxifen in reducing contralateral events in women with DCIS treated with BCS. In the UK/ANZ DCIS trial, for all patients randomized to tamoxifen or none, there was an overall significant reduction in all contralateral events (invasive and DCIS) between tamoxifen vs none, with an absolute 10-year reduction of 2.3% [24]. The literature review found no trials meeting our inclusion criteria for DFS or treatment adverse events.
- The relationship between ER and progesterone receptors (PgR) and the response to tamoxifen was evaluated in a retrospective analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 study [25]. After BCS and RT, ER-positive patients treated with adjuvant tamoxifen versus placebo showed significant decrease in any breast cancer event (HR, 0.58; 95% CI, 0.42 to 0.81); p=0.001) and any invasive breast cancer (HR, 0.53; 95% CI, 0.31 to 0.82; p=0.005); while reduction was also observed for any DCIS it was not significant. When patients were stratified by PgR, results were similar but were not more predictive when ER status was considered alone. There was no significant benefit in ER-negative DCIS in any setting.

b) Tamoxifen vs. Anastrozole

- There is a high level of certainty in the evidence to suggest there is no significant difference between tamoxifen or anastrozole in terms of recurrence rates. The IBIS-II DCIS trial found at seven years' follow-up, after adjusting for age, body mass index (BMI), use of menopausal hormone therapy before trial, grade, margins and RT, there was no significant difference in overall recurrence between the groups (67 anastrozole vs. 77 tamoxifen) [26]. Also, there was no significant difference between groups for ipsilateral invasive recurrence or DCIS ipsilateral recurrence. There was also no difference in recurrence rates if a patient had RT use at baseline [26]. The NSABP B-35 trial randomized postmenopausal women (ER or PgR positive) with locally excised DCIS or mixed DCIS/lobular carcinoma in situ (LCIS) after RT to receive 1mg oral anastrozole or 20 mg oral tamoxifen every day for five years [27]. There was a significant difference between anastrozole and tamoxifen and breast cancer-free interval (BCFI; i.e., any breast cancer recurrence event), where patients on anastrozole had a significant decreased BCFI. When looking at the individual events contributing to BCFI, there was a significant difference between groups for all invasive recurrence (p=0.01), but not DCIS recurrence (p=0.52). However, this beneficial effect only remained significant among women younger than 60 years of age (p=0.038).
- There were two moderate level RCTs that examined the differences between tamoxifen and anastrozole on the outcome of contralateral events. The IBIS-II trial analyses

adjusted for age, BMI, menopausal hormone therapy, grade, margins, and RT, which found similar numbers between anastrozole and tamoxifen for contralateral invasive recurrences and DCIS recurrences. In contrast, NSABP B-35 trial found a significant reduction in all contralateral breast cancer (CBC) in patients in the anastrozole group when compared to those in the tamoxifen group (p=0.032) [27]. On closer examination, this reduction remained significant for contralateral invasive recurrence (p=0.015) but not DCIS CBC (p=0.73). There were fewer event numbers for contralateral DCIS for both trials and larger confidence intervals giving very low certainty in the non-effect.

- Moderate certainty evidence suggests that either tamoxifen or anastrozole would be equally as effective in OS in women of all ages; however, for post-menopausal women younger than 60 years of age, there may be a greater benefit to anastrozole compared to tamoxifen. The NSABP B-35 found a significant interaction between treatment group and age when looking at DFS, where women younger than 60 years of age in the anastrozole group had greater DFS. There was no statistically significant benefit for women older than 60 years of age [27].
- Moderate certainty evidence suggests a difference in tamoxifen and anastrozole in terms of adverse events. IBIS-II DCIS trial reported the tamoxifen group had higher rates of endometrial, ovarian, and non-melanoma skin cancer and the anastrozole group had significantly higher rates of fractures and transient ischemic attacks [26,28]. The NSABP B-35 trial found a higher rate of thrombosis/embolism between groups, but no significant differences in uterine cancer. The authors report that there were no other striking differences between groups in terms of adverse events [27].

B. Mastectomy

The literature review found no trials meeting our inclusion criteria for endocrine therapy in the management of DCIS in mastectomy patients.

Justification for Recommendation 6

The Working Group members believed recurrence and DFS were critical outcomes and adverse events were an important outcome for recommendation development. The Working Group, including two patient representatives, were unanimous in their opinion that patients would value decrease recurrence and increased DFS in addition to acceptable adverse events.

There was moderate certainty to suggest a benefit with the addition of tamoxifen in reducing recurrence rates and contralateral events in women treated with BCS, particularly in women who are ER positive [25]. Results from the IBIS-II and NSABP-B-35 studies suggest no significant difference between tamoxifen or anastrozole as a choice of endocrine therapy in the management of DCIS to reduce recurrence rates. For post-menopausal women younger than 60 years of age, there may be a greater benefit to anastrozole compared to tamoxifen. While there are possible benefits in the prevention of recurrence events, there are also increased risks of toxicity and adverse events, such as endometrial cancer, deep vein thrombosis, and transient ischemic attack. It was the consensus of the Working Group that the risks and benefits of endocrine therapy, either tamoxifen or aromatase inhibitor, after BCS should be discussed with ER-positive DCIS patients.

The Working Group acknowledges that a lower dose of tamoxifen for a shorter period and reduced dose (i.e., 5 mg daily tamoxifen for 3 years) may also be an option for reducing recurrence in hormone-sensitive breast with similar or slightly lower toxicity than a full dose; however, this study [29] did not meet prespecified criteria. Physician-based preference or shared decision-making process should discuss each individual personal risk, the patient's values, preference of agent, the duration of agent, and potential cost involved.

IMPLEMENTATION CONSIDERATIONS

When implementing the recommendations, resource availability should be considered. In some healthcare settings or geographical locations, the availability of resources for certain treatments, such as breast reconstruction, breast irradiation and genetic testing, may be limited.

RELATED GUIDELINES

- Eisen A, Fletcher GG, Gandhi S, Mates M, Freedman OC, Dent SF, et al. Optimal systematic therapy for early female breast cancer. Toronto (ON): Cancer Care Ontario; 2014 Sep 30 [In Review 2019 Jan]. Program in Evidence-Based Care Evidence-Based Series No.: 1−21 IN REVIEW.
- Muradali D, Fletcher GG, Cordeiro E, Fienberg S, George R, Kulkarni S, et al. Preoperative Breast Magnetic Resonance Imaging Guideline. Toronto (ON): Ontario Health (Cancer Care Ontario); 2023 March 24. Program in Evidence Based Care Guideline No.: 1-25 GL.
- Zhong T, Spithoff K, Kellett S, Boyd K, Brackstone M, Hanrahan R, Whelan T. Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options. Toronto (ON). Cancer Care Ontario. Program in Evidence-Based Care Series No.: 17-10 REQUIRES UPDATING.

FURTHER RESEARCH

DCIS remains an area of active research. Continued research into molecular profiling may help identify which DCIS cases are likely to progress to invasive breast cancer and which can be safely management with less aggressive treatment or active surveillance. Also, studies aimed to optimize the use of RT, including the investigation of shorter treatment regimens or targeted RT techniques (e.g., stereotactic body RT) to minimize adverse side effects while maintaining effectiveness are ongoing.

GUIDELINE LIMITATIONS

This guideline does not cover diagnosis or staging (i.e., methods of diagnosis including mammography, magnetic resonance imaging biopsy, and histopathological evaluation or the staging/ classification of DCIS), follow-up and surveillance, quality of life and survivorship or patient education. The systematic review inclusion criteria were limited to RCTs for some questions. In the absence of any RCTs inclusion of retrospective studies may have provided additional information.

Management of Ductal Carcinoma in Situ of the Breast

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

New evidence involving the management of care in Ductal Carcinoma in Situ (DCIS) of the breast and its implication on patient treatment has emerged. It was decided to update and broaden the scope of the guideline of the 2018 guideline (Appendix 1).

GUIDELINE DEVELOPERS

This guideline was developed by the DCIS GDG (Appendix 2), which was convened at the request of the Disease Pathway Management Program of OH (CCO).

The project was led by a small Working Group of the DCIS GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, surgical oncology, and health research methodology. Other members of the DCIS GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

Two patients also participated as active members of the DCIS Working Group. The patient representatives attended and participated in Working Group meetings and teleconferences. They provided feedback on draft guideline documents throughout the entire practice guideline development process, communicating the perspective of patients and members of the public.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [30,31]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [32] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and consider the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability, and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines and Assessment of Guidelines

A search for existing guidelines is generally undertaken prior to search for existing systematic reviews and primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement to avoid the duplication of guideline development efforts. For this project, the following databases were searched for existing guidelines that addressed the research questions on August 1, 2022 with the search terms "Ductal Carcinoma in Situ", "DCIS", and "Breast": National Institute for Health and Care Excellence Evidence Search, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology (ASCO), National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, Cancer Council Australia, Geneva Foundation for Medical Education, and Research, American Society for Radiation Oncology (ASTRO), American College of Radiology and Alberta Health Services. MEDLINE and EMBASE were searched for guidelines for the period of 1996 to August 2022. Guidelines were considered potentially relevant if they were based on a systematic review that addressed at least one research question (see Section 4). Only English language evidence-based guidelines less than three years old were considered.

This search for existing guidelines yielded two guidelines [1,33]. The NCCN guideline [1] was not considered suitable for endorsement or adaptation as an update was in progress at the time of the search. While the Society of Surgical Oncology (SSO)/ASTRO/ASCO guideline was published more than three years ago, its currency, accuracy and validity of the evidence was evaluated in September 2019 by a guideline development panel and based on their recommendation, it was affirmed that an update to the guideline was not required. Its quality was assessed by using the AGREE II tool [34] and would only be considered for inclusion if a score above 50% on the rigour of development domain (assesses the methodological quality of the guideline) was obtained. The assessment results for the SSO/ASTRO/ASCO guideline are shown in Appendix 3. Although the authors of the guideline used a systematic review/meta-analysis as the evidence foundation [2], the recommendations they made were based mainly on clinical opinion. The Working Group members decided to develop recommendations based on current evidence for the Ontario context. The systematic review/meta-analysis [2] will be described in further detail below.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document,

or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CMA/Joule CPG Infobase database and the Guidelines International Network (GIN) Library.

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Management of Ductal Carcinoma in Situ of the Breast

Section 4: Systematic Review

INTRODUCTION

DCIS is a non-invasive breast cancer characterized as the proliferation of abnormal epithelial cells that are confined within the basement membrane of the mammary ducts [35]. If there was a disruption to the basement membrane layer, the diagnosis would change from DCIS to invasive breast cancer. Many DCIS lesions are nonpalpable and are identified by microcalcifications discovered at the time of routine screening mammography [36]. Among new diagnoses of breast cancer detected through screening, DCIS account for approximately one-fifth of all new diagnoses [37,38].

The management of DCIS depends on variety of factors, including the size and location of the tumour, the presence of genetic mutations, other risk factors, and the patient's overall health and preference. Treatment may include surgery, RT, hormonal therapy, or a combination of all. DCIS-M is a rare subtype of breast cancer that involves a small area of invasive cancer cells within the DCIS lesions. It is managed like pure DCIS, with the aim of removing the abnormal cells and preventing the cancer from spreading. The presence of microinvasion could indicate a higher risk of recurrence or progression to invasive disease [39].

Surgery is often the first line of treatment for DCIS, with the aim of removing the abnormal cells and preventing the cancer from spreading. This may involve a BCS, removing the tumour and the surrounding tissue or a mastectomy, removing the entire breast. Close or positive margins are a common problem that can occur during surgery, which may increase the risk of recurrence or requiring additional surgery. A meta-analysis has demonstrated that patients with positive margins have a higher risk of LR in comparison to patients with negative margins [40]; however, the threshold however of optimal margin width is unclear. RT may also be recommended to target any remaining cancer cells and reduce the risk of recurrence. More recently, there is new evidence about the role of hypofractionation and/or shorter duration of RT, and the emerging area of research of molecular profiling to help guide treatment decisions, including the use of RT. Hormonal therapy, such as tamoxifen or aromatase inhibitors, may also be recommended to reduce the risk of recurrence. In some cases, active surveillance or omission of RT may also be an option to women who are at low risk of recurrence.

Given the emergence of new evidence involving the management of care in DCIS of the breast and its implication on patient treatment, it was decided to update and broaden the scope of the guideline of the 2018 guideline (Appendix 1). The DCIS GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below. This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42023435123.

RESEARCH QUESTIONS

Table 4-1 includes the details of each research question. The setting included hospitals/cancer centres and the population included adults (>18 years, assigned female at birth) with DCIS or DCIS-M. The Working Group voted on the importance of each outcome of every research questions.

Table 4-1. Details of each research question

Research Question	Intervention / Indicator	Comparator	Outcomes	Inclusion Criteria	Subgroups
1. What is the optimal surgical treatment for patients with DCIS when considering DFS, recurrence, and significant complications after surgery (i.e. bleeding or infection)?	BCS	Mastectomy or active surveillance	Critical outcomes: DFS; Recurrence Important outcomes: Significant complications after surgery (i.e., bleeding or infection)	Fully published studies or abstracts of RCTs with at least 30 patients per arm or SR of RCT	DCIS-M; Low recurrence risk
2. What margin width minimizes the risk of recurrence, complications after surgery (i.e. bleeding, infection) and increases disease free survival in patients with DCIS receiving BCS	Margin: Positive (0mm) or close (0-2mm) or negative (>2mm)		Critical outcomes: DFS; Recurrence Important outcomes: Significant complications after surgery (i.e., bleeding or infection)	SR, meta-analysis of non-RCT and/or RCT, comparative studies (≥ 50 patients per group) that used methods to control potential confounders	N/A
2b After initial surgery of BCS or MX with suboptimal margin width (close or positive), should re-excision be considered to improve DFS, recurrence or reduce complications after surgery requiring reoperation within 30 days (i.e. bleeding or infection)	Re-excision/re-operate	No re-excision/re-operate	Critical outcomes: DFS; Recurrence Important outcomes: Significant complications after surgery that require reoperation within 30 days (i.e. bleeding or infection)	Fully published studies or abstracts of RCTs with at least 30 patients per arm or SR of RCT	DCIS-M
3. Should molecular profile testing be added to clinical evaluation to guide the use of any adjuvant therapy in patients with DCIS?	Residual risk subtype/Risk stratification Groups from Oncotype DX or DCISionRT or DCIS/DCISionRT Decision Score	Usual Care (clinicopathological factors)	Critical outcomes: Ipsilateral breast recurrence rate/Recurrence Rate, low in breast recurrence, RT benefit	Retrospective data or retrospective analyses of RCT	Type of Surgery (BCS; MX)
4. In DCIS patients who have undergone BCS or MX, should breast irradiation be offered to improve DFS and reduce recurrence with acceptable adverse events of irradiation?	Irradiation therapy of any type	No radiation or alternative radiation	Critical outcomes: DFS, recurrence Important outcomes: treatment adverse events	Fully published studies or abstracts of RCTs with at least 30 patients per arm or SR of RCT	Age, radiation schedule or dose; low risk; DCIS-M, oncotype DX or DCISionRT

5. In DCIS patients who have undergone BCS or MX, what is the role of endocrine therapy in the management of DCIS to improve DFS and reduce recurrence and contralateral events with acceptable treatment adverse events?	Endocrine therapy (tamoxifen or aromatase inhibitors)	No endocrine therapy or alternative endocrine therapy	Critical outcomes: DFS; recurrence; contralateral events; adverse events (venous thromboembolism, endometrial cancer, pulmonary embolism, stroke, MSK pain)	Fully published studies or abstracts of RCTs with at least 30 patients per arm or SR of RCT	Menopausal status, DCIS-M, RT or not, ER+, PR+, HER2

Abbreviations: BCS = breast conserving surgery; DCIS = ductal carcinoma in situ; DCIS-M = ductal carcinoma in situ microinvasion; DCISionRT = test to predict a patient's benefit from radiation therapy; DFS = disease-free survival; ER+ = estrogen receptor positive; HER2 = human epidermal growth factor receptor 2 (protein that accelerates breast cancer cell growth); MSK = musculoskeletal; MX = mastectomy; Oncotype DX = Breast Recurrence Score test for patients with early-stage HR+, HER2- breast cancer; RCT = randomized controlled trial; PR+ = progesterone receptor positive; RCT = randomized controlled trial; RT = radiotherapy; SR = systematic reviews

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Review

- Databases searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews
- Years covered: 2018 to January 7, 2023, updated November 27, 2023
- Search terms: See Appendix 4
- Selection criteria: English-language systematic review that covered any of the current guideline questions with similar inclusion/exclusion criteria that did not have an existing evidence-based guideline to endorse or adopt.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed with the ROBIS tool [41] and only systematic reviews with a low risk of bias rating on the ROBIS tool would be considered for inclusion. If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per research questions was selected by one reviewer (LDA) based on its age, quality, and the best match with our study selection criteria stated above.

