National Institute for Health and Care Excellence

Final

Early and locally advanced breast cancer: diagnosis and management

[N] Evidence reviews for further surgery after breast-conserving surgery based on tissue margins

NICE guideline NG101

Evidence reviews underpinning recommendations 1.3.2 to 1.3.5 in the NICE guideline

January 2024

Final

This evidence review was developed by NICE

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Contents

1 Further surgery after breast-conserving surgery based on tissue margins

1.1 Review question

What is the optimum tumour-free radial margin after breast-conserving surgery for adults with invasive breast cancer and/or ductal carcinoma in situ (DCIS) to minimise the risk of local recurrence and maximise overall survival and patient satisfaction?

1.1.1 Introduction

An important determinant of local recurrence is the surgical margin width (the distance from the breast cancer to the edge of the surgical excision) after breast conserving surgery. In cases where tumour cells are detected at the surgical margin (tumour at ink), then re-excision is recommended by the NICE guideline: Early and locally advanced breast cancer: diagnosis and management (NG101, published 2018). The 2018 committee noted the uncertainty surrounding the optimum margin width at which no further surgery would be recommended and that it was not possible based on the evidence available at that time to determine whether a radial margin of less than 2 mm, but greater than 0 mm would be suitable. They therefore recommended that where the tumour is within 2 mm of, but not at, the radial margins (greater than 0 mm and less than 2 mm) there should be a discussion of the benefits and risks of further surgery with the woman, taking into account her preferences and a number of medical factors. The committee also made a research recommendation to stimulate further research in this area.

The 2023 surveillance report identified a systematic review by Bundred at al. (2022) that could address the research recommendation and lead to a change in the existing recommendations. This current review aims to evaluate the new evidence on margin widths to try to answer the question about the optimum tumour-free radial margin after breast-conserving surgery. The modified PICO for this review is shown in Table 1.

1.1.2 Summary of the protocol

Table 1: Modified PICO

Population	**Inclusion:** Adults (18 or over) with invasive breast cancer and no distant metastases (M0) and/or ductal carcinoma in situ (DCIS) who have undergone breast conserving surgery with or without subsequent radiotherapy. **Exclusion:** • People who have had a mastectomy instead of breast conserving surgery • People who have had intraoperative radiotherapy • People who have had neoadjuvant therapy • People with multicentric breast cancer • People who have mastectomy by choice after breast conserving surgery based on their greater genetic risk of breast cancer (e.g., people with BRCA1 or BRCA2 gene mutations)
Exposure	1. Tumour free margin widths of greater than 0 mm and less than 2 mm.

	2. If the data from the majority of studies does not fit in category 1, then we will use tumour free margin widths of greater than 0 mm and less than or equal to 2 mm as the exposure. The margins must be assessed by a pathologist.
Comparator	• Tumour free margins of greater than or equal to 2 mm or tumour free margins of greater than 2 mm if option 2 in the exposure box is used (see above). • Any categories of exposure that fall between greater than 0 mm and less than or equal to 2 mm compared to each other.
Outcomes	**Primary outcomes:** • Local recurrence if reported and if not, locoregional recurrence • Distant recurrence • Overall survival • Breast cancer specific survival • Health related quality of life • Breast Q (patient reported outcome measure) **Secondary outcomes:** • Eventual mastectomy rates • Re-operation rates
Study type	• Randomised controlled trials (RCTs) • Any controlled, non-randomised studies • Cohort studies (prospective and retrospective observational studies) • Systematic reviews of the above studies

For the full protocol see Appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix K – Methods in this evidence review. The main methods used in the review are summarised below:

1. The studies were categorised into three populations:
    a. people with invasive breast cancer and with or without ductal carcinoma in situ (including studies with mixed populations of people with invasive breast cancer or with ductal carcinoma in situ, where the results were not presented separately).
    b. people with ductal carcinoma in situ alone
    c. people who have had neoadjuvant therapy (see protocol deviation below).

    The analyses were carried out and are reported separately for each of these groups.
2. If a study referred to ductal carcinoma but did not mention DCIS, it was included in the invasive breast cancer with or without DCIS category.
3. Some populations were excluded from the review protocol. These were:
    a. People who had intraoperative radiotherapy. These are a different population to people having radiotherapy post-surgery and they may need different tissue

margins. Intraoperative radiotherapy is not currently routinely recommended in NG101.

b. People with neoadjuvant therapy are excluded from this review because the committee thought that these people may be a separate population because of the potential effects of this therapy on breast tissue and overall survival.

c. People with multicentric disease as this is rarer and substantially different from unifocal and multifocal disease, which are more common.

4. We looked for RCTs but no relevant studies were identified using this study type. In the absence of RCTs, only cohort studies were included in the review.

5. Some of the studies used different definitions for each outcome. Therefore, the way the study described an outcome was compared to the definitions agreed by the committee to determine what each study was reporting. Definitions provided by the committee were:

   a. Local recurrence: recurrence within the ipsilateral breast.

   b. Locoregional recurrence: recurrence within the ipsilateral breast or axilla.

   c. Distant recurrence: recurrence occurring in distant sites or supraclavicular nodes.

   d. Re-operation rates: the number of people having further re-excisions or completion mastectomy after the first therapeutic breast conserving surgery excluding cosmetic effects of the surgery. Diagnostic operations were not counted as first surgery, so that people having a wide local excision after a diagnostic operation were not counted as having a reoperation.

   e. Eventual mastectomy rates: The number of people who had mastectomy at any time after breast conserving surgery.

6. Most studies reported local recurrence, which is a subset of locoregional recurrence (see definitions above). Data were initially analysed separately for local recurrence and locoregional recurrence before being pooled in 2 additional meta-analyses. This approach was taken based on committee input around the overlap of these outcomes and uncertainty associated with the way these particular outcomes are reported in different studies. It also increased the population size and the resulting statistical power of the analyses to detect a difference in effect.

7. Where more than 1 timepoint was reported we reported data at 5 years and 10 or more years. Data for time points of less than 5 years (see a protocol deviation for included studies with follow-up less than 5 years) and up to 7.5 years were included in the 5 year category, data for time points of greater than 7.5 years were included in the 10 years or more category. Where several time points were reported that could fit in the 10 years or more category, the latest time point was used.