Search for Primary Literature

For each outcome per research question, a search for primary literature was conducted on January 7, 2023. For any included systematic review, an updated search for primary literature was performed from the point in time that the existing systematic review search ended. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted. An updated search was conducted November 27th, 2023.

Literature Search Strategy

Based on the results of the search for systematic reviews, OVID MEDLINE and EMBASE databases were searched for years 2006 to present for each research question or parts thereof (see Appendix 4 for full search strategy). Clinicaltrials.gov was searched for ongoing trials to identify data from any existing trials.

Study Selection Criteria and Process

The inclusion criteria varied by question and are reported in Table 4-1. Articles published in a language other than English, letters, comments, and editorials were excluded. If an article focused on early breast cancer that included DCIS but did not provide a separate analysis it was excluded.

A review of the titles and abstracts was conducted by one reviewer (LDA). For studies that warranted full-text review, LDA and the Working Group members reviewed and discussed each article to confirm the final study selections.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by LDA, with all extracted data and information audited subsequently by an independent auditor. Ratios, including hazard ratios, were expressed with a ratio of <1.0 indicating that the outcome was better in the intervention group compared to the control group.

RCTs were assessed for the risk of bias using the second version of a the Cochrane Risk of Bias tool (ROB2) and all non-randomized comparative studies were assessed using the Cochrane Risk of Bias in Non-Randomized Studies- of Interventions (ROBINS-I) tool [42].

Synthesizing the Evidence

Meta-analyses were not planned as the direct comparison between studies was difficult to make since the definition of DCIS differed between studies (e.g., including inclusion of patients with DCIS-M, the different definition of margins and radical removal) and differences in follow-up times.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each research question, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using the GRADE approach.

RESULTS

The literature search from the Cochrane Library, MEDLINE, and EMBASE, after removal of duplicates, resulted in 3245 hits. Preliminary sorting resulted in 2,603 RCTs/comparative studies/non-randomized studies and 468 systematic reviews, meta-analyses, and guidelines (Appendix 5). The updated literature searched yielded 975 hits.

Search for Systematic Reviews

Literature search results and ROBIS

Of the systematic review or meta-analyses found in the literature search, 45 underwent full-text review and five of these [2,6,20,43,44] met the pre-planned inclusion criteria. These systematic reviews were assessed for quality using the ROBIS assessment [41] and the results can be seen in Appendix 3. As pre-planned criteria, only systematic reviews with low risk of bias rating on the ROBIS tool were included. Two of the five systematic reviews were excluded; the Garg et al [43] assessment showed high concerns based on limited information on eligibility criteria, identification and selection of studies, data collection and study appraisal process and lack of information pre-defined analyses reported and if between-study variation was minimal or addressed in the synthesis. The Yan et al [44] assessment identified a few areas of concern in the review process, which included lack of appropriate range of databases/electronic sources for published and unpublished reports, lack of detailed search strategy, possibility of missing studies and lack of formal quality assessment. The remaining three systematic reviews were rated as low concerns for risk of bias on the ROBIS tool. Kim et al [6] did have limited information on their search strategy, with no indication on whether clinical trial registries or contacting authors were contacted. Despite this, the Kim et al systematic review had low concerns for their methodology. Marinovitch et al [2] was rated for low concern overall, there was substantial effort had been made to identify as many relevant studies as possible, through a variety of methods and steps were taken to minimize error and bias when selecting studies for inclusion. There were no information on formal assessment of included studies however, there was sufficient study details available to allow the reader to interpret the results. Lastly, Shumway et al was rated for low concern overall for their methods [20].

Search for Primary Literature

Literature search results

A total of 3245 English and foreign-language studies were identified; of these, 105 were selected for full-text review. Of those, 22 met the pre-defined eligibility criteria for this systematic review [3-5,7-17,24-28,45-47]. The search flow diagram is available in Appendix 5.

Study Design and Quality

Twenty fully published reports and two abstracts were found. Among them, 16 were RCTs, three were non-randomized comparative studies and three were retrospective data. The characteristics and outcomes of the included studies are reported in Tables 4-2 to 4-8 and risk of bias assessment for each comparison per outcome for the included studies can be found in Appendix 6. Eleven RCTs were evaluated using the ROB-2 tool and three comparative studies were evaluated using the ROBINS-I tool [48]. In cases of publications with multiple follow up times, only the first publication was assessed for ROB. Approximately one-third of the fully published RCTs papers provided details of the randomization process suggesting allocation concealment. There was no indication that allocation was not concealed or that researchers influenced the treatment received. In the majority of trials, the baseline characteristics were well-balanced with respect to patient and disease characteristics, with the exception of the following trials: intention to use tamoxifen was well balanced but actual receipt varied in Radiation Therapy Oncology Group (RTOG) 9804 trial [14,15]; and differences in age, menopausal status, receipt of RT, and endocrine therapy duration [3]; and differences in age, tumour size, high nuclear grade, comedonecrosis and whether the patient had undergone hormonal therapy [4]. Livingston-Rosanoff et al and Tadros et al adjusted for differences in their analyses (both comparative trials). While not routinely reported, most trials appeared to be of open design without blinding of investigators or participants. The power and required sample size were calculated and reported in the majority of studies, but were not calculated/not reported in two trials [13,24]. Two trials were fully terminated early due to target accrual not met [14,26]. There were some conflict of interests in three studies [7,46][9], where authors on the manuscripts have received funding or own stocks in the molecular profile test, either Genomic Health Inc (creators of Oncotype DX) or Prelude (creators of DCISionRT).

Certainty of the evidence

The aggregate evidence certainty for each comparison of interventions ranged from very low to high after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach. Further details of each are discussed below but traditional GRADE summary tables for each outcome were not presented as the direct comparison between studies was difficult to make since the definition of DCIS differed among studies (e.g., including inclusion of patients with microinvasion DCIS, the different definition of margins and radical removal) and differences in follow-up times. For the same reason, a meta-analysis or network meta-analysis was inappropriate to perform.

Outcomes

Question 1. What is the optimal surgical treatment (BCS, mastectomy, or none) for patients with DCIS when considering DFS, recurrence, and significant complications after surgery (i.e., bleeding or infection)?

The literature review found no RCTs meeting our inclusion criteria for this research question.

Question 2a. What margin width minimizes the risk of recurrence, complications after surgery (i.e., bleeding, infection) and increases DFS in patients with DCIS receiving BCS or mastectomy?

A. BCS

The characteristics and outcomes of the included systematic review [2] and three comparative studies [3-5] comparing positive (0mm) versus close (greater than 0-2mm) or negative (>2mm) for women undergoing BCS are reported in Table 4-2. The overall certainty of the evidence of the three comparative studies was very low and the risk of bias of the two systematic reviews was considered low.

Recurrence

One systematic review with meta-analysis, including a total of 20 studies (two prospective designed and 18 retrospective) reported data on 7883 patients with DCIS with known margin status and 865 LR events [2]. The median proportion of patients receiving WBI across all the studies was 100% (interquartile range [IQR], 50.3% to 100%) and those receiving endocrine therapy was 20.8% (IQR 0.00% to 31.4%). The authors used two complementary meta-analytic approaches to address heterogeneity in classifications and reporting of margin data. In the frequentist approach, adjusting for median follow up-time, results revealed the odds of LR were associated with margin distance, showing relative to >0 or 1 mm, margin size of 2 mm, 3 or 5 mm, and 10 mm had comparable significant reductions in the odds of LR. The predicted probability of LR at 10 years for 2mm negative margins was 10.1% compared with 8.5% for 3 or 5mm and 11.7% for 10 mm. In the Bayesian network meta-analysis (adjusted for median follow-up), patients with negative margins showed similar reductions in the odds of LR between >0 or 1 mm, 2 mm, 3 mm, and 10 mm). The relative odds of LR between 10mm and 2mm showed no significant difference. The authors adjusted for various covariates (age; mid-point of recruitment period; endocrine therapy; high grade) in ways to deals with missing data and it did not alter the mean or estimates. There was no evidence that margins of wider than 2 mm were associated with additional reduction in women undergoing BCS and RT.

The certainty of evidence for recurrence from three comparative studies was very low (Table 4-2; [3-5]). The evidence was downgraded due to risk of bias according to the ROBINS-I tool, indirectness as one trial used self-report measures with unknown validity/reliability in one study and indirectness in reporting and definition of margin widths. In one study [3], when adjusting for age, menopausal status, and duration of endocrine therapy in a multivariate analysis with all patients, patients with positive margins (unknown distance) were twice as likely to have LR (HR, 2.49; 95% CI, 1.16 to 5.33; p=0.02); however, for patients with a margin distance of less than 2 mm, this effect was non-significant (HR, 1.70; 95% CI, 0.83 to 3.47; p=0.14). Patients who underwent RT with positive margins (unknown distance) were twice as likely to experience LR when compared to patients with negative margins of ≥2 mm (HR, 2.39; 95% CI 0.96 to 6.00; trend significance of p=0.06). In another comparison study, patient who underwent adjuvant RT, there was no significant difference in LR between those with margin width of ≥2 mm and <2 mm (HR, 0.77; 95% CI, 0.19 to 3.23; p=0.72) [4]. In patients not undergoing adjuvant RT, there was a significant difference in LR between those with margin width of <2 mm and ≥2 mm (HR, 5.49; 95% CI, 1.79 to 16.88; p=0.003). Patients with close negative margins (0.01-1.00 mm) not undergoing RT were also at a further LR increased risk compared to ≥2 mm margin width (HR 7.18; 95% CI, 2.34 to 21.98; p=0.0006). This risk was not seen in those who underwent adjuvant RT. In both studies, the interpretation of the results of patients with close/positive margins who did not receive radiation is limited by small numbers. In a large multinational pooled analysis of patient-level data of women with DCIS, margin status (involved margin status [<2 mm] vs. clear margin status [≥2 mm]) and 10-year cumulative incidence of ipsilateral DCIS and invasive IBC were compared. In women undergoing BCS with or without RT, risks for both ipsilateral DCIS (HR, 1.39; 95% CI, 1.04 to 1.87) and IBC (HR, 1.40; 95% CI, 1.07 to 1.83) were significantly higher with involved margins compared to clear margins [5].

DFS

There was no evidence found for the outcome of DFS for this question.

i. Significant complications after surgery requiring reoperations within 30 days

There was no evidence found for this outcome for this question.

B. Mastectomy

The characteristics and outcomes of the included systematic review and comparative study comparing positive (0 mm) versus close (>0-2 mm) or negative (>2 mm) are reported in Table 4-2. One systematic review with meta-analysis and one comparative study were found and the evidence of is considered low due to the heterogeneity among included studies in terms of patient characteristics, follow-up periods and inconsistency in the definition of close margin between trials. Eight of the 12 studies defined close margins as <2 mm, while the four remaining defined close margins as <1 mm.

Recurrence

One systematic review with meta-analysis was found comparing LR after mastectomy for DCIS patients with close or positive margins [6]. Kim et al. systematic review included 12 retrospective studies that included 2902 patients and according to their evaluation of the Newcastle-Ottawa Scale, the quality of all studies was high. Due to low heterogeneity, a fixed effect model was used to analyze RR. When comparing patients with positive or close margins to negative margins, there was a 3.72-fold higher risk of LR (RR, 3.72; 95% CI, 2.30 to 6.01). Patients with positive margins showed a 2.91-fold higher risk of LR when compared to patients with close margins (RR, 2.91; 95% CI, 1.14 to 7.41). Kim et al also conducted a subgroup meta-analysis based on the definition of close margins; studies defining close margins as less than 1mm had a LR of RR 7.06 (95% CI, 2.81to 17.71) and those defining as less than 2mm had a LR of RR 3.09 (95% CI, 1,75 to 5.46). It was also found that radiation was not associated with a lower risk of LR (RR, 0.50; 95% CI, 0.06 to 4.08) in close or positive margins. The authors note that close or positive margin after mastectomy is quite rare and prospective studies on this is non-existent, and thus summarizing the evidence using meta-analysis may assist in estimating LR rates after mastectomy. In a large multi-national pooled analysis of patient level data of women with DCIS, margin status (involved margin status (<2mm) versus clear margin status (≥ 2 mm) and 10-year cumulative incidence of ipsilateral IBC were compared. In women undergoing mastectomy, the risk for ipsilateral IBC was not significantly increased with involved margins (< 2mm) [5].

DFS

There was no evidence found for the outcome of DFS for this question.

Significant complications after surgery requiring reoperations within 30 days

There was no evidence found for this outcome for this question.

2b. After initial surgery of BCS or mastectomy with suboptimal margin width (close or positive), should re-excision be considered to improve DFS, recurrence, and reduce complications after surgery requiring reoperation within 30 days (i.e. bleeding or infection)?

The literature review found no RCTs meeting our inclusion criteria for this research question.

Table 4-2. Studies selected for inclusion for BCS and mastectomy comparing margin widths.

Author	# of patients and characteristics	Comparisons	Local Recurrence	Author's conclusions
Meta-Analysis: BCS				
Marinovich et al. 2016 [2] Systematic review and meta-analysis	7883 pts with known margin status across 10 studies (2 prospective and 18 retrospective). 100% receiving WBI and 20.8% received endocrine therapy. The median follow-up time was 78.3 months (IQR 59.0-94.7) and median prevalence of LR was 8.3% (IQR 5.0-11.9%).	Margin size of >0 or 1 mm vs. 2 mm vs. 3 mm or 5 mm or 10 mm	**Analysis 1: Random effect logistic modeling analysis (adjusted for median follow-up)** Relative to >0-1 mm, odd of LR were associated with margin distance, margin size of 2 mm (OR 0.51, 95% CI 0.31-0.85), 3 or 5 mm (OR 0.42, 95% CI 0.18-0.97), and 10 mm (OR 0.60, 95% CI 0.33-1.08) had similar reductions in the odds of LR. Pairwise analysis revealed no differences in OR between groups (all p>0.04) *Predicted probability of LR at 10 years:* 2 mm 10.1% (95% CI 6.3-16.0), 3 mm or 5 mm 8.5% (95% CI 3.6-18.9), 10 mm 11.7% (95% CI 6.7-19.4) **Analysis 2: Bayesian network meta-analysis (adjusted for median follow-up)** Similar reductions in odds of LR: >0 or 1 mm (0R 0.45, 95% CI 0.30-0.62), 2 mm (OR 0.32, 95% CI 0.21-0.48), 3 mm (OR 0.30, 95% CI 0.12-0.76) and 10 mm (OR 0.32, 95% CI 0.19-0.49) No difference in relative odds of LR between 10 mm and 2 mm (relative OR 0.99, 95% CI 0.61-1.64).	Margins that are >2 mm do not further reduce the odds of LR.
Comparative studies: BCS				
Livingston-Rosanoff et al, 2021 [3] Population-based cohort	559 women (74% were 50 years and older) following BCS with follow up surveys every 2 years that were confirmed with the review of medical reports. 77% received RT and 54% did not receive endocrine therapy	<2 mm vs. ≥2 mm vs. negative (unknown distance) vs. positive (unknown distance)	Age, menopausal status, radiation, duration of endocrine therapy and margin width were all associated with LR in univariate models. **Margin & LR: (**Adjusted for age, menopausal status, and duration of endocrine therapy (multivariable analyses) ≥2 mm (reference group, n=301) <2 mm (N=71) HR 1.70 (0.83-3.47), p=0.14 Negative (unknown distance) (N=87) HR 1.13 (0.56-2.29), p=0.73 Positive (unknown distance) (N=45) HR =2.49 (1.16-5.33), p=0.02 **Margin, LRR & receipt of RT:** Adjusted for age, menopausal status, and duration of endocrine therapy (multivariable analyses) ≥2 mm (reference group, n=230) <2 mm (N=64) HR 2.03 (0.89-4.64), p=0.09 Negative (N=65) HR 1.78 (0.78-4.06), p=0.17	Women with positive margins were twice as likely to experience LR.

			Positive (N=32), HR 2.39 (0.96-6.00), p=0.06 **Margin, LRR & no RT:** Adjusted for age, menopausal status, and duration of endocrine (multivariable analyses) ≥2 mm (reference group, n=67) <2 mm (N=7) HR 2.08 (0.44-9.80), p=0.36 Negative (unknown distance) (N=22) HR 0.39 (0.09-1.78), p=0.23 Positive (unknown distance) (N=22) HR 1.68 (0.45-6.24), p=0.44	
Schmitz et al. 2023 [5] Multi-national pooled analysis of patient-level data of four cohorts	47,695 DCIS pts 6.7-year follow-up duration; 15% BCS only, 36% BCS +RT; 3% BCS + ET; 14% BCS with RT & ET; 32% MX.	Involved margin status (<2 mm) vs. clear margin status (≥2 mm)	10-year cumulative incidence ipsilateral IBC: involved (5.8%) vs. clear (3.9%) 10-year cumulative incidence ipsilateral DCIS: involved (4.5%) vs. clear (2.5%) Multivariate Cox analyses: BCS with or without RT (N=32,638): Adjusted risk for Ipsilateral DCIS: clear (≥2 mm) reference; Involved (<2 mm) HR 1.39 (1.04-1.87), p=0.03 Adjusted risk for Ipsilateral IBC: clear (≥2 mm) reference; involved (<2 mm) HR 1.40 (1.07-1.83), p=0.02	Risk for ipsilateral IBC and ipsilateral DCIS significantly higher for DCIS with involved margins than clear margins in pts who underwent BCS ± RT.
Tadros et al. 2019 [4] Retrospective comparison (prospective database)	1491 patients who had undergone BCS between 1996-2010 with 80% having adjuvant RT and 44.9% having adjuvant hormonal therapy Median follow-up time 8.7 years	Close margins (<2 mm) vs. free margins ≥2 mm. Pts with close margins was divided into 2 groups for subgroup analysis 0.01-1.00 mm and 1.01 to 1.99 mm.	Most pts (N=1371, 92%) had free margins ≥2 mm, 99 had ≥1 mm and 21 had 1-2 mm **Margins, LRR and no RT** Age (>40 vs. ≤40) HR 2.08 (0.48-9.08, p=0.33 Margin (free vs. close) HR 5.49 (1.79-16.88), p=0.003 **Margins, LRR and RT** Age (>40 vs. ≤40) HR 2.72 (1.05-7.06) p=0.04 Margin (free vs. close) HR 0.77 (0.19-3.23), p=0.72 *Predicted 10-year LRR rate:* *No RT:* ≥2 mm vs. <2 mm (5.4% vs. 30.9%, p=0.0006) *RT:* ≥2 mm vs. <2 mm (3.3% vs. 4.8%, p=0.69)	Patients <40 years with margins <2 mm and no RT are at the highest risk of LR. There was no difference in LR among pts with close/free margins undergoing RT. A significant increase in 10-year LR in those not undergoing RT.
Meta-Analysis: Mastectomy				
Kim et al. 2020[6]	2902 DCIS patients treated by mastectomy across 12 retrospective studies.	Close or positive margins vs. negative margins	LR occurred in 5.3% with close or positive margins and 1.6% in negative margins. Pooled RR for LR was 2.91 (95% CI 1.14-7.41, p=0.03, I^2 0%) for positive margin (7.4%) and close margin (2.7%) Subgroup analyses for definition of close margin (<1 mm vs. 2 mm)	Mastectomy positive margin rate is associated with greater risk of LR. <1mm showed 2.3-fold

	According to authors' NOS, they are high quality.		Close margin <1 mm (N=4 studies) = RR 7.06 (95% CI 2.81-17.71, p<0.01, I^2 10% Close margin <2 mm (N=8 studies) = RR 3.09 (95% CI 1.75-5.46, p<0.01, I^2 12%) There was no decreased risk of LR with RT (RR 0.50; 95% CI 0.06-4.08, p=0.52, I^2 0%) in pts with close or positive margins	higher risk compared to 2 mm margin definition
Comparative studies: Mastectomy				
Schmitz et al. 2023 [5] Multi-national pooled analysis of patient level data of four cohorts	47,695 DCIS pts 6.7 follow up duration; 15% BCS only, 36% BCS +RT; 3% BCS + ET; 15% BCS with RT & ET; 32% MX.	Involved margin status (<2 mm) vs. Clear margin status (≥2 mm)	Multivariate Cox analyses: (N=15,057): Adjusted risk for Ipsilateral IBC: clear (≥2 mm) reference; involved (<2 mm) HR 0.51 (0.23-1.14), p=0.10	Risk for ipsilateral invasive breast cancer and ipsilateral DCIS significantly higher for DCIS with involved margins than clear margins in pts who underwent BCS ± RT.

Abbreviations: BCS = breast conserving surgery; CI = confidence interval; DCIS = ductal carcinoma in situ; ET = endocrine therapy; f/u = follow-up; HR = hazard ratios; IBC = invasive breast cancer; IQR = interquartile range; LR = local recurrence; LRR = locoregional recurrence; MX mastectomy; NOS = Newcastle–Ottawa Scale; OR = odds ratio; pts = patients; RR = residual risk; RT = radiotherapy; WBI = whole breast radiation therapy

3. Should molecular profile testing be added to clinical evaluation to guide the use of any adjuvant therapy in patients with DCIS?

A. Oncotype DX

The characteristics and outcomes of the included studies [7,8] investigating whether the molecular profile test Oncotype DX could be added to the clinical evaluation through CP characteristics to guide the use of any adjuvant therapy in patients with DCIS are reported in Table 4-3. The certainty of the evidence was downgraded to very low due to risk of bias as they were a single arm study with no comparison, indirectness, and imprecision and there was potential conflict of interest in one study as authors received funding and owned stocks in Genomic Health Inc (the creators of Oncotype DX; [7]). In Rakovitch et al [7], Oncotype DCIS (DCIS score) was examined in a cohort of patients treated by BCS ± RT. In a subgroup analysis, most patients with low-risk CP features (i.e., low or intermediate nuclear grade DCIS, wide clear margins and tumour size smaller than 2.5 cm, majority 50 years or older at diagnosis) also had a low-risk DCIS score, and their treatment by BCS alone also had an expected low risk of LR (10.1% at 10 years). There was also a group of patients that had the same CP features during the same period and same treatment of BCS alone who were identified as having a high-risk DCIS score with a higher risk of LR (19.6% at 10 years) and a reduction in LR after RT. While this could suggest that DCIS score contributes to additional information to recurrence risk beyond that of CP features, it is important to note that the number of cases in the subset of high-risk DCIS score was smalland only included patients with negative margins [7]. An exploratory analysis by Leonard et al (2021) that retrospectively examined the association between 12-gene Oncotype DX and relevant CP factors with recurrence in a pooled cohort of women treated with local excision and accelerated PBI found the DCIS score was significantly associated with LR (p=0.01), but CP factors were not associated with LRR [8]. These results are highly variable due to the small number of LR events, the limited follow-up time and wide confidence intervals.

B. DCISionRT

The characteristics and outcomes of the included studies [9] investigating whether the DCISionRT test could be added to the clinical evaluation through CP characteristics to guide the use of any adjuvant therapy in patients with DCIS are reported in Table 4-3. The certainty of the evidence was considered very low, downgraded due to risk of bias (conference abstract) and imprecision as only one study. There was potential conflict of interest as some of the authors work for Prelude DX, the creators of DCISionRT.

In the Rabinovitch et al abstract [9], four international cohorts of DCIS patients (n=926) treated with BCS (negative margins) with or without RT had their tissues analyzed according to the DCISionRT with residual risk subtype (RRt). Patients were re-classified as low risk group (DS [validated score] ≤2.8 without RRt; 37% of sample) or high-risk group (63% of sample), comprising both elevated risk (DS >2.8 without RRt) and residual risk (DS >2.8 with RRt) group. Fifty-one percent of patients with CP low-risk 9804-like features and 58% of favourable age/nuclear grade were re-classified as DCISionRT high risk and showed significant RT benefit and absolute 10-year IBR reduction (see Table 4-3). Twenty-three percent of CP high-risk group of no 9804-like features and 31% of non-favourable age/nuclear grade were re-classified as DCISionRT low risk, where RT did not significantly reduce IBR in these groups.

Table 4-3. Studies selected for inclusion for molecular profiling

<table>
<tr><th>Author</th><th>Number of patients and characteristics</th><th>Comparisons</th><th>Local Recurrence</th><th>Author's conclusions</th></tr>
<tr><td colspan="5">Oncotype DX</td></tr>
<tr><td>Rakovitch et al. 2017 [7]

Ontario DCIS cohort

Population-based cohort analysis</td><td>DCIS pts treated by BCS ± RT (571 with BCS alone, 689 with BCS + RT). Median f/u 9.4 yrs. Pts with "low risk DCIS" = (N=286)</td><td>DCIS score

"low risk DCIS" defined as CP features of low or intermediate nuclear grade DCIS, wide clear margins, and tumour size smaller than 2.5cm (N=286)</td><td>Predicted risk of LR (10 years) in a subgroup of pts with "low-risk DCIS" treated after year 2000 and BCS alone:
-80.0% had low DCIS score and 10.1% of them had a 10-year risk of LR after BCS alone.
-8.5% had high risk DCIS score and 19.6% of them had a 10-year risk of LR after BCS alone

Low risk DCIS pts receiving BCS alone vs. BCS + RT and predicted risk of LR (10 years):
Having a low DCIS score (none vs. RT): 10.1% (95% CI=6.9%-14.8%) vs. 6.0% (CI 4.1%-8.9%)
Having a high-risk DCIS score (none vs. RT): 19.6% (CI 12.8%-29.5%) vs. 11.9% (CI 7.8%-18.0%)</td><td>Molecular assay improves the assessment of recurrence risk after treatment by BCS beyond CP features</td></tr>
<tr><td>Leonard et al. 2021 [8]

Exploratory Pooled cohort analysis
NCT01188145
NCT01185132</td><td>104 DCIS pts, median age of 60 (range: 40-79). 79% postmenopausal. All treated with local excision followed by APBI</td><td>12 gene breast DCIS score

CP factors</td><td>Differences between two datasets - one accounted for 17% of the entire cohort had younger cohort and slightly lower ER+ pts. Other group had higher proportion of pts with DCIS score <39.

DCIS score significantly associated with LR in univariable modeling (HR 10.3 (95% CI 1.7, 198.4), p=0.01). None of the CP factors (age at diagnosis, menopausal status, central nuclear grading, presence of comedonecrosis, size, multifocality or margin width) correlated with locoregional recurrence.
All results highly variable due to the small number of events</td><td>DCIS score might be able to better stratify "low risk" pts who might be eligible for APBI.</td></tr>
<tr><td colspan="5">DCISionRT</td></tr>
<tr><td>Rabinovitch et al. 2023 [9] abstract</td><td>926 DCIS pts from four international cohorts (median f/u 8.5 years) treated with BCS (neg margins) with (n=641) and without RT (n=335)</td><td>DCISionRT Low Risk (DS ≤2.8 without RRt)

High risk (elevated risk DS >2.8 without RRt and residual risk DS >2.8. with RRt)</td><td>
<table>
<tr><th></th><th colspan="4">DCISionRT Low Risk</th></tr>
<tr><th></th><th></th><th colspan="3">10 yearr IBR risk</th></tr>
<tr><th>CP groups</th><th>N (%)</th><th>No RT (%), 95% CI</th><th>RT (%) 95% CI</th><th>HR</th></tr>
<tr><td>Overall</td><td>338 (37%)</td><td>5.6 (3-12)</td><td>4.8 (3-9)</td><td>0.8 (0.3,2-3), p= 0.71</td></tr>
<tr><td>RTOG 9804-like- "good risk" (low risk)</td><td>232 (49%)</td><td>5.5 (2-14)</td><td>5.5 (3-11)</td><td>0.96 (0.3-3.3), p=0.96</td></tr>
</table>
</td><td>DCISionRT showed to be a better predictor of 10-year IBR risk and RT benefit compared to CP criteria alone.</td></tr>
</table>

		Low-risk CP group (RTOG 9804-like)*	Not RTOG 9804-like (high risk)	106 (23%)	5.9 (2-22)	3.0 (1-12)	0.5 (0.1-3.8), p=0.52
			Age ≥50 and Grade 1 or 2 (low risk)	190 (42%)	6.3 (2-16)	6.3 (3-14)	0.9 (0.3-3.0), p=0.88
			Age <50 or Grade 3 (high risk)	148 (31%)	4.4 (1-17	3.0 (1-9)	0.7 (0.1-4.0), p=0.70

	DCISionRT High Risk			
		10 yr IBR risk		
CP groups	N (%)	No RT (%), 95% CI	RT (%) 95% CI	HR
Overall	588 (63%)	25.7 (14-30)	8.0 (3-9)	0.2 (0.1-0.5), p<0.001
RTOG 9804-like "good risk" (low risk)	240 (51%)	19.5 (11-34)	6.8 (4-13)	0.3 (0.1-0.7), p=0.007
Not RTOG 9804-like (high risk)	348 (77%)	30.5 (21-43)	8.7 (6-14)	0.23 (0.1-0.4), p<0.001
Age ≥ 50 and Grade 1 or 2 (low risk)	263 (58%)	18.4 (11-30)	7.2 (4-13)	0.34 (0.2-0.8), p=0.012
Age <50 or Grade 3 (high risk)	325 (69%)	34.3 (25-48)	8.5 (5-14)	0.2 (0.1-0.4), p<0.001

Abbreviations: APBI = accelerated partial breast radiotherapy; BCS = breast conserving surgery; CI = confidence interval; CP= clinicopathological; DCIS = ductal carcinoma in situ; DS =Decision Score; ER+: estrogen receptor positive; f/u = follow up; Gy = Gray (unit); HR = hazard ratio; IBR = ipsilateral breast recurrence; LR = local recurrence; Oncotype DX = Breast Recurrence Score test for patients with early-stage hormone-receptor positive, human epidermal growth factor receptor 2 negative breast cancer; pts = patients; RRt= Residual Risk Subtype; RT = radiotherapy; RTOG 9804 = Radiation Therapy Oncology Group 9804

*RTOG 9804-like criteria (Nuclear Grade 1 or 2, non-palpable, screening detected, negative margins)

4. In DCIS patients who have undergone breast-conserving surgery or mastectomy, should breast irradiation be offered to improve disease-free survival and reduce recurrence with acceptable adverse events of irradiation?

A. BCS

Irradiation (RT) vs. none

The characteristics and outcomes of the included RCTs comparing RT versus no RT are reported in Table 4-4. There was a total of nine full-text publications reporting on four trials with multiple follow-up times [10-15,24,45,46]. The certainty of the evidence for each comparison varied from low to high.

Recurrence

Nine full-text publications on four trials with multiple follow-up times reported on the effects of RT versus none for recurrence rates. There is high certainty of the evidence that suggest that the addition of RT after BCS could reduce recurrence rates and there is also high certainty of evidence regarding a long-term beneficial effect of RT. Evidence was downgraded due to risk of bias.

The effects of postoperative RT after BCS were examined in the SweDCIS RCT trial of women five years after randomization, and showed a significant reduction in the risk of IBR in patients undergoing RT [10]. At 20 years' follow-up, patients in the RT arm showed an absolute risk reduction of 12.0% and relative risk reduction of 37.5% [11]. The absolute risk reduction for in situ ipsilateral breast event (IBE) was 10% and 2.0% for invasive. The EORTC 10853 trial had two publications for 10-year [12] and 15-year results. At 10-year follow-up, RT after BCS reduced LR, DCIS recurrence and invasive recurrence risk when compared with BCS alone [12]. At 15 years, treatment with adjuvant RT approximately halved the risk of LR [13]. RT also reduced the risk of pure DCIS and invasive LR at 15 years. In another RCT, the RTOG 9804 trial randomized women with good risk (i.e., mammographically detected low- or intermediate-grade DCIS, measuring <2.5 cm with margins ≥3mm) to RT or none after BCS [14]. At a median follow-up time of seven years, IBR was significantly less with the addition of RT versus no RT (0.9% vs. 6.7%; p<0.001) [14]. At 15-year cumulative IBR, rates remained significantly lower for patients in the RT group (7.1% vs. 15.1%; p=0.007) [15]. Similarly, rates of invasive LR were lower in the RT group (5.4% vs. 9.5%, p=0.027). When conducting a multivariable analysis, RT and tamoxifen use were associated with lower IBR [15].