8. Two studies including people who had neoadjuvant therapy were used in the invasive breast cancer with or without DCIS analyses, but it was decided that the proportion of people having this treatment was too low to have an effect on the results (Chae et al. 2022 and Maishman et al. 2017 included 4.4% and 11.1% of participants with neoadjuvant therapy respectively). As we agreed at the protocol stage to include studies with under 25% of the participants having taken neoadjuvant therapy these studies were not downgraded for their applicability to this evidence review.

9. One systematic review (Bundred et al. 2022) was identified as a source of data for people who have invasive breast cancer. In some cases, the authors had contacted the

original study authors for data in comparisons of interest, and where this data has been used it is detailed in our evidence table for the systematic review (Bundred, 2022). We also contacted the primary author (James Bundred) for clarification of some points relating to the systematic review and would like to thank him for his helpful responses.

10. The Risk Of Bias In Non-randomised Studies - of Exposure (ROBINS-E) tool was used to assess risk of bias in each study. This was considered the most appropriate method because the surgical margins could not be assigned to people as an intervention, but were based on what was achieved during surgery (i.e., an exposure). This also allowed us to use the risk of bias assessments from the systematic review by Bundred et al. 2022. Although the systematic review by Bundred et al. 2022 used an earlier prepublication version of the ROBINS-E tool we used the published version because the contents of the tool did not change substantially between these versions. We updated their assessments of the risk of bias due to confounding for studies that were unadjusted or partially adjusted to match our judgement with the rest of our included studies. We gave an assessment of high risk of bias to studies that were unadjusted and an assessment of serious concerns of bias to studies that were partially adjusted.

11. The subgroup analyses in the protocol (radiotherapy, age, subsequent systemic treatment) were not carried out in most cases because the data was too limited to have separate analyses for each of these subgroups. For radiotherapy, limited subgroup analyses were possible. Any studies with characteristics of these subgroups have been highlighted in footnotes of forest plots and were discussed with the committee in the meeting. These discussions are summarised in the committee's discussion of the evidence.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 22 August 2023. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Epistemonikos, HTA (Health Technology Assessment) (CRD), International Health Technology Assessment Database (INAHTA) and MEDLINE ALL (Ovid). Full search strategies for each database are provided in Appendix B.

The database searches were supplemented with additional search methods. Forwards citation searching was conducted on Web of Science (Clarivate). Full details are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 22 August 2023. The following databases were searched: EconLit (Ovid), Embase (Ovid), HTA (Health Technology Assessment) (CRD), International Health Technology Assessment Database (INAHTA) and MEDLINE ALL (Ovid). Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

1. For outcomes where we decided that any statistically significant difference was important, we used the line of no effect as one of the downgrades for imprecision. The quality of the outcome was therefore downgraded once for imprecision if either end of the 95% confidence interval crossed the line of no effect. To be consistent with the 2018 update methods we planned to use an event size of 300 events for the second

downgrade based on optimal information size calculations that suggested that at least 300 events were needed to adequately detect an effect. However, few studies reporting hazard ratios provided this information and so it was decided to use sample size instead as a more readily available measure to ensure that all studies would have the potential to be downgraded twice. A minimum sample size of 500 was selected to allow for the possibility of 300 events. As a result, the quality was downgraded a second time if the number of participants for an outcome was less than 500.

2. There were 6 studies with follow-up times between 4 and 4.7 years (Biglia et al. 2014; Choi et al. 2018; Kuru et al. 2020; Lin et al. 2020; MacDonald et al. 2005; Vos et al. 2017). It was considered that the follow-up was close enough to 5 years, therefore, these studies were included. Mannu et al., 2020 did not provide a mean or median follow up but divided the population into follow up categories in the summary of the study population characteristics table (Table 1 in the study). For people who had radiotherapy 64% fell onto the 0-4 year category and 36% fell into the 5 years and over categories. In contrast for people who didn't have radiotherapy 39% fell in the 0-4 years follow up and 61% fell into the 5 years and over categories. This study was included but the data for people who had radiotherapy was downgraded once for indirectness. The 'without radiotherapy' data was not downgraded for indirectness as the majority of people fell within the follow-up time of interest.

3. Mannu et al., (2020) provided their results as adjusted rate ratios. This was not an outcome measure in the review protocol, but a protocol deviation was carried out to include this data as it looked at surgical margins, had many of the adjustments in our protocol, and was of interest to the committee. However, we also included unadjusted event data to allow comparisons of margin sizes smaller than the ≥ 5 mm reference category for the adjusted rate ratios.

4. People who had neoadjuvant therapy before breast conserving surgery were initially excluded from this review because the committee thought that these people were a separate population due to this treatment. The committee also noted that there was a gap in the guideline regarding margin widths for further surgery for these people. However, since the searches for the evidence for included populations also identified studies for people treated with neoadjuvant therapy and there were very few of them, we decided that this did not warrant an additional separate review, and to present this evidence to the committee in the same meeting.

1.1.4 Effectiveness of further surgery evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 1980 references (see Appendix B for the literature search strategy). Evidence from the NG101 2018 update (6 references), evidence identified from the list of references of included studies (3 references) was also reviewed. In total, 1,989 references were identified for screening at title and abstract level against the review protocol, with 1,937 references excluded at this level. 10% of references were screened separately by two reviewers with 95% agreement. Discrepancies were resolved by discussion.

The full texts of 52 cohort studies and systematic reviews of cohort studies were ordered for closer inspection. Thirty of these studies met the criteria specified in the review protocol (Appendix A). For a summary of the included studies see Table 2, Table 3 and Table 4.

Of the 30 included studies:

- For the analysis of margins in people with invasive breast cancer with/ without DCIS there were 18 included studies.
    - One was a systematic review (Bundred et al. 2022) from which 13 studies were included in the invasive breast cancer analysis (see the full evidence table for the review in Appendix D – Effectiveness of further surgery evidence for a list of the included and excluded studies with reasons). The primary studies were also identified by the search we carried out.
    - 4 additional studies were identified that were not in Bundred et al. 2022.
- For people with DCIS alone there were 9 studies.
- For people who had taken neoadjuvant therapy there were 3 studies.

As per the protocol deviation above we included studies for people who had taken neoadjuvant therapy as an additional analysis. We found three studies (Choi et al. 2018, Lin et al. 2020 and Rouzier et al. 2001) on margin widths for further surgery for people who have had neoadjuvant therapy. There was a study (Bhatti et al. 2014) including between 29% to 33% of people with neoadjuvant therapy. This study was excluded because it did not meet the inclusion criterion in the protocol of having less than 25% people with neoadjuvant therapy. Bhatti et al. 2014 was not added to the studies including people who had neoadjuvant therapy before breast conserving surgery because in those studies all people had neoadjuvant therapy and only a third of participants in Bhatti et al. 2014 had neoadjuvant therapy. See Table 5 for a summary of these included studies.