DFS

Six full-text publications on three trials with multiple follow-up times reported on the effects of RT versus none and DFS or OS [10-15]. There is moderate certainty of evidence that suggests that the addition of RT after BCS does not alter survival rates. The evidence was downgraded due to inconsistency and indirectness as there were a small number of events and the studies used different survival outcomes.

At five years' follow-up, the SweDCIS trial showed in an overall analysis of event-free survival that the RT group had fewer events when compared to the no RT group (p<0.001 log-rank test [10]); however, at 20 years' follow-up, the lower risk in the RT arm was nonsignificant [11]. Similarly, the EORTC 10853 results at 10 years [12] and 15 years [13] showed no differences in OS and the RTOG 9804 trial found no difference between groups for DFS and OS at seven years' [14] or 15 years' [15] follow-up.

Treatment Adverse Events

Two full-text publications on one trial with multiple follow-up times reported on the effects of RT versus none on adverse events [14,15]. The certainty of the evidence was low to

indicate a slight increase in the number of adverse events with the addition of RT. The evidence was downgraded due to risk of bias. Patients in the RTOG 9804 trials in the RT group had higher rates of grade 1 and 2 acute toxicities when compared to patients in the no RT group (76% vs. 30%, p<0.001); however, rates for grade >3 toxicities were similar [14]. There was a slightly higher rate of late grade 1 toxicities (30%) than grade 2 (4.6%) or 3 (0.7%), and no grade 4 or 5 toxicities [14]. At 13.9 years' follow-up, grade 3 late RT toxicities was 1.0% and there were no grade 4 or 5 toxicities [15].

RT Tumour Boost vs. None

The characteristics and outcomes of the included RCTs comparing RT tumour boost versus no tumour boost can be found in Table 4-4. A total of two full-text publications were found [16,17]. The certainty of the evidence was moderate to high.

Recurrence

One RCT examined the effects of RT tumour bed boost versus no tumour bed boost after WBI and BCS on the outcome of recurrence [16]. There is high level of certainty to suggest that the additional RT tumour bed boost following WBI could reduce recurrence rates. Results from a large sample of women from 11 countries revealed that women randomized to the RT tumour boost after postoperative WBI significantly decreased LR. The five-year free from LR rates for the boost group was 97.1% and for the no-boost group was 92.7%, an absolute gain in local control of 4.4% at five years with boost radiation. Almost one-half of the LR were invasive in both the boost versus no boost groups. When looking at five-year free from disease recurrence rate, the boost group was 93.7% and the no boost group was 89.6% (p=0.0042). Further, it was found in multivariate model adjusting for age, endocrine therapy use, and WBI dose fractionation that tumour bed boost and tumour size were independent risk factors for LR.

DFS

One RCT examined the effects of RT tumour bed boost versus no tumour bed boost after WBI and BCS on the outcome of DFS [16]. The BIG 3-07/TROG 07.01 international RCT found that there were no significant differences in five-year OS between patients randomized to the tumour bed boost group versus the no tumour bed boost after WBI (p=0.47 [16]). There is moderate certainty of evidence suggesting an OS benefit with the additional of tumour bed boost; however, the evidence from one RCT at mean follow-up of 6.6 years.

Treatment Adverse Events

Two RCTs reported on the outcome of treatment adverse events in tumour bed boost versus no tumour bed boost [16]. There is moderate certainty in the evidence to suggest that the additional boost to the tumour bed is associated with an increase in treatment adverse events. The evidence was downgraded due to risk of bias. The BIG 3-07/TROG 07.01 international RCT found that the addition of tumour bed boost was associated with significantly higher rates of grade ≥2 breast pain and induration, but no significant increase in RT pneumonitis, cardiac disease, or RT-related malignancy. There were no grade 5 events and grade 4 events were rare [16]. Further, the BONBIS phase III trial evaluated the role of a localized RT boost in DCIS patients and reported acute toxicities (during and up to 3 months after RT completion) as part of their quality assurance program and found that localized boost significantly increases the rate of grade ≥2 breast erythema, dermatitis, and grade 2 hyperpigmentation. Cardiac or lung toxicities were not reported.

Conventional WBI vs. Hypofractioned WBI

The characteristics and outcomes of the included RCT comparing CRT versus HFRT can be found in Table 4-4. One full-text publication was found and the certainty of the evidence was considered high [16].

Recurrence

One RCT examined the effects of CRT versus HFRT on the outcome of recurrence [16]. There is high level of certainty to suggest that moderate HFRT is as effective as CRT in women with non-low-risk DCIS after BCS. In their large sample of women from 11 countries examining CRT (50 Gy in 25 fractions for 5 weeks) versus HFRT (42.5 Gy in 16 fractions for 3.5 weeks), there was no statistically significant differences in five-year free from LR between the two groups. An analysis involving all patients found that the five-year free from LR rate was 94.9% in both groups (p=0.85). When looking at five-year free from disease recurrence rate for all patients, the CRT group was 91.0% and the HFRT group was 92.4% (p=0.46).

DFS

The literature review found no trials meeting our inclusion criteria for this outcome.

Treatment Adverse Events

The literature review found no trials meeting our inclusion criteria for this outcome.

Accelerated PBI vs. WBI

The characteristics and outcomes of the included SR comparing PBI versus WBI are reported in Table 4-4. One systematic review with two trials was found and the certainty of the evidence was considered moderate.

Recurrence

There is moderate level of certainty to suggest that PBI is as effective as WBI in terms of recurrence rates among patients with DCIS. A high-level systematic review with meta-analysis of the NSABP-39 [18] and RAPID [19] trials did not observe a significant difference in 10-year recurrence rates among patients treated with PBI compared with WBI (HR,1.26; 95% CI, 0.004 to 45.14; I^2 = 35.10) [20]. There was no further information on which DCIS patients may or may not be favourable candidates for PBI.

DFS

The literature review found no trials meeting our inclusion criteria for this outcome.

Treatment Adverse Events

The literature review found no trials meeting our inclusion criteria for this outcome.

a) Subgroup analyses

i. ***Age***

Five full-text publications reported subgroup analyses on age as a risk factor for LR in patients undergoing RT. There is moderate certainty evidence that suggests older women (≥50 years) respond to RT differently than younger women (<50 years); there is evidence to also suggest this is also holds true for boost RT. In the SweDCIS trial, Holmberg et al [45] found there was trend toward significance of increasing effect of RT by age (p=0.07) at a mean of eight years' follow-up. A further analysis showed that the cumulative incidence was higher in the youngest age group and lower in those aged ≥65 years, showing a modest absolute risk reduction in the younger women and substantial reduction in new IBE for older women.

However, in the control group, the younger and older women had similar risk [45]. At 20 years' follow-up, relative risk reduction in IBE achieved with RT was significantly reduced in older age women at diagnosis (i.e., age 52-60 years, HR, 0.43; 95% CI, 0.27 to 0.71 vs. age ≥62, HR, 0.35; 95% CI, 0.22 to 0.57). This effect remained for in situ IBE regardless of age, but the effect was mainly only seen only among older patient groups for invasive IBE [11]. Similarly, in a multivariate subgroup analysis in Bijker et al [12], younger age (≤40 years) was found to be a significant risk factor for LR, with a 10-year event-free survival of 66% compared to 81% for patients older than 40 years (HR, 1.95; 95% CI, 1.26 to 3.01; p=0.0021). In the UK/ANZ DCIS trial, tumour blocks were not originally collected at trial entry but diagnostic slides were collected retrospectively for 1224 of the 1694 patients; results showed that RT was more effective in women older than 50 years of age compared to those younger than 50 years [24]. In an exploratory analysis conducted in the BIG 3-07/TROG 07.01 study, there were no significant differences in age and the effect of tumour bed boost on LR [16]. There also was no significant difference found for tumour size, nuclear grade, comedonecrosis, surgical margin width, or endocrine therapy use.

*i. **Molecular profiling***

There were two full publications investigating the use of the molecular profile test DCISionRT in a subgroup analysis of women from the SweDCIS trial (see Table 4-4). The certainty in this evidence is very low due to indirectness and imprecision as there were fewer patients than in the original cohort available for analysis, lower number of events and wider confidence intervals. In addition, there is evidence of publication bias as authors received funding and own stocks in Prelude DX, the creators of DCISionRT [46].

In a validation study of the DCISionRT, a subgroup analysis of women with DCIS from the SweDCIS trial with complete data and negative margins were divided in elevated (DS >4) and low (DS ≤3) risk group via DCISionRT [46]. It was found that RT significantly decreased the 10-year ipsilateral recurrence (absolute decrease 15.5%) and 10-year invasive recurrence rate (absolute decrease 9.3%); however, with the low-risk group, there was no significant difference in either recurrence rate. While these data suggest that DCISionRT may identify a low-risk patient group that may not benefit from RT, there is little certainty in the effect. Using the cohort of women from the SweDCIS trial, Warnberg et al compared the 10-year absolute LR risk (invasive and DCIS) in five strategies: RT to none, RT to all, RT to high-risk women defined by DCISionRT, modified RTOG 9804 criteria, and Swedish Guidelines [47]. Using DCISionRT spared 48% from RT with 8.1% less recurrences when compared with RT to none and the RTOG 9804 modified criteria spared 39% from RT, with 9.7% fewer recurrences.

B. Mastectomy

No RCT evidence was found for DCIS patients who have undergone mastectomy and whether breast irradiation should be offered to improve DFS and reduce recurrence and treatment adverse events.

Table 4-4. Studies meeting inclusion criteria for radiation therapy and breast conserving surgery

Author	Patients (n) and characteristics	Comparisons	Recurrence (REC)	Disease free survival (DFS)	Adverse Events	Author's conclusions
RT vs. none						
Bijker et al. 2006 [12] EORTC 10853- 10 yr results	March 1986- July 1996 1010 women with DCIS after BCS Pts with lesions up to 5 cm without evidence of micro invasion or Paget's disease. Median age 53 years. Pt tumour and treatment characteristics well balanced.	No RT (n=503) Vs. RT (50 Gy/25 fx; n=507)	**LR:** No RT (N=132) vs. RT (N=75), HR=0.53 (0.40-0.70), log-rank p<0.0001). 10 yr event-free estimate = No RT 74% vs. RT 85% **DCIS REC**: No RT (N=67) vs. RT (N=36), HR=0.52 (0.34-0.77), log rank p=0.0011 10 yr event-free estimate = No RT 86% vs. RT 93% **Invasive REC**: No RT (N=66) vs. RT (N=40), HR=0.58 (0.39-0.86), log rank p=0.0065 10 yr event-free estimate = No RT 87% vs. RT 92% **Risk factors** (N=775 of sample) ≤40 vs. >40 = 10 yr event free 81% vs. 66%, HR = 1.95 (1.26-3.01), p =0.0021 Margins (Free vs. Not Free) = 10 yr event free 81% vs. 68%, HR =-1.89 (1.37-2.63), p=0.001	10-yr OS rate was 95% in both arms.	NR	Trial continues to show that RT after BCS reduces LR risk compared to BCS alone. The reduced LR risk caused by RT at 10 yrs f/u has not resulted in survival differences.
Donker et al. [13] EORTC 10853 15 yr results			LR occurred in 30% (N=149) no RT vs. 17% (N=85) RT Treatment with RT approx. halved LR risk (HR 0.52, CI 0.40-0.68), p<0.001 15 yr LR-free rates: No RT 69% vs. RT 82% RT reduced the risk of pure DCIS LR (HR =0.49 (0.33-0.73, p=0.003) and invasive LR (HR =0.67 (0.42-0.87) p=0.007) 15 yr DCIS LR free rate: No RT 84% vs. RT 92% 15 yr invasive LR-free rate: No RT 84% vs. RT 90% Risk of LR was highest during the first 5 yrs after random assignment: hazard rate 4%/yr no RT, 2%/yr RT. The risk then decreased at 10 yrs and 15 yrs.	No difference in BCSS (HR= 1.07,0.60-1.91) or OS (HR=1.02, 0.71-1.44)	NR	Trial continues to show RT after BCS reduces LR risk in the long term. Resulting in overall lower risk of mastectomy.
Cuzick et al. 2011 [24] UK/ANZ DCIS trial:	1701 Pts with unilateral or bilateral DCIS, completely excised. Pts/surgeon	1030 randomly assigned to RT vs. or no RT	**RT vs. no RT** **All new breast events:** 10.6% vs. 23.2%; HR 0.41, 95% CI 0.30-0.56, p<0.0001 **Ipsilateral invasive:** 3.3% vs. 9.1%, HR 0.32 CI 0.19-0.56, p<0.0001	NR	NR	Confirms long-term beneficial effect of RT.

Author	Patients (n) and characteristics	Comparisons	Recurrence (REC)	Disease free survival (DFS)	Adverse Events	Author's conclusions
12.7 yr f/u May 1990-Aug 1998	decided together whether to enter pt into the 4-way 2×2 randomization or 1 of 2 separate 2-way randomization with elective choice for the other treatment. Analysis of each of the two treatment comparisons was restricted randomly assigned pts.	RT was 50 Gy/25 fx/5 wks (2 Gy/day on weekdays; tumour dose fx 82). Did not recommend boost treatment at excision. TMX: 20 mg/daily/5 yrs	**Ipsilateral DCIS**: 3.8% vs. 9.7%, HR 0.38, CI 0.22-0.63, p<0.0001 **Contralateral breast cancer:** 3.3% vs. 4.1%, HR 0.84, CI 0.45-1.58, p=0.6			
Emdin et al. (2006) [10] SweDCIS 5.4 yr f/u	1046 pts with BCS randomized to RT or control between 1987-1999. Baseline characteristics well-balanced.	RT (n=415; 50Gy/25fx/ 5 wks or 54Gy in 2 series w/ gap of 2 wks). No boost vs. none (n=520)	**IBR:** 161 (44 RT; 117 no RT): HR 0.33 (95% CI 0.24-0.47), p<0.0001 **Recurrent DCIS**: 92 (23 RT; 69 no RT): HR 0.31 (CI 0.20-0.50), p=not reported **Ipsilateral Inv REC**: 69 (21 RT; 48 no RT): HR 0.41 (CI 0.24-0.69), p=not reported **5 yr cumulative incidence of LR:** RT 7% (CI 5-10%), no RT 22% (18-26%), Overall HR 0.33 (0.24-0.47), p=not reported	Significant difference between groups with less events in the RT (p<0.001 log-rank test). N at risk: 321 RT vs. n 282 no RT	NR	RT gave a reduction in ipsilateral recurrence during 5 yr f/u. No diference on the risk of invasive or in situ recurrence.
Holmberg et al. 2008 [45] SweDCIS 8.4 yr f/u			**IBR:** 175 (64 RT; 141 no RT) Overall absolute risk reduction from RT on IBR 16% at 10 yrs (95% CI 10.3% vs. 21.6%); RR 0.40 (0.30-0.54), p nr Invasive ipsilateral events: 59.4% RT vs. 45.4% no RT.	NR	NR	

Author	Patients (n) and characteristics	Comparisons	Recurrence (REC)	Disease free survival (DFS)	Adverse Events	Author's conclusions
Warnberg et al. 2014 [11] SweDCIS 17.4 yr f/u			**IBR** 258 (93 RT; 165 no RT) Cumulative risk (20 yrs): 20% RT (16-24%) vs. 32% No RT (28.0-36.0%) ARR at 20 years was 12.0% (6.5-17.7) with relative risk reduction 37.5% ARR for DCIS 10% (6.0-14.0%) and invasive 2% (-3.0-7.0) with relative risk reduction of 67% and 13%. **Contralateral:** RT 67 vs. no RT 48. Risk was not sig. increased after 22 yrs.	non significant lower risk in the RT arm (HR 0.84 (CI 0.65-1.09), p ns)	NR	The balance between the benefit of LR protection and harms of RT currently speak in favour of RT.
Warnberg et al. 2021 [46] SweDCIS trial Subgroup analysis with DCISionRT	Sub-sample from SweDCIS trial of 504 women with complete data (tumour blocks/ slides) with DCISionRT data and negative margins. No difference in RT vs. no RT.	RT (n=247) vs. no RT 257) DCISionRT score low DS ≤3 vs. elevated DS>3	BCS w/out RT, relative 10-yr event rate increased with increasing continuous DS. Total ipsilateral recurrence (10 yrs): Elevated risk (w/out RT vs. RT): 23.8% vs. 8.3%, HR 0.32 (0.17-0.58), p<0.001 Low risk (w/out RT vs. RT): 12.9% vs. 7.2% HR 0.53 (0.28-1.02), p=0.059 Ipsilateral invasive recurrence (10 yrs) Elevated risk (w/out RT vs. RT) 12.4% vs. 2.1%, HR 0.24 (0.08-0.74), p=0.013 Low risk (w/out RT vs. RT): 7.7% vs. 6.5%, HR 0.84 (0.30-2.31, p=0.73	NR	NR	RT was beneficial for elevated DS pts by not low DS
Warnberg et al. 2023 [47] SweDCIS trial Subgroup analysis with DCISionRT	Sub-sample from SweDCIS trial of 504 women with complete data (tumour blocks/ slides) with DCISionRT data and negative margins	RT to none RT to all RT per DCISionRT RT per RTOG 9804* RT per SwG**	90 developed recurrences after 10 yrs: 59 new DCIS and 31 invasive recurrences 10-year absolute local recurrence risk (invasive/DCIS) RT to none: 18.6% (8.4/10.2) RT to all : 7.8% (4.7/3.1) RT per DCISionRT: 10.5% (5.3/5.2) RT per RTOG 9804*: 8.9% (3.5/5.4) RT per SwG*: 8.6% (3.6/5.0)	NR	NR	Omitting RT in pre-specified low-risk groups seems reasonable and with. little effect on recurrence rates at 10 years.
McCormick et al. 2015[14]	Dec 1999-July 2006; N=636, median age 58 DCIS was unicentric, low	RT to whole breast (50gy/25fx or 50.4Gy/28 fx) or	I**BR** RT (5 & 7 yrs): 0.4% & 0.9% vs. no RT (5 & 7 yrs): 3.5% vs. 6.7% (log-rank/gray's test, HR 0.11 (95% CI 0.003-0.47), p<0.001	No difference in OS (HR 1.56 (0.81-3.01) or DFS (HR 0.84 (0.53-1.32)	RT arm higher rates of grade 1 and 2 acute toxicities (76% vs. 30%, p<0.001)	Trial successfully identified women of good risk and showed

Author	Patients (n) and characteristics	Comparisons	Recurrence (REC)	Disease free survival (DFS)	Adverse Events	Author's conclusions
Median 7.17 yrs f/u RTOG 9804	or intermediate nuclear grade, and less than 2.5 cm on pathology or imaging, Older than 26 years old. TMX use optional. Closed early due to not meeting targeted accrual.	42.5Gy/16fx; no boost), w/ or w/out TMX (20mg/d/5y) None with/without TMX (20mg/d/5y) 62% TMX use	Rates by TMX and nuclear grade: 1.2% (yes/low), 5.3% (yes/low), 2% (no/low), 8.4% (no/intermediate) **Invasive IBR** at 7 yrs: RT 3.9% vs. no RT 4.8% (log rank/gray's test, HR 1.07 (CI 0.48-2.39)	*secondary endpoint. Not powered for this.	≥grade 3 was 4% in both arms Late RT toxicities was grade 1 (30%), grade 2 (4.6%), grade 3 (0.7%) No grade 4 or 5	the addition of RT decreased LR.
McCormick et al. 2021 [15] 13.9 y/u			f/u data n=629; 52 IBR, 14 RT 38 no RT **Cumulative IBR (@ 10 yrs & 15 yrs):** RT: 1.5% (95% Ci (0.5-3.7); 7.1% (4.0-11.5) No RT: 9.2% (6.2-13.0); 15.1% (10.8-20.2) HR=0.36 (CI 0.20-0.66), p=0.007 **Invasive IBR:** N = (10 RT; 23 no RT) **(@ 10 & 15 yrs)** RT: 0.4% (0-1.9); 5.4% (2.7-9.5) No RT: 4.3 (2.3-7.2); 9.5% (6.0-13.9) HR=0.44 (0.21-0.91; p=0.024) Median time to IBR: 11 yrs RT vs. 7 yrs no RT Multivariable analysis, RT significantly reduced IBR (HR = 0.34 (0.19-0.64, p=0.007) and tamoxifen use (HR=0.45 (0.25-0.78, p=0.0047)	No significant difference in OS or DFS.	Late RT toxicities: Grade 1 or 2: NR Grade 3: 1.0% No grade 4 or 5	Long-term data confirms RT reduces incidences of RT in good-risk DCIS
Boost vs. No Boost						
Bourgier et al. 2021 [17] BONBIS trial NCT00907868.	Nov 2008-July 2014 2004 DCIS pts who received BCS Multicentre prospective phase 3	Arm A (n-1002; no boost; WBI); 50 Gy/25fx over 5 wks Arm B (n=1002; boost 2Gy/fx, up to	NR	NR	Arm A vs. Arm B **breast erythema (%):** grade 2: 22.4 vs. 38.3 grade 3: 2.1 vs. 5.4 **dermatitis (%):** grade 2: 0.6 vs. 2.3 grade 3: 0.1 vs. 0.4 **Hyperpigmentation (%):**	Addition of a boost to the tumour bed increased the severity of acute skin toxicities.

Author	Patients (n) and characteristics	Comparisons	Recurrence (REC)	Disease free survival (DFS)	Adverse Events	Author's conclusions
Quality assurance procedure	randomized trial.	16-Gy localized boost, WBI + boost)			grade 2: 3.6 vs. 6.9 grade 3: none No acute lung or cardiac toxicity was observed Grade ≥2 acute skin toxicity reported in 39.5% of pts. Smoking history and large breast CTV were predictors of these events.	
Chua et al. 2022[16] BIG 3-07 & TROG 07.01 June 2007-June 2014 CT00470236 Median f/u 6/6 yrs	International study involving 11 countries, centres chose to participate in 1 of 3 WBI categories: *Category A* (1:1:1:1:): boost vs. no boost and CRT vs. HFRT) or *Category B*: (1:1): boost vs. no boost after WBI or *Category C* (1:1) boost vs. no boost after HFRT	Boost (16 Gy/8fx/1.5 wks) Vs. No Boost	Total 1608 pts; boost 805 vs. 803, Adjusted for age, endocrine therapy use, WBI dose fractionation 5-year free from LR rate: No boost 92.7% vs. boost 97.1% (HR 0.47 (95% CI 0.31-0.72, p<0.001 Absolute gain at 5yrs: 4.4% No boost 44% vs. 45% Boost LR were invasive LR in same quadrant 81% no boost vs. 73% in boost Tumour bed boost and tumour size were independent risk factors for LR in multivariate model. 5-yr free from disease REC rate: No boost 89.6% vs. boost 93.7%, HR 0.63 (0.446-0.87), p=0.042	5 yr OS: boost 98.2% vs. 99.0%, HR 0.81 (0.45-1.45, p=0.47)	Grade 4 events were rare; no grade 5 Boost group had higher rates of ≥ grade 2 breast pain (10% vs. 14%, p=0.003) & induration (6% vs. 14%, p=0.001). No interaction with WBI fractionation. No sig increases in RT pneumonitis, cardiac disease or RT-related malignancy for boost gr.	Tumour bed boost after WBI decreases local recurrence in women with resected, non-low risk DCIS. Bost associated with increase in grade 2 or higher late breast pain and induration compared to no boost. Grade 4 were rare and no Grade 5.
CRT vs. HFRT						
Chua et al. 2022[16] BIG 3-07 & TROG 07.01	International study involving 11 countries, centres chose to participate in 1	CRT: 50Gy/25fx/5 wks)	Total 1608 (831 WBI, 777 HFRT), Adjusted for age, endocrine therapy use and boost use 5-yr free from LR rate: WBI Cat A:	NR	MR	Moderately hypofractionated WBI was safe and effective as convention WBI

Author	Patients (n) and characteristics	Comparisons	Recurrence (REC)	Disease free survival (DFS)	Adverse Events	Author's conclusions
June 2007-June 2014 CT00470236	of 3 WBI categories: *Category A* (1:1:1:1:): boost vs. no boost and CRT vs. HFRT) or *Category B:* (1:1): boost vs. no boost after WBI or *Category C* (1:1) boost vs. no boost after HFRT	HFRT (42.5 Gy/ 16fx/3.5wks)	CRT 94.4% vs. HFRT 93.7%, HR 0.94, CI 0.51-1.73, p=0.84 All pts: CRT 94.9% vs. HFRT 94.9% (HR 0.94, CI 0.51-1.74, p= 0.85) Interaction between tumour bed boost and WBI dose fractionation not significant (Cat A HR 1.09 (0.32-3.76, p=0.89; All pts HR 0.94 (0.41-2.18, p=0.89) 5 yr free from REC rate: WBI Cat A: CRT 90.0% vs. HFRT 92.4%, HR 0.79 (0.47-1.31) p=0.36 All pts: CRT 91.0% vs. HFRT 92.4%, HR 0.83 (0.50-1.38), p=0.46			for women with resected, non-low risk DCIS
APBI vs. WBI						
Shumway et al. 2023 [20].	Meta analysis of the NSABP-39 and RAPID trial	APBI vs. WBI	APBI vs. WBI IBR (10 yrs) HR 1.26; 95% CI 0.004-45.14; I^2=35.10%. APBI 3DCRT vs. WBI IBR (10 yrs) HR 1.21; 95% CI 0.006-22.96, I^2=0%)	NR	NR	Findings suggest that PBI is comparable to WBI.

Abbreviations: ANZ = Australia and New Zealand; ARR = absolute risk estimate; BCS = breast conserving surgery; BCSS = breast cancer–specific survival; Cat = category; CI = confidence interval; CRT = conventional radiotherapy; CTV = clinical target volume; DCIS = ductal carcinoma in situ; DCIS-M = ductal carcinoma in situ microinvasion; DCISionRT = test predicting an individual patient's benefit from radiation therapy; DFS = disease free survival; DS = Decision Score; EORTC = European Organisation for Research and Treatment of Cancer; f/u = follow up; fx = fraction; Gy = Gray (unit); HFRT = hypofractionated radiotherapy; HR = hazard ratio; IBR = ipsilateral recurrences; LR = local recurrence; NR = not reported; OS = overall survival; Pt = patient; REC = Recurrence; RR = residual risk; RT = radiotherapy; RTOG 9804 = Radiation Therapy Oncology Group 9804; SweDCIS = Swedish Ductal Carcinoma in Situ; SwG = Swedish National Guideline; TMX = tamoxifen; UK = United Kingdom; WBI = Whole breast irradiation; wks = weeks; yr = year

*****RTOG 9804 was modified in this study to screen-detected, non-palpable, NG 1-2 lesions, size ≤2.5cm, and with negative margins

5. In DCIS patients who have undergone BCS or mastectomy, what is the role of endocrine therapy in the management of DCIS to improve DFS and reduce recurrence (invasive or non-invasive) and contralateral events with acceptable treatment adverse events?

A. BCS

Tamoxifen vs. none

The characteristics and outcomes of the included one RCT comparing tamoxifen versus none (or placebo) are reported in Table 4-5. The certainty of the evidence was considered low [24,25].

Recurrence

One RCT comparing tamoxifen versus none reported on the outcome of recurrence [24]. There is moderate level of certainty in the evidence that there is a benefit to tamoxifen in reducing recurrence in women with DCIS treated with BCS. The evidence was downgraded due to imprecision as the number of events were lower in some comparisons.

A large trial conducted by UK/ANZ DCIS randomized women in a 2×2 factorial trial of RT (50Gy/25 fractions/5 weeks), tamoxifen (20 mg/5 years), or both [24]. At a median follow-up of 12.7 years, when looking at all patients randomized to tamoxifen or none, patients in the tamoxifen group had significantly fewer new breast events compared to those not receiving tamoxifen (18.1% vs. 24.6%, p=0.002); specifically, tamoxifen reduced the rate of recurrence of ipsilateral DCIS events, but not ipsilateral invasive events. When patients were analyzed based on who received RT or not, it was found that in patients not receiving RT, tamoxifen significantly reduced the rate of recurrence of ipsilateral DCIS events, but not ipsilateral invasive events [24]. In patients receiving RT, there was no significant reduction in either ipsilateral DCIS or invasive events between tamoxifen versus none [24]. It is important to note the number of ipsilateral events was much lower in those receiving RT than non-RT (44 vs. 249).

Contralateral Events

The UK/ANZ DCIS trial also compared tamoxifen versus none on the outcome of contralateral events. There is moderate level certainty of evidence that there is a benefit to tamoxifen in reducing contralateral events in women with DCIS treated with BCS. The evidence was downgraded due to imprecision as the number of contralateral events was lower.

When looking at all patients randomized to tamoxifen or none, the trial found an overall significant reduction in all contralateral events (invasive and DCIS) between tamoxifen versus none, with an absolute 10-year reduction of 2.3% [24]. Overall, the data suggest that with the use of tamoxifen, there was an absolute 10-year reduction of 6.5% for all new breast events [24]. When patients were analyzed based on who received RT or not, it was found that patients not receiving RT, tamoxifen significantly reduced contralateral events between those receiving tamoxifen vs. none. In patients receiving RT, there was no significant reduction in contralateral event; however, the number of events was low, and the confidence intervals were large.

DFS

The literature review found no trials meeting our inclusion criteria for this outcome.

Treatment Adverse Events

The literature review found no trials meeting our inclusion criteria for this outcome.

Subgroup analyses

ER positive/negative

In a retrospective analysis of the NSABP B-24 study, Allred et al [25] evaluated the relationship between ER and PgR and the response to tamoxifen. After BCS and RT, ER-positive patients treated with adjuvant tamoxifen versus placebo showed significant decrease in any breast cancer event (HR, 0.58; 95% CI 0.42 to 0.81; p=0.001) and any invasive breast cancer (HR, 0.53; 95% CI, 0.31 to 0.82; p=0.005); while reduction was also observed for any DCIS it was not statistically significant. When patients were stratified by PgR receptor, results were similar but were not more predictive when ER status was considered alone. There was no significant benefit that was observed in ER-negative DCIS in any setting. A multivariable analysis of patients with available ER status results found that treatment (whether placebo or tamoxifen) and age at entry (≤49, ≥50 years) were significant predictors of subsequent breast cancer.

In the IBIS-II DCIS trial at 12 years' follow-up ER-positive breast cancers were non-significantly reduced by 28% with anastrozole compared to tamoxifen (58 vs. 82, HR, 0.72; 95% CI, 0.52 to 1.01; p=0.056) and no effect for ER-negative cancer. Similarly, invasive ER-positive cancer was also reduced non-significantly by 24% (44 vs. 59; HR, 0.76; 95% CI, 0.51 to 1.12, p=0.17) [28].

Tamoxifen vs. Anastrozole

The characteristics and outcomes of the included two RCT comparing tamoxifen and anastrozole are reported in Table 4-5. Two full-text publications were found and the certainty of the evidence was considered moderate to high [26,27]

Recurrence

There were two full publications and one abstract of high level RCTs that examined the differences between tamoxifen and anastrozole on the outcome of recurrence [26-28] . There is high level of certainty in the evidence to suggest that there is no significant difference between tamoxifen or anastrozole as a choice of endocrine therapy in the management of DCIS to reduce recurrence rates. In the IBIS-II DCIS trial, postmenopausal women with locally excised DCIS were randomized to receive 1 mg oral anastrozole or 20 mg oral tamoxifen every day for five years. After a median follow-up of 7.2 years, after adjusting for age, BMI, menopausal hormone therapy, grade, margins and RT, there was no statistically significant difference in overall recurrence between the groups (67 anastrozole vs. 77 tamoxifen) [26]. Further, there was a non-statistically significant difference between groups for ipsilateral invasive recurrence or DCIS ipsilateral recurrence. The authors also did not find a different effect on recurrence when a patient had RT use at baseline (54 recurrences with RT vs. 30 with no RT). For invasive recurrence, anastrozole was not any more effective on women who had RT at baseline versus those that did not. There continued to be no significant differences at 12-year follow-up [28].

The NSABP B-35 trial randomized postmenopausal women with locally excised DCIS or mixed DCIS/LCIS who were ER or PgR positive after RT to receive 1 mg oral anastrozole or 20 mg oral tamoxifen every day for five years [27]. There was a significant difference between anastrozole and tamoxifen and BCFI (i.e., any breast cancer recurrence event), where patients on anastrozole had a significantly decreased BCFI. When looking at the individual events contributing to BCFI, there was a significant difference between groups for all invasive recurrence (p=0.01), but not DCIS recurrence (p=0.52). However, this beneficial effect only remained significant among women younger than 60 years of age (p=0.038).