The clinical evidence study selection is presented as a PRISMA diagram in Appendix D – Effectiveness of further surgery evidence.

See section 1.1.12 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in

Appendix J – Excluded studies.

1.1.5 Summary of studies included in the effectiveness of further surgery evidence

The radial margin width column lists the margin widths of interest for this review – both as the exposure and comparators.

Table 2 Summary of the characteristics of the systematic review

Author (year)	Primary studies that have been used from this review	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Bundred (2022)	Behm 2013 Biglia 2014 Bodilsen 2016 Goldstein 2003 Kreike 2008 Lupe 2011 Maishman 2017 Peterson 1999 Smith 2014 Smitt 2003 Tang 2019 Tyler 2018 Varghese 2008	**Inclusion criteria** Patients undergoing curative breast conserving surgery for early stage invasive breast cancer (stage I-III) Study allowed an estimation of outcomes in relation to margin status Followed up patients for a minimum of 60 months	Tumour between 0.1 and 2 mm from ink Tumour between 0.1 and 1 mm from ink Tumour between 1.1 and 2 mm from ink >2 mm from ink	To be adequately adjusted a study must adjust for age, tumour stage, grade, chemotherapy, radiotherapy **OR** must contain exclusively patients (>95%) receiving chemotherapy/ radiotherapy if not adjusting for these covariates.	Local recurrence Distant recurrence Overall survival	Low

Author (year)	Primary studies that have been used from this review	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
		Exclusion criteria Patients with ductal carcinoma in situ only Patients treated with neoadjuvant chemotherapy Patients who had a mastectomy				

Table 3 Summary of studies included in the review for people with invasive breast cancer with or without DCIS

The radial margin width column lists the margin widths of interest for this review – both as the exposure and comparators. Studies were rated as partially adjusted if they adjusted for some, but not all, of the confounders listed in the review protocol in Appendix A. In some cases unadjusted data was used to allow comparisons of the margins of interest.

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Behm (2013)	N=2,300	1mm 2mm 5mm	Partially adjusted for: • Age • Total tumour size	Locoregional recurrence	Moderate

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Australia Retrospective cohort study Follow-up: Mean 7.9 years	Participants were treated with either breast conserving surgery or mastectomy for invasive breast cancer. The study included a mixed population with 63.6% of participants having invasive breast cancer with ductal carcinoma in situ. Key exclusion criteria: Patients with Paget's disease of the breast, phyllodes tumour, invasive breast cancer of special types, bilateral or metachronous breast cancer and those with evidence of distance metastasis at the time of surgery were excluded from the study.		• Invasive tumour grade • Oestrogen/progesterone receptor status • Lymphovascular invasion • Lymph node involvement • Hormone/chemotherapy/radiotherapy received • Ductal carcinoma in situ involvement	Distant recurrence	
Biglia (2014) Italy Retrospective cohort study Follow-up: Median 47.5 months (4 years)	N=1339 Women with invasive or in situ breast cancer treated with breast conserving surgery and radiotherapy were included. The study included a mixed population with 3.7% of participants having invasive breast cancer with ductal carcinoma in situ. Exclusion criteria were not reported.	≤ 2mm >2mm	Partially adjusted for: • Age • Tumour size • Histology • Grading • Multifocality • Histotype • Presence of lymphovascular invasion • Nodal status • Oestrogen and progesterone receptor status • Oncogene HER-2 and Ki67 expression	Local recurrence	Moderate

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Bodilsen (2016) Denmark Retrospective cohort study Follow-up: Median 5.3 years	N=1519 Women <75 years, with unilateral, invasive breast cancer treated with breast conserving surgery and radiotherapy were included. The study included a mixed population with 11% of participants having invasive breast cancer with ductal carcinoma in situ. Key exclusion criteria: women who underwent a mastectomy within 2 months of breast conserving surgery. Women receiving neoadjuvant therapy.	>0mm to 1mm ≥ 5mm	Unadjusted analysis	Distant recurrence	High
Chae (2022) South Korea Retrospective cohort study Follow-up: Median 6 years	N=542 Women with newly diagnosed invasive breast cancer treated with breast conserving surgery were included. The study included a mixed population, however proportion of participants with DCIS not reported. Key exclusion criteria: carcinoma in situ and those who did not undergo re-excision.	≤ 2mm >2mm	Partially adjusted for: • Tumour size • Nodal status • Multifocality • Hormone receptor, HER-2 • Adjuvant radiotherapy	Locoregional recurrence	Moderate
Goldstein (2003)	N=583	0.1 to 1mm 1.1 to 2mm 2.1 to 3mm	Unadjusted analysis	Local recurrence Distant recurrence	High

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
US Retrospective cohort study Follow-up: Median 8.7 years	Women with invasive or in situ breast cancer treated with breast conserving surgery and radiotherapy were included. The study included a mixed population with 35.5% of participants having invasive breast cancer with ductal carcinoma in situ. Exclusion criteria were not reported.				
Guinot (2018) Spain Prospective cohort study Follow-up: Mean 127 months (10.6 years)	N=382 Women with invasive or in situ breast cancer treated with breast conserving surgery and with positive or close surgical margins <5mm. The study included a mixed population with 60% of participants having invasive breast cancer with ductal carcinoma in situ. Key exclusion criteria: Refused re-excision for margins	≤ 2mm >2mm to <5mm	Unadjusted analysis	Breast-cancer specific survival	High
Kreike (2008) The Netherlands Retrospective cohort study	N=1024 Women with invasive or in situ breast cancer treated with breast conserving surgery were included. The study included a mixed population with 51.3% of participants having invasive breast cancer with ductal carcinoma in situ.	Within 1mm ≥1mm	Partially adjusted for: • Age • Vascular invasion • Quantity and type of in situ component	Local recurrence	Moderate