Contralateral Events

Two publications of two RCT trials examined the difference between tamoxifen and anastrozole on the outcome of contralateral events. There is moderate level of certainty in

the evidence, and it was downgraded due to inconsistency between the two trials on the effect on invasive CBC and fewer events/larger confidence intervals for DCIS contralateral events. The IBIS-II DCIS trial looked at differences in contralateral events between anastrozole and tamoxifen. Analyses adjusted for age, BMI, menopausal hormone therapy, grade, margins, and RT found similar numbers between anastrozole and tamoxifen for contralateral invasive recurrences and DCIS recurrences. In contrast, the NSABP B-35 trial found a significant reduction in all CBC in patients in the anastrozole group when compared to those in tamoxifen (0.032) [27]. When looking more closely, this reduction remained significant for contralateral invasive recurrence (p=0.015) but not DCIS CBC (p=0.73). There were fewer event numbers for contralateral DCIS for both trials and larger confidence intervals giving very low certainty in the non-effect.

DFS/OS

One RCT examined the effects of tamoxifen versus anastrozole on the outcome of DFS and OS [27]. There is moderate level of certainty in the evidence to suggest that tamoxifen or anastrozole are equally as effective for OS in women of all ages and DFS in women older than 60 years of age as a choice of endocrine therapy. There was significant interaction found between treatment group and age when looking at DFS, where women younger than 60 years of age in the anastrozole group had greater DFS. There was no statistically significant effect for women older than 60 years of age.

Adverse Events

Two full-text publications and one abstract on two RCTs examined differences in adverse events between tamoxifen and anastrozole [26-28]. There is moderate level of certainty in the evidence to suggest a difference in tamoxifen or anastrozole in terms of adverse events. The evidence was downgraded due to small number of events. At seven years' follow-up the IBIS-II DCIS trial reported that patients taking tamoxifen had significantly higher rates of endometrial cancer, deep vein thrombosis (without pulmonary embolism), and musculoskeletal (any event) when compared with anastrozole (see Table 4-5). Anastrozole was associated with significantly higher rates of transient ischemic attack compared with tamoxifen. At the 12-year follow-up, tamoxifen use was associated with significantly higher rates of endometrial, ovarian and non-melanoma cancers and anastrozole was associated with higher rates of fractures and transient ischemic attacks. Margolese et al [27] found a higher rate of thrombosis/embolism in tamoxifen users compared to anastrozole users, but no significant differences in uterine cancer. The authors report that there were no other striking differences between groups in terms of adverse events.

B. Mastectomy

The literature review found no trials meeting our inclusion criteria for endocrine therapy in the management of DCIS in mastectomy patients.

Table 4-5. Studies selected for inclusion for endocrine therapy

Author	Number of patients and characteristics	Comparisons	Recurrence	Contralateral events	DFS or adverse events	Author's conclusions
TMX vs. placebo/none						
Allred et al. 2012[25] Retrospective analysis of the NSABP B-24 RCT trial	ER and PgR in a subset of DCIS pts (N=731; 41% of original study population) after BCS and RT (50 Gy no longer than 8 wks). Pts were originally randomized to placebo vs. TMX (10 mg/2× daily) and continued for 5 yrs. Median time in study was 14.5 yrs	Placebo vs. TMX in ER positive and ER negative patients	Adjusted for age at entry (≤49, ≥50 yrs) over all f/u time: ER positive (placebo vs. TMX) Any: BC: 31% vs. 20%; HR*=0.58 (0.42-0.81), p=0.001 IBC: 19% vs. 12%; HR*=0.53 (0.31-0.82), p=0.005 DCIS: 12% vs. 9%; HR* =0.66 (0.39-1.12), p=0.12 ER negative (placebo vs. TMX) BC 27% vs. 25%; HR*= 0.88 (0.49-1.59), p=0.68 IBC 15% vs. 11%; HR*= 0.69 (0.30-1.59), p=0.38 DCIS 12% vs. 15%; HR=1.15 (0.50-2.65), p=0.75 PTs with ER-positive DCIS who received adjuvant tamoxifen vs. placebo had significant reductions in any BC or IBC events. No significant reductions in ER negative DCIS in any setting. Multivariate analyses Pts with known ER status (N=732) Treatment (placebo vs. TMX HR=0.643 (0.481-0.861) p=0.03 Age at entry, (≤49, ≥50 yrs), HR=0.609 (0.457-0.812) p<0.001	NR	NR	A significant benefit for adjuvant tamoxifen in patients with ER-positive DCIS after standard therapy.

Author	Number of patients and characteristics	Comparisons	Recurrence	Contralateral events	DFS or adverse events	Author's conclusions
			Results were similar in PgR and receptor (ER and/or PgR status) but not as predictive as ER alone			
Cuzick et al. 2011[24] UK/ANZ DCIS trial: 12.7 yr f/u May 1990-Aug 1998	2×3 factorial Women had locally excised DCIS (n=1701; 1694 analyzed) 912 pts chose to enter 2×2 randomization 782 pts chose randomization to one of the treatments randomly assigned pts.	RT: 50 Gy/25 fx/5 wks (n=267) TMX: 20mg/d for 5 yrs (n=576) RT + TMX (n=316) No adjuvant treatment (n=544) Did not recommend boost treatment at excision.	**(1) Pts randomized to TMX or none:** **All pts:** All new breast events: 18.1% vs. 24.6%; HR 0.71 (CI 0.58-0.88) p=0.002 Ipsilateral Invasive 6.8% vs. 6.9%, HR 0.95 (0.66-1.38), p=0.79) Ipsilateral DCIS 8.6% vs. 12.1% HR 0.70 (0.51-0.86), p=0.03 **Pts with No RT (TMX vs. none):** All new breast events: 14.6% vs. 20.7%, HR.71 (0.57-0.87). p=0.001 Ipsilateral Invasive(N=97): 5.5% vs. 6.0%, HR 0.89 (0.59-1.33), p=0.6 Ipsilateral DCIS (N=15): 7.4% vs. 10.4%, HR 0.71 (0.51-0.99), p=0.04. **Pts with RT (TMX vs. none)** All new breast event: 4.1% vs. 5.6%, HR = 0.99 (0.61-1.59) p=0.8 Ipsilateral Invasive (N=19): 1.3% vs. 0.9%, HR=1.41 (0.54-3.70), p=0.5 Ipsilateral DCIS (N=23): 1.1% vs. 1.7%, Hr 0.68 (0.29-1.59), p=0.4 **2) Pts randomized to RT or no RT:** **Pts receiving TMX****	**(1) Pts randomized to TMX or none:** **All pts:** Contralateral all (N=55): 1.9% vs. 4.2%, HR 0.44 (0.25-0.77), p=0.005 Contralateral Invasive (N=37): 1.5% vs. 2.7%, HR 0.47 (0.24-0.94), p=0.03 Contralateral DCIS (N=15) 0.3% vs. 1.3%, HR 0.36 (0.11-1.12), p=0.08 **Pts with No RT (TMX vs. none):** Contralateral all (N=37) 0.9% vs. 3.1%, HR 0.27 (0.12-0.59), p=0.001 **Pts with RT (TMX vs. none):** Contralateral all (N=18): 1.1% vs. 1.1%, HR 0.99 (0.39-2.49), p=1.0 **2) Pts randomized to RT or no RT** **Pts receiving TMX**** All new breast events: 5.4% vs. 11.7%, HR 0.44 (0.32-0.60), p<0.001 Contralateral all (N=17): 1.5% vs. 1.4%, HR 1.10 (0.43-2.86), p=0.8	NR	

Author	Number of patients and characteristics	Comparisons	Recurrence	Contralateral events	DFS or adverse events	Author's conclusions
			All new breast events (N=87): 5.4% vs. 11.7% HR 0.44 (0.32-0.60), p<0.0001 Ipsilateral invasive (N=32): 1.9% vs. 4.1%, HR 0.44 (0.21-0.93), p=0.03 Ipsilateral DCIS (N=31): 1.5% vs. 4.3%, HR 0.35 (0.16-0.78), p=0.01			
TMX vs. ANA						
Forbes et al. 2016 [26] IBIS-II DCIS Mar 2003-Feb 2012 7.2 yrs f/u	2980 Women aged 40-70 yrs w/ DCIS diagnosed 6 mths before randomization. DCIS-M <1 mm permitted. No TMX pts. 71% had RT. Locally excised ER positive or PgR positive from 236 centres in 14 countries	1 mg/d oral ANA (N=1471) vs. 20 mg/d oral TMX (N=1509). Given daily basis for 5 yrs. Pts took 2 tablets/day (TMX + ANA placebo or TMX placebo + ANA)	ANA vs. TMX- Adjusted for age, BMI, menopausal hormone therapy, grade, margins, RT **All**: 67 (5%) vs. 77 (5%); HR 0.83, 95% CI 0.59-1.18, p=0.31 **Invasive all**: 37 (3%) vs. 47 (3%), HR 0.72 (0.46-1.14), p=0.16 **Ipsilateral invasive**: 20 (1%) vs. 22 (1%), HR 0.77, 95% CI 0.40-1.48, p=0.44 **DCIS all:** 29 (2%) vs. 30 (2%), HR 0.98, 95% CI 0.57-1.69, p=0.95 **Ipsilateral DCIS:** 21 (1%) vs. 23 (2%), HR 1.03 (0.55-1.91), p=0.93 Estimate for 5 yrs REC 2.5% (CI 1.8-3.5) vs. 3.0 % (2.2-4.0) Estimate for 10 yrs REC 6.6% (CI 4.9-8.8) vs. 7.3% (CI 5.7-9.4) RT use vs. no RT use (all): 54 vs. 30, HR 0.77 (0.49-1.21), p=0.25	ANA vs. TMX- Adjusted for age, BMI, menopausal hormone therapy, grade, margins, RT Contralateral invasive: 17 (1%) vs. 25 (1%), HR 0.68, 95% CI 0.36-1.29, p=0.24 Contralateral DCIS: 8 (<1%) vs. 6(<1%), Hr 1.02, 95% CI 1.02 (0.33-3.18), p=0.97	ANA vs. TMX **Endometrial cancer:** 1 vs. 11, OR 0.09 (0.002-0.64), p=0.0044 **Pulmonary embolism:** 5 vs. 8, OR 0.64 (0.16-2.23), p=0.43 **Deep vein thrombosis (without pulmonary embolism)** = 2 vs. 16, OR 0.13 (0.01-0.54), p=0.0011 **Cerebrovascular accident**: 13 vs. 4, OR 3.36 (1.04-14.18), p=0.025 **Transient ischemic attack:** 13 vs. 5, OR 2.69 (0.90-9.65), p=0.05 **Musculoskeletal (any):** 929 vs. 811, OR 1.49 (11.28-1.74), p<0.0001	
Sestak et al. 2020			Total of 221 breast recurrences (7.4%)	NR	214 cancers other than breast were reported,	No clear efficacy difference,

Author	Number of patients and characteristics	Comparisons	Recurrence	Contralateral events	DFS or adverse events	Author's conclusions
(abstract) [28] 11.6 yrs f/u			ANA vs. TMX Any recurrence: 102 vs. 119, HR=0.89 (0.67-1.14) ER positive 58 vs. 82, HR 0.72 (0.52-1.01) ER negative 24 vs. 15 HR 1.63 (0.86-3.11) Invasive: 66 vs. 76, Hr 0.89 (0.64-1.23) ER positive: 44 vs. 59, HR 0.76 (0.51-1.12) ER negative: 17 vs. 12 HR 1.44 (0.69-3.02) DCIS: 35 vs. 42, HR 0.85 (0.54-1.33) ER positive 14 vs. 23 HR 0.62 (0.32-1.21) ER negative 7 vs. 3 2.38 (0.61-9.20)		non-significatly decreased with ANA (97 vs. 117, OR 0.84 (0.63-1.12, p=0.22) ANA vs. TMX Endometrial (2 vs. 13, OR 0.16 (0.02-0.69) ovarian cancer (1 vs. 9, OR =0.11 (0.003-0.82) non melanoma skin cancer (11 vs. 21, OR not reported) Fractures 181 vs. 145, OR 1.32 (1.04-1.68) Transient ischemic attacks 15 vs. 5, OR 3.10 (1.07-10.92)	although data suggest possible greater efficacy for ANA over TMX for prevention of ER-positive breast cancers. Clear differences in adverse events, and ANA may be more appropriate for some women with contraindications for TMX
Margolese et al. 2016 [27] NSABP B-35 Jan 2003-June 2006 f/u 9 years	3104 pts postmenopausal DCIS or mixed DCIS/LCIS, had lumpectomy followed by WBI who were ER or PgR positive	1 mg/d oral ANA + placebo for TMX (n= 1552) or 20 mg/d of TMX + placebo of ANA (n= 1552). Both for 5 years after 1st dose.	TMX vs. ANA All new breast cancer: 122 vs. 90, HR 0.73(0.56-0.96), p=0.023 Invasive: 69 vs. 43, HR 0.62 (0.42-0.90), p=0.012 DCIS: 53 vs. 46, HR 0.88 (0.59-1.30), p=0.52 Ipsilateral REC: all: 55 vs. 47. HR 0.83 (0.56-1.22), p=0.34 5-yr estimate 96.3% in both 10 yr estimate: 89.1% TMX vs. 93.1% in ANA	Reduction in CBC in ANA HR 0.64 (CI 0.43-0.96), p=0.032 Reduction in invasive CBC in ANA HR 0.52 (0.31-0.88, p=0.015) TMX vs. ANA CBC all: 60 vs. 39, HR 0.64 (0.43-0.96), p=0.032 Inv CBC: 40 vs. 21 HR 0.52 (0.31-0.88), p=0.015 DCIS CBC: 20 vs. 18 HR 0.90 (0.47-1.69), p=0.73	**DFS**: 495 total (260 TMX; 235 ANA); HR 0.89, Ci 0.75-1.07, p=0.21 **5 yr DFS estimates**= 91.6% (CI 90.0-92.9=2) TMX vs. 91.5% (CI 89.9-92.5) ANA **10 yr DFS estimates** = 77.9% (CI 75.0-80.6) TMX vs. 82.7% (CI 80.4-84.7) ANA Sig interaction between treatment group and age, effect only sig for those <60 yrs (HR 0.69 (0.51-0.93), p=0.015)	ANA provides a benefit in treatment of DCIS, in reducing invasive cancer and less frequent adverse reactions.

Author	Number of patients and characteristics	Comparisons	Recurrence	Contralateral events	DFS or adverse events	Author's conclusions
			Sig interaction between age and treatment group <60 vs. ≥60 yrs: beneficial effect of ANA only among <60 yrs (HR 0.53 (0.35-0.80), p=0.003		No difference in OR (HR 1.11 CI 0.83-1.48, p=0.48) No interaction between age/treatment NS difference in uterine cancer (RR 0.47 CI0.18-1.15). thrombosis/embolism (17 in TMX vs. 4 ANA), no other striking difference between groups	

Abbreviations: ANA = Anastrozole; ANZ = Australia and New Zealand; BC = breast cancer; BCS = breast conserving surgery; BMI = body mass index; CBC = contralateral breast cancer; CI = confidence interval; DCIS = ductal carcinoma in situ; DFS = disease free survival; ER = estrogen receptor; f/u = follow-up; fx = fraction; Gy = gray (unit); HR = hazard ratio; HR = hazard ratio; IBC = invasive breast cancer; IBIS = International Breast Cancer Intervention Study; Inv = invasive; LCIS = lobular carcinoma in situ; mg/d = milligram per day; MSK = musculoskeletal; NR = not reported; NS = no significant; NSABP = National Surgical Adjuvant Breast and Bowel Project; OR = odds ratio; PG = progesterone; PgR = progesterone receptor; Pt = patient; RCT = randomized controlled trial; REC = recurrence; RT = radiotherapy; sig = significant; TMX = tamoxifen; UK = United Kingdom; WBI = Whole breast irradiation; wks = weeks

*HR adjusted by age at entry (≤49, ≥50 yrs) over all follow-up time)
****** Patients randomized to RT vs. no RT and not receiving TMX is reported under question 4.

Ongoing, Unpublished, or Incomplete Studies

A list of ongoing, unpublished, or incomplete studies located in the literature search or from clinicaltirals.gov is given in Appendix 7. This list is not meant to be all-inclusive, and it is likely other trials are also ongoing.

DISCUSSION

This document represents a review of the evidence, and an evidence-based guideline for the management of DCIS. The management of a patient with DCIS can depend on a variety of factors, including the extent of disease in relation to the patient's breast size, the presence of genetic mutations, any contraindications to RT and the patient's overall health and preference.

Standard primary treatment of DCIS is surgery, either BCS (with the presumption of additional adjuvant breast irradiation) or mastectomy (with the option of reconstruction). More recently, a number of clinical trials have proposed the non-operative approach of active surveillance with mammograms and physical examination [49-51]. One of the objectives of this systemic review was to assess the comparative effectiveness of either surgery or active surveillance; however, at this time there are no completed RCTs available and thus no strong evidence to support one treatment strategy over another. Therefore, it was the consensus of the Working Group that the clinical standard treatment for DCIS involve surgical excision, offering patients a choice between BCS and total mastectomy with the option of reconstruction. Using shared decision-making, the patient and surgeon should consider factors such as individual patient preferences, tumour characteristics (ER positivity and extent of disease), health conditions and the risks and benefits of each treatment option. Active surveillance remains an area of ongoing investigation with several ongoing RCTs contrasting active surveillance to conventional surgical treatment (i.e. LORIS, LORD, and COMET trials; see Appendix 7) and may be an area of consideration for certain patients with contraindications or personal preferences precluding surgical excision of disease.

The surgical treatment of DCIS involves complete excision to negative margins, with the cosmetic outcome of BCS directly correlated to minimizing the excision of uninvolved healthy breast tissue. Close or positive margins can therefore occur, typically identified on the surgical pathology report. The evidence found in this systematic review suggests that margin width of at least 2 mm is associated with a reduced risk for LR [2-4,6]. Margins >2 mm did not further reduce the odds of LR in BCS patients undergoing RT. However, a re-excision to margins even greater than 2 mm may be considered for BCS patients declining RT [2]. It was therefore the recommendation of the Working Group that for patients undergoing BCS or mastectomy, maintaining a surgical margin width of at least 2 mm is optimal to minimize the risk of LR. Our systematic review found no RCTs investigating additional surgery in patients with suboptimal margin width (close or positive). It was therefore the consensus of the Working Group that in cases of close margins (<2 mm), a patient-centred discussion should evaluate the risks of further surgery (re-excision or mastectomy) against the risk of recurrence. In instances where re-excision versus boost RT is being contemplated for close margins, multidisciplinary discussions between surgical and radiation oncologists should occur to tailor an optimal treatment plan. For patients with positive margins, re-excision should be considered. These recommendations acknowledge the variability in benefits and harms based on patient and disease characteristics, highlighting the importance to consider factors such as comorbidities, patient preferences, DCIS extent and breast volume/shape, life expectancy and contraindications to or unwillingness to receive RT.

The standard of care for patients undergoing BCS is to receive RT. The current review found strong certainty in the evidence that the addition of RT was shown to significantly reduce the risk of recurrence [10-15,24,45,46]. This is consistent with similar previous trials conducted

in the 1980s and 1990s [52-55]. With regard to impact on survival with the addition of RT, there were no differences observed across the SweDCIS, EORTC 10852, and RTOG 9804 trials at various follow-up points [10-15]; however, the certainty in this evidence was considered moderate as many of the studies were not powered for survival outcomes and the event rates were low. There was however moderate certainty in the evidence to suggest that the addition of RT could increase adverse events. The RTOG 9804 trial found a slight increase in grade 1 and 2 acute toxicities with adjuvant RT following BCS, but grade 3 or higher toxicity rates were similar between the RT and no RT group. It was the recommendation of the Working Group that women who have undergone BCS with negative margins should be offered adjuvant RT. While the current review found no evidence to support adjuvant RT for women who have undergone mastectomy, it was the expert opinion of the Working Group that adjuvant chest wall irradiation should be considered only for the cohort for patients with positive margins (tumour on ink).

Recently, a large phase III RCT demonstrated that the addition of boost dose to WBI resulted in a lower recurrence rate among non-low risk DCIS patients undergoing BCS [16]. The BIG 3-07/TROG 07.01 trial demonstrated that the addition of boost dose resulted in a significant 4.4% absolute gain in local control at five years, resulting in a 97.1% five-year LR-free rate for the boost group compared to 92.7% for the no-boost group [16]. While the evidence also suggests with moderate certainty that the addition of a tumour bed boost does not significantly impact OS, there is a strong certainty that the additional boost is associated with an increase in treatment-related adverse events [16]. The BIG-3-07/TROG 07.01 trial demonstrated higher rates of grade ≥2 breast pain and induration in the boost group [16]. The BONBIS phase III trial supported these finding by reporting increase rates of ≥2 breast erythema, dermatitis, and grade 2 hyperpigmentation with localized boost irradiation [17]. Toxicity associated with boost doses is concerning, and the risk and benefits of any boost dose should be carefully weighed. It was the recommendation of the Working Group that for women with close margins (<2 mm) where re-excision surgery was not performed, a multidisciplinary discussion regarding the option of RT boost in addition to adjuvant RT should occur.

The BIG 3-07/TROG 07.01 trial further demonstrated that moderately HFRT was as effective as CRT in women with non-low-risk BCS, with no statistically significant differences in five-year locoregional or overall recurrence-free survival [16]. It was the consensus of the Working Group that patients should be offered HFRT of 42.5 Gy in 16 fractions or equivalent regimen (e.g., 40 Gy in 15 fractions). The Working Group recognizes that even shorter regimens (e.g. 26 Gy in 5 fractions) may also be offered, extrapolating from the FAST-Forward randomized trial for invasive breast cancer which showed that 26 Gy in five fractions over one week was non-inferior to moderate HFRT both for local control and normal tissue toxicity at five years [21].

Moreover, PBI was found to be as effective as WBI in terms of recurrence rates, based on evidence from a systematic review of two trials supporting the use of PBI [20], however specific details to characterize which DCIS patients would be suitable for PBI were not provided. Consistent with the ASTRO guideline [22,23], the Working Group recommends PBI could be considered in carefully selected patients exhibiting 'good risk' or low-risk DCIS, meeting the criteria outlined by the RTOG 9804 trial [14].

The management of DCIS may include the addition of endocrine therapy (tamoxifen or an aromatase inhibitor) following definitive surgery, plus or minus RT as required. A retrospective analysis of the NSABP B24 trial revealed significant benefit in terms of reduced recurrence rates for patients who were ER positive taking tamoxifen versus placebo after BCS and RT [25]. This is consistent with the UK/ANZ DCIS trial, which also showed reduced ipsilateral recurrence and a reduction in the rate of contralateral primary disease in patients treated with tamoxifen [24]. The IBIS-II and NSABP B-35 trials demonstrated no significant difference in

recurrence rate between tamoxifen or anastrozole, with the exception of a cohort of post-menopausal women younger than 60 years of age, where there may be greater benefit with the addition of anastrozole compared to tamoxifen [26,27]. As expected, the addition of endocrine therapy for the prevention of recurrence events is also associated with an increased risk of toxicity and adverse events. The IBIS-II DCIS trial reported that the use of tamoxifen was associated with higher rates of endometrial, ovarian, and non-melanoma skin cancer, while patients treated with anastrozole had significantly higher rates of fractures and transient ischemic attacks [26,28]. The NSABP B-35 trial demonstrated a higher rate of thrombosis/embolism in patients treated with tamoxifen, but no significant difference in the rate of uterine cancer in either treatment arm [27].

The Working Group acknowledges while a reduced dose of tamoxifen for a shorter period of time (i.e., 5 mg daily tamoxifen for 3 years) may also be an option for reducing risk of recurrence in hormone-sensitive or unknown DCIS with similar or slightly lower toxicity compared with the full dose as found in the TAM-01 study [27], this study did not meet prespecified criteria of this systematic review as the number of patients with DCIS comprised less than 80% of the patient population and did not provide a separate analysis. Therefore, no recommendations can be made regarding the use of low-dose tamoxifen in patients treated by BCS for DCIS. The Working Group recommends that the risk and benefits of endocrine therapy be discussed with patients after BCS for ER-positive disease, with a focus on individual patient risk of ipsilateral recurrence and contralateral primary disease, along with their treatment preferences.

Lastly, this current review investigated whether molecular profile testing could be added to the clinical evaluation using CP factors to guide the use or non-use of any adjuvant endocrine therapy in patients with DCIS. Two studies [7,8] on Oncotype DX were found that suggested that the Oncotype DX Breast DCIS score could contribute to additional information to prognosticate the recurrence risk beyond that of CP factors; however, the certainty in the evidence is very low and further research is needed to establish its clinical utility.

CONCLUSIONS

This comprehensive review on the management of DCIS provides valuable insights useful in clinical decision-making for healthcare providers. The choice of surgical treatment needs to be a patient-centred one, offering women the choice between BCS (with adjuvant breast irradiation offered as a clinical standard) or total mastectomy (with the option of reconstruction, ideally in the immediate setting). This decision-making process is underscored by a careful consideration of individual factors, such as patient characteristics (including breast size and volume) and personal preference, disease extent, comorbidities, and life expectancy. Regardless the choice of BCS or mastectomy, the evidence suggests that a margin width of at least 2 mm is optimal to minimize the risk of LR.

The use of adjuvant RT significantly reduces the risk of LR in patients treated with BCS, with HFRT demonstrating comparable effectiveness to CRT. The risks and benefits of adding boost RT doses (in patients treated by BCS who have close or positive margins, as well as the post-mastectomy patients with positive margins) should be made in a multidisciplinary fashion. The use of PBI can be considered a viable alternative to WBI in carefully selected patients meeting pre-specified criteria such as low risk DCIS with a low volume of disease.

In summary, the findings outlined in this systematic review collectively contribute to the evolving landscape of DCIS treatment, emphasizing the importance of a tailored, evidence-based approach to optimize patient outcomes. These recommendations may evolve or change pending the completion of ongoing trials and future work, evaluating the safety of active surveillance in DCIS and the use of genomic profiling to guide the use of adjuvant hormonal therapy.

Management of Ductal Carcinoma in Situ of the Breast

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 11 members of the GDG Expert Panel, 11 members voted for a total of 100% response in January 2024. Of those who voted, 11 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Comment about Recommendations 3-1: Many surgeons do not re-excise positive posterior margins when surgery was down to pectoralis fascia. It would be helpful to include a comment on this.	We have added a comment about this.
2. Consider adding "the option of immediate lumpectomy reconstruction in the case of BCS should be offered if a patient is deemed an appropriate candidate" to Recommendation 1.	We have added the suggested content to Recommendation 1.
3. The review considered DCIS with and without microinvasion. Would clinical management be affected by grade of DCIS (low vs. high)?	We have modified the recommendation that women with DCIS who have undergone BCS with negative margins should be offered adjuvant WBI regardless of the grade of DCIS.
4. DCIS-M is not defined in the recommendation section.	We have clarified the abbreviation definition.
5. Consider rewording the qualifying statement in Recommendation 2, second bullet and Recommendation 3, third bullet, to improve clarity.	We have modified the bullets for better clarity.
6. Comment that there was noticed there was no recommendation made specifically regarding radiation boost ranges	We have added radiation boost range to the qualifying statement, Recommendation 5.
7. Comment about Recommendation 5.3: Unaware of evidence suggesting benefit for adjuvant RT even with positive margins from DCIS in the setting of mastectomy and would challenge a statement suggesting adjuvant chest wall irradiation should be considered.	We have modified the recommendation and added a qualifying statement. It is not clear if PMRT is beneficial in this setting given there are few studies that specifically examine the LR risk post-mastectomy with positive margins with or without PMRT. Furthermore, while close or positive margins increase the risk of LR in this setting, overall, the LR risk is relatively low (5.3%) [6]. It was the expert opinion that PMRT is not indicated in this setting, but it is reasonable to consider chestwall irradiation in patients who have undergone mastectomy with

	multiple positive margins (tumour on ink) that cannot be surgically excised.

RAP Review and Approval

Three RAP members reviewed this document in December 2023/January 2024. The RAP approved the document. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Could some statement about the extent of DCIS for BCS be made? The recommendations do not include this information explicitly and it is important to consider.	We have added a qualifying statement that it was the expert opinion of the Working Group that one could safely extrapolate the benefits of adjuvant RT with more than 5cm of DCIS where complete excision is achieved.
2. Suggested edits to improve clarity to Section 2.	We have modified Section 2 with the suggested edits to improve clarity.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers (Appendix 2). Two responses were received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					2
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.					2
4. Rate the completeness of reporting.				1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?					2
6. Rate the overall quality of the guideline report.					2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					2
8. I would recommend this guideline for use in practice.					2

9. What are the barriers or enablers to the implementation of this guideline report?	None listed.

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. The role of post operative imaging in the management of close and positive DCIS margins was not mentioned. Does more imaging to determine obvious residual disease play a role in the decision to re-excise vs boost radiation?	We have added a qualifying statement to Recommendation 1: The use of imaging modalities to assess for residual disease in patients with positive markings post BCS is outside the scope of this guideline but the Working Group consensus favours positive margins being treated surgically given perceived low sensitivity for detecting residual disease versus postoperative changes in patients having undergone recent surgery with all imaging modalities.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Three hundred and twenty-five surgeons, medical oncologists, radiation oncologists with an interest in breast cancer (or with no specified area of interest) or individuals with an interest in breast cancer (medical oncologists, surgical oncologists, radiation oncologists) in the PEBC database were contacted by email to inform them of the survey. Thirty-two responses (9.8%) responses were received, and an additional 25 stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 32 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. The guideline did not discuss the emerging data on the role or HER2 Receptor status/treatment in DCIS	This study did not meet prespecified criteria of this systematic review.
2. Suggest adding "evidence does not strong favour" to beginning of Recommendation 1 and 6.	The Working Group has decided to leave the recommendations as is.
3. Suggest mentioning RT option after BCS for context in Recommendation 1 as an enabler to patients making the decision about BCS vs mastectomy (and state "see Recommendation 5 below")	We have added a phrase in a qualifying statement to indicate that RT options after BCS are covered in Recommendation 5 below.
4. Since there is a lack of conclusive evidence for Recommendation 4 consider adding "Molecular profile testing should be confined to ongoing research"	The Working Group has added this phrase to recommendation 4.
5. Would consider adding most recent trial on low dose tamoxifen (TAM-01)	This study did not meet prespecified criteria of this systematic review as the number of DCIS patients comprised less than 80% of the patient population and

	did not provide a sperate analysis. More information can be found on page 51.
6. Recommendation 5.1 should be reworded to give an age component with lower Grade DCIS as there is much discussion globally to de-escalate therapy for elderly women	The Working Group has decided to leave the recommendation as it. The potential risks and benefits of adjuvant irradiation should be discussed between individual patient and clinicians.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original Version 1998	Up to 1998	Full Report	Web Publication	N.A.
Updated Version 2 September 2006	1998-2006	Full Report	Updated web publication.	Literature update
Endorsed Version 3 January 2018	2006-June 2017	New data found and added a Section 4: Document Summary and Review Tool	Updated web publications	Endorsed 2006 recommendations
Version 4	2006 - November 2023	New Report	Web Publication	

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Appendix 2: Affiliations and Conflict of Interest Declarations

GUIDELINE DEVELOPMENT GROUP		
WORKING GROUP		
Name	**Speciality**	**Declarations of interest**
Muriel Brackstone	Surgical oncologist, professor Western University, Victoria & Children's Hospital	None declared
Nadia Califaretti	Medical oncologist Grand River Regional Cancer Centre	None declared
Lisa Durocher	Health Research Methodologist Program in Evidence-based Care	None declared
Andrea Eisen	Medical oncologist Odette Cancer Centre	None declared
Sarah Knowles	Medical oncologist, assistant professor St. Joesph's Health Care Centre	None declared
Anne Koch	Radiation oncologist Princess Margaret Hospital	None declared
Taude Plexman	Patient representative, Executive Director, Enliven Cancer Care Muskoka	None declared
Abeer Salim	Patient representative Patient and Family Advisor Ontario Health	None declared
EXPERT PANEL		
Name	**Speciality**	**Declarations of interest**
Anita Bane	Breast pathologist Toronto General Hospital: University Health Network	None declared
Ryan Carlson	Radiation oncologist Health Sciences North Regional Cancer Program	None declared
Jessica Conway	Medical oncologist Royal Victoria Hospital	None declared
Harriet Feilotter	Senior Scientist- molecular pathology Queen's Cancer Research Institute	None declared
Samantha Fienberg	Radiologist Cancer Care Ontario, Ontario Health	None declared
Leta Forbes	Medical oncologist Cancer Care Ontario, Ontario Health	None declared

Sonal Gandhi	Medical oncologist Odette Cancer Centre Sunnybrook Health Sciences Centre	Has received $500 or more in a single year in a consulting capacity for Lily AD BOARD, Agendia AD BOARD, AZ AD BOARD, and Novartis AD BOARD (stipends total ~$5,000)
Renee Hanrahan	Medical oncologist Collingwood General and Marine Hospital Royal Victoria Regional Health Centre	None declared
Glykeria Martou	Assistant Professor, Plastic Surgeon Queen's University Kingston General Hospital Hotel Dieu Hospital	None declared
Francisco Perera	Radiation oncologist London Regional Cancer Program	None declared
Christiaan Stevens	Radiation oncologist Royal Victoria Hospital	None declared
REPORT APPROVAL PANEL		
Name	**Speciality**	**Declarations of interest**
William K. Evans	Medical Oncologist Oncosynthesis Consulting Inc.	None declared
Michelle Ghert	Surgeon Juravinski Cancer Centre, Hamilton Ontario, Canada	None declared
Jonanthan Sussman	Radiation Oncologist Juravinski Cancer Centre, Hamilton Ontario, Canada	None declared
TARGETED PEER REVIEW		
Name	**Speciality**	**Declarations of interest**
Petrina Causer	Radiologist Community Hospital- North York General Hospital Toronto, Ontario, Canada	None declared
Ralph George	Surgery St. Michael's Hospital Toronto, Ontario, Canada	Has been a co-principal for the PET ABC study, which looked at PET for staging LABC.