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Follow-up: Median 13.3 years	Exclusion criteria were not reported.				
Kuru (2020) Turkey Retrospective cohort study Follow-up: Median 56 months (4.7 years)	N=628 Participants with T1 and T2 invasive breast cancer treated with breast conserving surgery were included. The study included a mixed population with all participants having invasive breast cancer with ductal carcinoma in situ. Key exclusion criteria: people receiving neoadjuvant chemotherapy.	Within 2mm ≥ 2mm	Unadjusted analysis	Local recurrence	High
Lupe (2011) Canada Retrospective cohort study Follow-up: Median 5.2 years	N=2264 Participants with T1-T3, any pN, M0 invasive breast cancer, who were treated with breast conserving surgery and radiotherapy were included. The study included a mixed population with 28.8% of participants having invasive breast cancer with ductal carcinoma in situ. Key exclusion criteria: women who underwent complete mastectomy, women who did not receive whole breast	< 2mm ≥ 2mm	Unadjusted analysis	Local recurrence Locoregional recurrence Distant recurrence Overall survival Breast-cancer specific survival	High

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
	radiotherapy or received partial radiotherapy/non-standard radiotherapy technique.				
Maishman (2017) UK Prospective cohort study Follow-up: Median 7.3 years	N=1395 Women aged 18-40 years at breast cancer diagnosis, who were treated with breast conserving surgery with or without radiotherapy were included. Key exclusion criteria: metastatic disease at presentation	0.1 to 2mm 0.1 to 1mm 1.1 to 2mm >2mm	Partially adjusted for: • Age • T stage • N stage • Histology • Boost dose radiotherapy • Focality	Local recurrence Distant recurrence	Moderate
Peterson (1999) US Prospective cohort study Follow-up: Median 6.1 years	N=1021 Women with clinical stage 1 and stage 2 invasive breast cancer, who were treated with breast conserving surgery and radiation therapy were included. Exclusion criteria were not reported.	≤2mm >2mm	Unadjusted analysis	Local recurrence Locoregional recurrence Distant recurrence Overall survival Breast-cancer specific survival	Very High
Smith	N=5974	<2mm	Unadjusted analysis	Local recurrence	High

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
(2014) Canada Retrospective cohort study Follow-up: Median 8 years	Women =>50 years, with pT2 pN0 invasive breast cancer who were treated with breast conserving surgery and whole breast radiotherapy were included. Key exclusion criteria: DCIS, node positive disease, treatment with mastectomy, no adjuvant whole breast radiotherapy	≥2mm			
Smitt (2003) US Retrospective cohort study Follow-up: Mean 6 years	N=397 Women with stage 1 or 2 invasive breast cancer who were treated breast conserving surgery and radiotherapy were included. Exclusion criteria were not reported.	≤2mm ≥2mm	Unadjusted analysis	Local recurrence	High
Tang (2019) UK Retrospective cohort study	N=1045 Women with invasive breast cancer treated with breast conserving surgery were included. Key exclusion criteria: women who did not receive radiotherapy.	<1mm ≥1mm	Partially adjusted for: • Age • Tumour size • Grade • Oestrogen receptor status • Final node grouping	Local recurrence	Moderate

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Follow-up: Median 89 months (7.4 years)					
Tyler (2018) Canada Retrospective cohort study Follow-up: Median 8 years	N=10,863 Women with pT1-T3, pN0-N3, M0 invasive cancer, who were treated with breast conserving surgery and radiotherapy were included. Key exclusion criteria: women with DCIS, neoadjuvant chemotherapy and partial breast radiotherapy.	<2mm ≥2mm	Partially adjusted for: • Age • Grade • Lymphovascular invasion • Number of positive nodes • Use of boost radiotherapy • Use of systemic therapy • Breast cancer subtype	Local recurrence Breast cancer specific survival	Moderate
Varghese (2008) UK Retrospective cohort study Follow-up: Median 9 years	N=173 Participants with early breast cancer with invasive tumours <=1cm, treated with breast conserving surgery were included. The proportion of people with DCIS was 41.7%. Key exclusion criteria: participants requiring mastectomy to clear mastectomy.	Within 1mm ≥1mm	Unadjusted analysis	Local recurrence	High

Study details	Population	Radial margins of interest	Confounders the study adjusted for	Outcomes	Risk of bias
Vos (2017) The Netherlands Retrospective cohort study Follow-up: Median 57 months (4.7 years)	N=499 Participants undergoing breast conserving surgery for invasive breast cancer or ductal carcinoma in situ, who did not receive neoadjuvant chemotherapy were included. Key exclusion criteria: Stage T4 disease.	Invasive <2mm Invasive ≥2mm DCIS <2mm DCIS ≥2mm	Unadjusted analysis	Re-operation rates	High

Table 4 Summary of studies for people with DCIS only

The radial margin width column lists the margin widths of interest for this review – both as the exposure and comparators. Studies were rated as partially adjusted if they adjusted for some, but not all, of the confounders listed in the review protocol in Appendix A. In some cases unadjusted data was used to allow comparisons of the margins of interest.

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
Dick (2011) US	N=994 Women with DCIS were included.	Radial margins of: Within 2mm ≥2mm	Partially adjusted for: • Age • Race • Number of comorbid conditions • Historic subtype	Local recurrence	High

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
Retrospective cohort study Follow-up: Median 5 years	Participants with a history of cancer were excluded.		• Multifocality • Treatment • Year • Census level percent black • Census level percent below poverty • Insurance status and type • Histologic subtype • Mammographic tumour size • Presence of extensive DCIS • Nuclear grade • Menopausal Status • Calcifications • Tamoxifen use • Method of detection		
Ekatah (2017) UK Retrospective cohort study Follow-up: Median 7.2 years	N=466 Women with pure DCIS and were treated with breast-conserving surgery. Key exclusion criteria: Microinvasive cancers.	<1mm 1-2mm >2mm	Partially adjusted for: • Age • Tumour size • Tumour grade • Radiotherapy • Comedo necrosis • ER Status • Hormone treatment • Margin width	Local recurrence	High

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
Fregatti (2019) Italy Prospective cohort study Follow-up: Median 90 months (7.5 years)	N=388 Women with DCIS who underwent breast conserving surgery with or without post-operative radiotherapy. Exclusion criteria were not reported.	0.1-0.9mm 1-1.9mm ≥2mm	Multivariate analysis was not used because it compares positive vs negative margins. Outcomes were extracted from the Kaplan-Meier curves, which are unadjusted values.	Local recurrence	High
Livingston-Rosanoff (2021) US Prospective cohort study Follow-up: 19 years	N=559 Women diagnosed with ductal carcinoma in situ, treated with breast conserving surgery were included. Key exclusion criteria: Unknown diagnosis date. No publicly available phone number. Unable to complete phone interview	<2mm >2mm	Partially adjusted for: • Age • Menopausal status • Duration of endocrine therapy Locoregional recurrence outcome only adjusted for age	Locoregional recurrence	High
MacDonald	N=445	0.1-1.9 mm	Partially adjusted for:	Local recurrence	High

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
(2005) US Retrospective cohort study Follow-up: Median 57 months (4.7 years)	Participants with pure ductal carcinoma in situ, who were treated with local wide excision alone were included. Key exclusion criteria: people receiving neoadjuvant chemotherapy.	1.0-1.9mm 2.0-2.9mm	• Age • Nuclear grade • Tumour size • Necrosis Local recurrence outcome not adjusted		
Mannu (2020) UK Retrospective cohort study Follow-up: from 0 to 14 years	N=13,381 Screen detected DCIS in England April 2000 to March 2014 Key exclusion criteria: invasive cancer (other than non-melanoma skin cancer) before DCIS, invasive breast cancer or death from breast cancer or chemotherapy within six months of DCIS diagnosis. Bilateral DCIS. Unilateral	1 mm 2 mm 3-4 mm ≥5mm	Unadjusted event data was used to allow comparisons between margins other than ≥5mm. Rate ratios were adjusted for: year of diagnosis, age at diagnosis, region, time since diagnosis, DCIS size, DCIS grade, laterality of DCIS (partially adjusted according to the list of factors in the protocol)	Local recurrence	High for unadjusted data. Moderate for adjusted rate ratio data.

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
	DCIS, no surgery recorded.				
Shaikh (2016) US Retrospective cohort study Follow-up: Median 8.3 years	N=498 Women diagnosed with DCIS who underwent breast conserving surgery, and received whole breast radiotherapy and tumour bed boost were included. Key exclusion criteria: women with invasive breast cancer, underwent mastectomy, received hypofractionated radiotherapy, male patients.	>0 to ≤2mm >2mm	Unadjusted	Re-operation rates	High
Solin (2005) Canada, France, The Netherlands, US	N=1003 Women diagnosed with unilateral DCIS, with no concurrent invasive carcinoma who underwent breast conserving surgery,	<2mm to ≤2mm >2mm	HR data partially adjustedfor: • Age • Final margin status • Mammographic findings • Institution at which patient was treated	Local recurrence	High

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
Retrospective cohort study Follow-up: Median 8.5 years	and received whole breast radiotherapy were included. Key exclusion criteria: women with invasive breast cancer, women with bilateral disease, palpable mass or nipple discharge, prior breast cancer, concurrent breast cancers except nonmelanoma skin cancer, whole breast radiotherapy dose <cGy4000, adjuvant systemic therapy.		• Date of treatment • Location of the primary tumour • Total radiation dose Event data unadjusted		
Van Zee (2015) US Retrospective cohort study Follow-up: Median 75 months (6.2 years)	N=2996 Women diagnosed with DCIS who were treated underwent breast conserving surgery with or without radiotherapy were included. Key exclusion criteria: synchronous or	≤2mm >2mm – 10mm	Some outcomes partially adjusted for: • Age • Family history • Presentation • Nuclear grade • Number of excisions • Endocrine therapy • Year of surgery Outcome of interest was unadjusted event data.	Locoregional recurrence	High

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
	metachronous bilateral DCIS.				

Table 5 Summary of studies of people who had neoadjuvant therapy

The radial margin width column lists the margin widths of interest for this review – both as the exposure and comparators. Studies were rated as partially adjusted if they adjusted for some, but not all, of the confounders listed in the review protocol in Appendix A. In some cases unadjusted data was used to allow comparisons of the margins of interest.

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
Choi (2018) US Retrospective cohort study Follow-up: Median 57 months (4.7 years)	N=382 Women with invasive or in situ breast cancer treated with breast conserving surgery and whole breast radiotherapy were included. The study included a mixed population with 3.7% of participants having invasive breast cancer with ductal carcinoma in situ. Participants who underwent neoadjuvant endocrine therapy alone were excluded.	≤ 1mm 1.1-2mm	Unadjusted data used	Local recurrence	High

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
Lin (2020) Taiwan Retrospective cohort study Follow-up: Median 47 months (3.9 years)	N=161 Women with breast cancer who received neoadjuvant chemotherapy and underwent breast conserving surgery and received radiotherapy were included. Key exclusion criteria: women with bilateral breast cancer or receiving ongoing neoadjuvant chemotherapy.	1mm to 2mm≥2mm	Unadjusted data used	Locoregional recurrence	High
Rouzier (2001) France Retrospective cohort study Follow-up: Median 93 months (7.7 years)	N=257 Women with T1-T3 invasive breast cancer, treated with neoadjuvant chemotherapy followed by lumpectomy and radiation therapy were included.	≤2mm >2mm	Partially adjusted for: • age • initial clinical tumour size • histologic grade • oestrogen status • S-phase fraction • clinical regression • clinical tumour size at surgery • pathologic tumour size,	Local recurrence Distant recurrence	Moderate for local recurrence/ High for distant recurrence

Study details	Population	Radial margins	Confounders the study adjusted for	Outcomes	Risk of bias
	Key exclusion criteria: women with inflammatory, bilateral or T4 breast tumours or metastatic disease.		• pathologic residual disease • initial clinical lymph node status • pathologic nodal status • chemotherapy regimen • radiation boost Unadjusted analysis (event data used for distant recurrence)		

See Appendix D for full evidence tables.

1.1.6 Summary of the further surgery evidence

Clinical decision thresholds for minimally important differences (MIDs) were used to interpret the evidence. The line of no effect (in this case represented by 1.0) was used as a clinical decision threshold for the outcomes of local or locoregional recurrence, distant recurrence, overall survival and breast cancer specific survival as detailed in the protocol. The NICE default clinical decision thresholds of 0.8, 1.25 were used for the outcome of re-operation rates.