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Appendix 3: Quality assessment results for relevant guideline and systematic review

Guideline quality assessment results using AGREE tool

Guideline	Domain 1: Scope and Purpose	Domain 2: Stakeholder involvement	Domain 3: Rigor of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence
SSO/ASTRO/ ASCO	82%	50%	58%	69%	14%	75%

Systematic review risk of bias assessment results using ROBIS tool

Review	Phase 2				Phase 3
	1. STUDY ELIGIBILITY CRITERIA	2. IDENTIFICATION AND SELECTION OF STUDIES	3. DATA COLLECTION AND STUDY APPRAISAL	4. SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Garg et al.	☹	☹	☹	?	☹
Kim et al.	☺	☺	☺	☺	☺
Marinovitch	☺	☺	☹	☺	☺
Shumway et al	☺	☺	☺	☺	☺
Yan et al.	☺	☹	☹	☺	☹

☺ = low risk; ☹ = high risk; ? = unclear risk

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Appendix 4: Literature Search Strategy

Medline and Embase (search for all research questions, but surgical margins):

1. exp ductal breast carcinoma in situ/ or Carcinoma, Intraductal, Noninfiltrating/ or dcis.mp. or ductal carcinoma in situ.mp. or (ductal carcinoma adj2 microinvas:).mp.
2. (exp breast ductal carcinoma/ or exp carcinoma, ductal, breast/) and (microinvas: or ((limited or focal or suggestive) adj2 invasion)).ti,kw,ab.
3. 1 or 2
4. exp practice guideline/ or guideline.pt. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti,kw. or exp Consensus Development Conference/ or exp Consensus/ or exp Consensus Development Conferences as Topic/
5. exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.
6. exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trials as topic/ or exp controlled clinical trial/ or "controlled clinical trial (topic)"/ or controlled clinical trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treble$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (rct or phase III or phase IV or phase 3 or phase 4 or randomi$: or randomly).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
7. (oncotype DX or (oncotype$ or 12 gene or recurrence score) or molecular profiling).mp. or molecular fingerprinting/ or DCISionRT.mp. or (7 gene or DCIS biosignature).mp. or 21-gene assay recurrence score.mp. or 12 gene expression assay.mp.
8. 3 and (4 or 5)
9. limit 8 to yr=2017-current
10. limit 9 to english
11. remove duplicates from 10
12. 11 not (comment or letter or note or editorial or case reports or historical).pt.
13. (3 and 6) not 10
14. remove duplicates from 13
15. limit 14 to yr=2006-current
16. 15 not (comment or letter or note or editorial or case reports or historical).pt.
17. limit 16 to english

18. (3 and 7) not 10
19. remove duplicates from 18
20. limit 19 to yr=2006-current
21. 20 not (comment or letter or note or editorial or case reports or historical).pt.

Embase & Medline : surgical margins

1. exp ductal breast carcinoma in situ/ or Carcinoma, Intraductal, Noninfiltrating/ or dcis.mp. or ductal carcinoma in situ.mp. or (ductal carcinoma adj2 microinvas:).mp.
2. (exp breast ductal carcinoma/ or exp carcinoma, ductal, breast/) and (microinvas: or ((limited or focal or suggestive) adj2 invasion)).ti,kw,ab.
3. 1 or 2
4. Margin.mp.
5. Margins.mp
6. Marginal.mp.
7. 4 or 5 or 6
8. 3 and 7
9. Limit 8 to yr=2006-current
10. Limit 9 to english
11. Remove duplicates from 10
12. 11 not (comment or letter or note or editorial or case reports or historical).pt.

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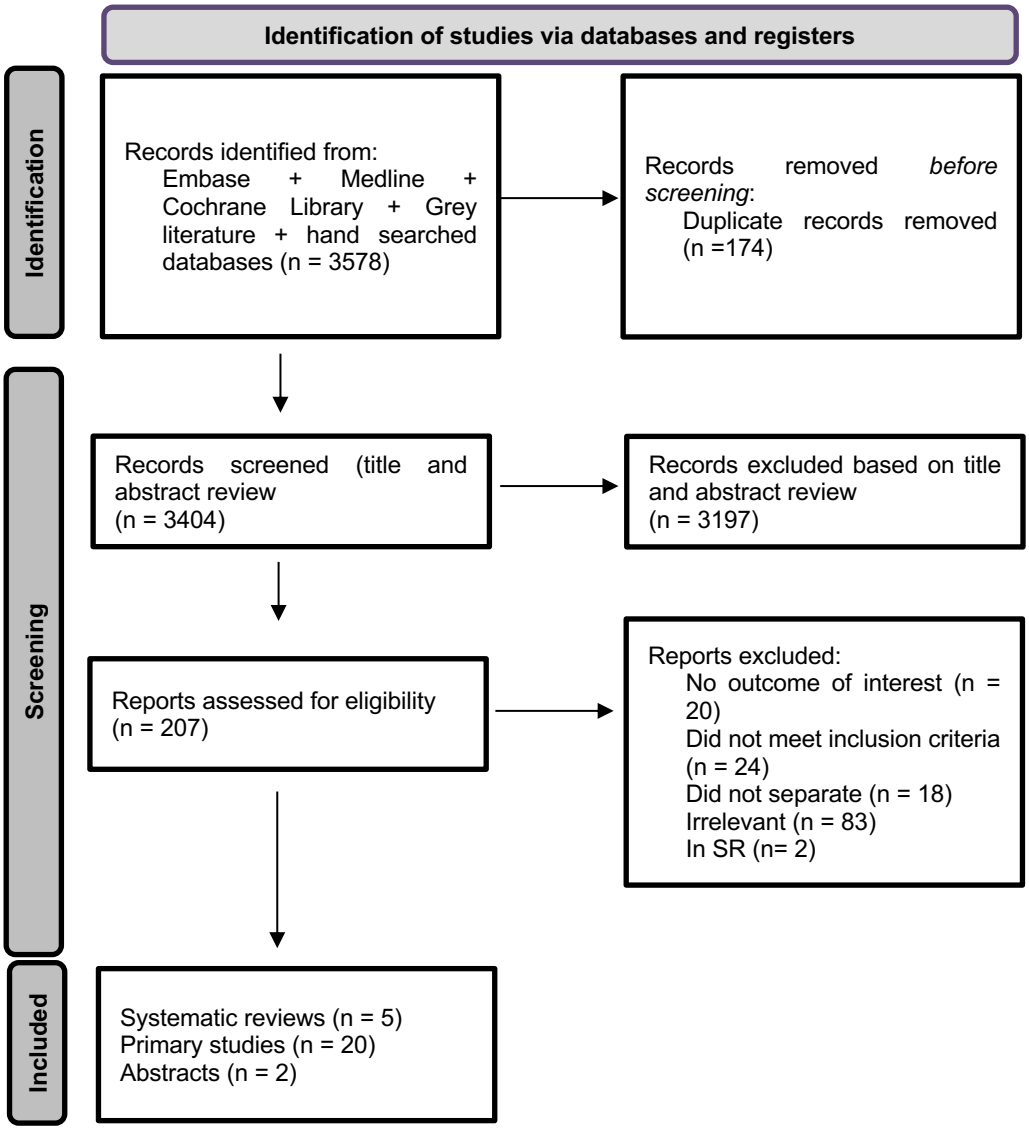
Appendix 5: PRISMA Flow Diagram



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Appendix 6: Results of risk of bias assessment of included studies

Randomized Controlled trial (ROB-2)

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Allred et al. 2012	ER positive	ER negative	Recurrence	!	+	+	+	!	!
Bijker et al 2006	RT	No RT	Overall survival	+	+	+	+	!	!
Bijker et al 2006	RT	No RT	Recurrence	+	+	+	+	!	!
Donker et al. 2013	RT	No RT	Recurrence	+	+	+	+	!	!
Donker et al. 2013	RT	No RT	Overall Survival	+	+	+	+	!	!
Bourgier et al. 2021	Boost	No Boost	Adverse events	!	+	+	-	+	-
Emdin et al. 2006	RT	No RT	Recurrence	+	+	+	+	!	!
Emdin et al. 2006	RT	No RT	DFS	+	+	+	+	!	!
Warnberg et al. 2014	RT	No RT	Recurrence	+	+	+	+	!	!
Warnberg et al. 2014	RT	No RT	DFS	+	+	+	+	!	!
McCormick et al 2015	RT	No RT	Recurrence	!	+	+	+	!	!
McCormick et al 2015	RT	No RT	DFS	!	+	+	+	!	!
McCormick et al 2015	RT	No RT	Adverse events	!	+	+	+	!	!
Chua et al. 2022	Boost	No Boost	Recurrence	+	+	+	+	+	+
Chua et al. 2022	Boost	No Boost	DFS	+	+	+	+	+	+

Chua et al. 2022	Boost	No Boost	adverse events	+	+	+	+	+	+
Chua et al. 2022	HFRT	CRT	Recurrence	+	+	+	+	+	+
Cuzick et al 2011	RT	No RT	Recurrence	+	+	+	+	+	+
Cuzick et al 2011	TMX	No TMX	Recurrence	+	+	+	+	+	+
Forbes et al. 2016	ANA	TMX	Recurrence	+	+	+	+	+	+
Forbes et al. 2016	ANA	TMX	Contralateral Events	+	+	+	+	+	+
Magolese et al. 2016	ANA	TMX	Recurrence	+	+	+	+	!	!
Magolese et al. 2016	ANA	TMX	Contralateral events	+	+	+	+	!	!
Magolese et al. 2016	ANA	TMX	DFS	+	+	+	+	!	!
Magolese et al. 2016	ANA	TMX	Adverse events	+	+	+	+	!	!

Non- randomized comparative studies (ROBINS-I)

Study and Outcome		Domain 1: Blinding due to confounding	Domain 2: Bias in selection of participants into the study	Domain 3: Bias in classification of interventions	Domain 4: Bias due to Deviation from Intended Intervention	Domain 5: Bias due to Missing Data	Domain 6: Bias in Measurement of Outcome	Domain 7: Bias in selection of the Reported Results	Overall Risk of Bias (per outcome)
Livingstone-Rosanoff et al.	Recurrence	Serious	Moderate	Moderate	Moderate	Serious	Serious	Serious	Serious
Schmitz et al.	Recurrence	Serious	Moderate	Moderate	Moderate	Serious	Serious	Serious	Serious
Tadros et al.	Recurrence	Serious	Serious	Moderate	Moderate	Serious	Moderate	Serious	Serious

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Appendix 7: Ongoing Trials (on July 26th, 2023)

Title and Protocol ID	Study details and Status
Surgical treatment/Active Surveillance	
A Randomized Phase 2 Study Comparing Surgical Excision Versus Neoadjuvant Radiotherapy Followed by Delayed Surgical Excision of Ductal Carcinoma In Situ (NORDIS)- NCT03909282	Phase 2 trial surgical excision vs. neoadjuvant radiotherapy + delayed surgical excision of DCIS (NORDIS; est completion 2025).
Impact of Neoadjuvant Hormonal Therapy on the Surgical Management of Extensive Ductal Carcinomas in Situ (NORNE001)- NCT04666961	Phase 2 trial investigating neoadjuvant tamoxifen or anastrozole and delayed surgical excision of DCIS (est completion 2024).
Comparing an Operation to Monitoring, With or Without Endocrine Therapy (COMET) Trial For Low Risk DCIS-- NCT02926911	Phase 3 prospective randomized trial comparing surgery +/- radiation with choice of endocrine therapy and active monitoring with choice of endocrine therapy (est completion 2028).
Management of Low-Risk (Grade I and II) DCIS (LORD)- NCT02492607	Non randomized trial examining wide local excision +RT or wide local excision or mastectomy vs. active surveillance (est completion 2029)
A trial comparing surgery with active monitoring in low risk DCIS (UK-LORIS)	A phase 3 trial comparing surgery (+/- RT and/or hormonal therapy) and active monitoring. Recruitment for this trial has ended (est completion unknown).
Prospective Evaluation of Breast-Conserving Surgery Alone in Low Risk Ductal Carcinoma in Situ (ELISA)- NCT04797299	Prospective cohort study to evaluate whether the combination of clinicopathological factors and the use of Oncotype DX DCIS score can avoid radiation in women with low-risk DCIS who have had BCS (est completion 2035).
Wide Excision Alone as Treatment for Ductal Carcinoma In Situ of the Breast- NCT00165256	Phase 2 study to determine if wide excision (surgical removal) alone is adequate treatment for small, grade 1 or 2, DCIS of the breast (est completion 2023) (surgery vs. observation)
Management after DCIS after primary treatment	
Radiotherapy Versus Low-Dose Tamoxifen Following Breast Conserving Surgery for Low Risk Breast Ductal Carcinoma in Situ -NCT04046159	Phase 3 trial comparing RT (50Gy/25 fx or 40.05 Gy/15 fx) vs. low-dose tamoxifen (5mg QD for 10 yrs) in low-risk and estrogen receptor-positive DCIS (est completion 2025)
Testing an Active Form of Tamoxifen (4-hydroxytamoxifen) Delivered through the Breast Skin to Control Ductal Carcinoma in Situ (DCIS) of the Breast- NCT02993159	Phase 2 trial comparing 2mg once daily per breast of 4-hydroxytamoxifen topical gel vs. 20 mg daily oral tamoxifen citrate (est completion 2023)

Hypofractionated Partial Breast Irradiation in Treating Patients with Early Stage Breast Cancer- NCT03077841	Phase 2/3 trials comparing hypofractionated partial breast irradiation daily for 5 days (+ possible 3 boost fractions at discretion of the doctor) vs. standard irradiation daily for 15 days (+ possible 5 boost fractions at discretion of the doctor; est completion 2024).
Single-arm confirmatory trial of endocrine therapy alone for estrogen receptor-positive, low risk ductal carcinoma in situ of the breast (JCOG1505, LORETTA trial)	Trial comparing endocrine therapy alone vs. non in low-risk estrogen receptor positive patients (est completion unknown)
Molecular Testing	
The AUS-PREDICT Registry for DCIS Patients with DCISionRT Testing- NCT04916808	Prospective cohort study of patients diagnosed with DCIS and to create a database of patients, test results, treatment decisions, and outcomes to determine the utility of DCISionRT (est completion 2024)
The PREDICT Registry for DCIS Patients with DCISionRT Testing NCT03448926	Prospective cohort study of patients diagnosed with DCIS and to create a database of patients, test results, treatment decisions, and outcomes to determine the utility of DCISionRT (est completion 2025)

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