The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables:

For outcomes without a defined MID or where the MID is set as the line of no effect (local or locoregional recurrence, distant recurrence, overall survival and breast cancer specific survival), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

For outcomes with a defined MID (re-operation rates), the results were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

Invasive breast cancer with or without DCIS

Table 6 Local recurrence – Hazard ratios at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
2 (Keike 2008, Tang 2019)	Radial margins 0.1 to <1 mm vs ≥1 mm	1554	HR 1.71 (1.13, 2.58)	moderate	Effect favours margin ≥1 mm
1 (Maishman 2017)	Radial margins 0.1 to 1 mm vs >2 mm	938	HR 1.41 (0.93, 2.14)	low	Could not differentiate
4 (Biglia 2014, Maishman 2017, Peterson 1999, Tyler 2018)	Radial margins 0.1 to 2 mm vs >2 mm	13266	HR 1.45 (1.04, 2.03)	moderate	Effect favours margin >2 mm
3 (Maishman 2017, Peterson 1999, Tyler 2018)	Sensitivity analyses removing without Biglia 2014 (larger margin includes 2 mm): radial margins 0.1 to 2 mm vs >2 mm	11962	HR 1.63 (0.93, 2.87)	low	Could not differentiate
1 (Maishman 2017)	Radial margins 1.1 to 2 mm vs >2 mm	797	HR 1.81 (0.95, 3.45)	low	Could not differentiate

Table 7 Local recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm	139	RR 1.45 (0.06, 34.97)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm	153	RR 0.63 (0.04, 9.84)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm	104	RR 0.43 (0.02, 10.43)	very low	Could not differentiate

4 (Kuru 2020 (A), Lupe 2011 (A), Smith 2014 (A), Smith 2003 (B))	Radial margins 0.1 to <2 mm vs ≥2 mm	8491	RR 2.53 (0.91, 7.03)	very low	Could not differentiate

(A) Radial margins 0.1 to < 2mm vs. ≥ 2mm
(B) Radial margins 0.1 to 2 mm vs. > 2mm

Table 8 Local recurrence – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Varghese 2008 – with radiotherapy (A), Varghese 2008 – without radiotherapy (B))	Radial margins 0.1 to <1 mm vs ≥1 mm	161	RR 2.24 (0.47, 10.73)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm	139	RR 2.07 (0.62, 6.92)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm	153	RR 0.91 (0.41, 1.99)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm	104	RR 0.44 (0.13, 1.52)	very low	Could not differentiate

(A) Varghese 2008 reported number of events and totals
(B) Varghese 2008 reported RR and 95% CI

Table 9 Locoregional recurrence – Hazard ratios at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Chae 2022)	Radial margins 0.1 to 2 mm vs >2 mm	542	HR 4.65 (1.84, 11.75)	moderate	Effect favours margin >2 mm
1 (Behm 2013)	Radial margins 0.1 to 1 mm vs >5 mm	701	HR 4.35 (1.67, 11.33)	moderate	Effect favours margin >5 mm
1 (Behm 2013)	Radial margins 1.1 to 2 mm vs >5 mm	701	HR 1.55 (0.44, 5.46)	low	Could not differentiate

Table 10 Locoregional recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Lupe 2011)	Radial margins 0.1 to <2 mm vs ≥2 mm	2056	RR 1.79 (0.62, 5.18)	very low	Could not differentiate

Table 11 Locoregional recurrence – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Peterson 1999)	Radial margins 0.1 to 2 mm vs >2 mm	529	RR 2.21 (1.27, 3.85)	low	Effect favours margin >2 mm

Table 12 Pooled data combining local and locoregional recurrence – Hazard ratios at 10-year follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
2 (Behm 2013, Masihman 2017)	Radial margins 0.1 to 1 mm vs >2 mm	1524	HR 2.27 (0.76, 6.77)	very low	Could not differentiate
5 (Biglia 2014, Chae 2022, Maishman 2017, Peterson 1999, Tyler 2018)	Radial margins 0.1 to 2 mm vs >2 mm	13808	HR 1.99 (1.14, 3.48)	low	Effect favours margin >2 mm
2 (Behm 2013, Masihman 2017)	Radial margins 1.1 to 2 mm vs >2 mm	1383	HR 1.75 (0.99, 3.11)	low	Could not differentiate

Table 13 Pooled data combining local and locoregional recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm	139	RR 1.45 (0.06, 34.97)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm	153	RR 0.63 (0.04, 9.84)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm	104	RR 0.43 (0.02, 10.43)	very low	Could not differentiate
4 (Kuru 2020 (A) Lupe 2011 (A) Lupe 2011 (C) Smith 2014 (A) Smitt 2003 (B))	Radial margins 0.1 to <2 mm vs ≥2 mm	10547	RR 2.30 (1.05, 5.02)	very low	Effect favours ≥2 mm

(A) Radial margins 0.1 to < 2mm vs. ≥ 2mm
(B) Radial margins 0.1 to 2 mm vs. > 2mm
(C) Data reported separately for locoregional recurrence

Table 14 Pooled data combining local and locoregional recurrence – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Varghese 2008 – with radiotherapy (A), Varghese 2008 – without radiotherapy (B))	Radial margins 0.1 to <1 mm vs ≥1 mm	161	RR 2.24 (0.47, 10.73)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm	139	RR 2.07 (0.62, 6.92)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm	153	RR 0.91 (0.41, 1.99)	very low	Could not differentiate

1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm	104	RR 0.44 (0.13, 1.52)	very low	Could not differentiate
1 (Peterson 1999 (C))	Radial margins 0.1 to 2 mm vs >2 mm	529	RR 2.21 (1.27, 3.85)	low	Effect favours margin >2 mm

(A) Varghese 2008 reported number of events and totals
(B) Varghese 2008 reported RR and 95% CI
(C) Data on locoregional recurrence

Table 15 Distant recurrence – Hazard ratios at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Bodilsen 2016)	Radial margins 0.1 to 1 mm vs ≥5 mm	1425	HR 1.20 (0.44, 3.27)	very low	Could not differentiate

Table 16 Distant recurrence – Hazard ratios at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
2 (Behm 2013, Maishman 2017)	Radial margins 0.1 to 1 vs >2 mm	2889	HR 1.32 (0.97, 1.78)	low	Could not differentiate
2 (Behm 2013, Maishman 2017)	Radial margins 0.1 to 2 vs >2 mm	3238	HR 1.39 (1.14, 1.70)	moderate	Effect favours margin >2 mm
2 (Behm 2013, Maishman 2017)	Radial margins 1.1 to 2 vs >2 mm	2857	HR 1.40 (1.03, 1.91)	moderate	Effect favours margin >2 mm

Table 17 Distant recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect

1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive carcinoma	82	RR 1.80 (0.66, 4.91)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive carcinoma	86	RR 1.98 (0.72, 5.41)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive carcinoma	86	RR 1.10 (0.34, 3.52)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive or in situ carcinoma	139	RR 1.24 (0.47, 3.28)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma	153	RR 1.36 (0.55, 3.38)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma	104	RR 1.09 (0.36, 3.35)	very low	Could not differentiate
1 (Lupe 2011)	Radial margins 0.1 to <2 mm vs ≥2 mm - invasive or in situ carcinoma	2056	RR 1.36 (0.79, 2.34)	very low	Could not differentiate

Table 18 Distant recurrence – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive carcinoma	82	RR 1.18 (0.60, 2.32)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive carcinoma	86	RR 2.38 (1.00, 5.68)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive carcinoma	86	RR 2.01 (0.82, 4.95)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive or in situ carcinoma	139	RR 0.80 (0.43, 1.49)	very low	Could not differentiate
1 (Goldstein 2003)	Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma	153	RR 1.57 (0.74, 3.33)	very low	Could not differentiate

1 (Goldstein 2003)	Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma	104	RR 1.97 (0.88, 4.40)	very low	Could not differentiate
1 (Peterson 1999)	Radial margins 0.1 to 2 mm vs >2 mm - invasive or in situ carcinoma	529	RR 0.95 (0.54, 1.68)	very low	Could not differentiate

Table 19 Overall survival – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Lupe 2011)	Radial margins 0.1 to <2 mm vs ≥2 mm	2202	RR 1.02 (0.61, 1.71)	very low	Could not differentiate

Table 20 Overall survival – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Peterson 1999)	Radial margins 0.1 to 2 mm vs >2 mm	614	RR 0.89 (0.50, 1.57)	very low	Could not differentiate

Table 21 Breast cancer specific survival – Hazard ratios at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Tyler 2018)	Radial margins 0.1 to <2 mm vs ≥2 mm	10551	HR 1.25 (0.98, 1.59)	low	Could not differentiate

Table 22 Breast cancer specific survival – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Lupe 2011)	Radial margins 0.1 to <2 mm vs ≥2 mm	2056	RR 1.28 (0.64, 2.53)	very low	Could not differentiate

Table 23 Breast cancer specific survival – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Peterson 1999)	Radial margins 0.1 to 2 mm vs >2 mm	529	RR 1.08 (0.57, 2.05)	very low	Could not differentiate
1 (Guinot 2018)	Radial margins 0.1 to 2 mm vs 3 to 4 mm (actuarial survival data)	128	RR 2.74 (0.61, 12.37)	very low	Could not differentiate

Table 24 Re-operation rates – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Vos 2017)	5 years follow-up: radial margins 0.1 to <2 mm vs ≥2 mm	296	RR 9.05 (1.10, 74.22)	very low	Effect favours margin ≥2 mm

Ductal carcinoma in situ only

Table 25 Local recurrence - Hazard ratios at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Solin 2005)	Radial margins 0.1 to 1.9 mm vs. ≥2 mm	757	HR 1.90 (1.08, 3.36)	low	Favour margin width > 2mm

Table 26 Local recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
2 (Fregatti 2019, MacDonald 2005)	Radial margins 0.1 to 0.9mm vs. ≥ 2mm	491	RR 1.12 (0.66, 1.88)	very low	Could not differentiate
2 (Dick 2011, Solin 2005)	Radial margins 0.1 to 1.9mm vs. ≥ 2mm	1705	RR 1.54 (0.95, 2.49)	very low	Could not differentiate
2 (Fregatti 2019, MacDonald 2005)	Radial margins 1.0 to 1.9mm vs. ≥ 2mm	426	RR 1.24 (0.62, 2.50)	very low	Could not differentiate

Table 27 Local recurrence – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Solin 2005)	Radial margins 0.1 to 1.9mm vs. ≥ 2mm	757	RR 1.66 (1.02, 2.69)	low	Favours larger margin
1 (Ekatah 2017)	Radial margins 1 to 2mm vs. > 2mm	456	RR 0.79 (0.36, 1.73)	very low	Could not differentiate

Table 28 Local recurrence invasive – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Ekatah 2017)	Local recurrence for invasive*: Radial margins 1 to 2 mm vs. >2 mm	456	RR 0.50 (0.11, 2.24)	very low	Could not differentiate

* 466 patients with DCIS were included in the study. There were 44 in breast tumour recurrences in the 466 patients of which 27 were DCIS and 17 were invasive cancer.

Table 29 Local recurrence DCIS – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Ekatah 2017)	Local recurrence for DCIS*: Radial margins 1 to 2 mm vs. >2 mm	456	RR 1.01 (0.37, 2.79)	very low	Could not differentiate

* 466 patients with DCIS were included in the study. There were 44 in breast tumour recurrences in the 466 patients of which 27 were DCIS and 17 were invasive cancer.

Table 30 Local recurrence (invasive breast cancer) – Event data at 0 to 14 years follow-up*

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Mannu 2020)	Radial margins 1 mm vs. 2 mm (surgery with radiotherapy)	855	RR 1.35 (0.37, 4.99)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. 2 mm (surgery without radiotherapy)	2094	RR 0.81 (0.46, 1.43)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. 2 mm (pooled total: surgery with or without radiotherapy)	2949	RR 0.88 (0.52, 1.48)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. ≥2 mm (surgery with radiotherapy)	3723	RR 2.24 (0.84, 6.00)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. ≥2 mm (surgery without radiotherapy)	7658	RR 1.20 (0.75, 1.92)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. ≥2 mm (pooled total: surgery with or without radiotherapy)	11381	RR 1.32 (0.87, 2.02)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 to 2 mm vs. 3 to 4 mm (surgery with radiotherapy)	1539	RR 1.44 (0.48, 4.28)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 to 2 mm vs. 3 to 4 mm (surgery without radiotherapy)	3578	RR 1.19 (0.75, 1.89)	very low	Could not differentiate

1 (Mannu 2020)	Radial margins 1 to 2 mm vs. 3 to 4 mm (pooled total: surgery with or without radiotherapy)	5117	RR 1.23 (0.80, 1.88)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 2 mm vs. 3 to 4 mm (surgery with radiotherapy)	1128	RR 1.23 (0.33, 4.56)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 2 mm vs. 3 to 4 mm (surgery without radiotherapy)	2556	RR 1.29 (0.77, 2.18)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 2 mm vs. 3 to 4 mm (pooled total: surgery with or without radiotherapy)	3684	RR 1.28 (0.79, 2.09)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 to 2 mm vs. ≥3 mm (surgery with radiotherapy)	3723	RR 2.16 (0.94, 4.96)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 to 2 mm vs. ≥3 mm (surgery without radiotherapy)	7658	RR 1.49 (1.04, 2.12)	low	Favours larger margin
1 (Mannu 2020)	Radial margins 1 to 2 mm vs. ≥3 mm (pooled total: surgery with or without radiotherapy)	11381	RR 1.57 (1.13, 2.17)	low	Favours larger margin

** Study reported the number of people with follow-up times in 5 year intervals from 0-4 years to 14 years. Results were not stratified by follow-up time and mean follow-up time is not reported*

Table 31 Local recurrence (invasive breast cancer) – Rate ratios at 0 to 14 years follow-up*

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Mannu 2020)	Radial margins 1 mm vs. ≥5 mm (surgery with radiotherapy)	2595	RR 2.49 (0.64, 9.69)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. ≥5 mm (surgery without radiotherapy)	5082	RR 1.34 (0.69, 2.60)	low	Could not differentiate
1 (Mannu 2020)	Radial margins 1 mm vs. ≥5 mm (pooled total: surgery with or without radiotherapy)	7677	RR 1.51 (0.83, 2.74)	low	Could not differentiate
1 (Mannu 2020)	Radial margins 2 mm vs. ≥5 mm (surgery with radiotherapy)	2628	RR 2.08 (0.48, 9.01)	very low	Could not differentiate

1 (Mannu 2020)	Radial margins 2 mm vs. ≥5 mm (surgery without radiotherapy)	5172	RR 2.03 (1.16, 3.55)	moderate	Favours larger margin
1 (Mannu 2020)	Radial margins 2 mm vs. ≥5 mm (pooled total: surgery with or without radiotherapy)	7800	RR 2.04 (1.21, 3.43)	moderate	Favours larger margin
1 (Mannu 2020)	Radial margins 3 to 4 mm vs. ≥5 mm (surgery with radiotherapy)	2868	RR 1.58 (0.39, 6.40)	very low	Could not differentiate
1 (Mannu 2020)	Radial margins 3 to 4 mm vs. ≥5 mm (surgery without radiotherapy)	5564	RR 1.27 (0.70, 2.30)	low	Could not differentiate
1 (Mannu 2020)	Radial margins 3 to 4 mm vs. ≥5 mm (pooled total: surgery with or without radiotherapy)	8432	RR 1.31 (0.76, 2.27)	low	Could not differentiate

** Study reported the number of people with follow-up times in 5 year intervals from 0-4 years to 14 years. Results were not stratified by follow-up time and mean follow-up time is not reported*

Table 32 Local regional recurrence– Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
2 (Livingston-Rosanoff 2021, Zee 2015)	Radial margins ≤ 2mm vs. >2mm (with radiotherapy)	1054	RR 1.55 (1.03, 2.33)	low	Favour margin width > 2mm
2 (Livingston-Rosanoff 2021, Zee 2015)	Radial margins ≤ 2mm vs. >2mm (without radiotherapy)	610	RR 1.50 (1.07, 2.10)	low	Favour margin width > 2mm

Table 33 Re-operation rates – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Vos 2017)	Radial margins < 2mm vs. ≥2mm	77	RR 1.58 (0.43, 5.87)	very low	Could not differentiate

Table 34 Re-operation rates – Event data at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Shaikh 2016)	Radial margins < 2mm vs. ≥2mm	487	RR 0.49 (0.35, 0.69)	very low	Clinically meaningful effect (favours margin width < 2mm)

Neoadjuvant therapy

Table 35 Local recurrence – Hazard ratios at 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Rozier 2001)	Radial margins ≤ 2mm vs. > 2mm	218	HR 2.48 (1.26, 4.88)	low	Favour margin width > 2mm

Table 36 Local recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Choi 2018)	Radial margins 1 to 2mm vs. > 2mm	277	RR 0.46 (0.13, 1.61)	very low	Could not differentiate

Table 37 Distant recurrence – Event data at 5 and 10 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Rouzier 2001)	Radial margins ≤ 2mm vs. > 2mm	218	RR 1.10 (0.67, 1.80)	very low	Could not differentiate
1 (Rouzier 2001)	Radial margins ≤ 2mm vs. > 2mm	218	RR 1.13 (0.78, 1.65)	very low	Could not differentiate

Table 38 Local regional recurrence – Event data at 5 years follow-up

Number of studies	Outcome	Sample size	Effect estimate	Quality	Interpretation of effect
1 (Lin 2020)	Radial margins 1 to 2mm vs. > 2mm	133	RR 1.07 (0.25, 4.52)	very low	Could not differentiate

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A literature search was performed to identify published economic evaluations relevant to this review question, with the search strategy detailed in Appendix B – Literature search strategies. This search retrieved 11 studies after de-duplication. All studies were excluded at title and abstract screening.

1.1.7.2 Excluded studies

All studies were excluded at title and abstract screening.

1.1.8 Summary of included economic evidence

No relevant health economic studies were identified for inclusion in this review.

1.1.9 Economic model

Original health economic modelling was not prioritised for this review question.

1.1.10 Unit costs

Resource	Unit costs	Source
Unilateral wide local excision	£2,782	National Schedule of NHS costs 2019/20, HRG code JA20F, Unilateral Major Breast Procedures with CC score 0-2
Bilateral wide local excision	£3,863	National Schedule of NHS costs 2019/20, HRG code JA21B, Bilateral Major Breast Procedures with CC score 0
Unilateral mastectomy	£4,511	National Schedule of NHS costs 2019/20, weighted average of JA38A, JA38B, JA38C, Unilateral Major Breast Procedures with Lymph Node Clearance with CC scores 0-5+
Bilateral mastectomy	£6,193	National Schedule of NHS costs 2019/20, HRG code JA39Z, Bilateral Major Breast Procedures with Lymph Node Clearance

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

Breast conserving surgery aims to remove the tumour and sufficient surrounding tissue to minimise the risk of local and distant recurrence and therefore improve survival. As a result, the committee agreed that the critical outcomes for this review on surgical margins were local recurrence (and the related locoregional recurrence), distant recurrence, overall survival and breast cancer specific survival. In addition to these disease related outcomes the committee acknowledged the importance of patient satisfaction and quality of life as these can be severely impacted by the need for more than one surgical procedure and therefore need to be considered alongside the clinical outcomes. As a result, the Breast Q outcome and quality of life outcomes were also of critical importance for decision making. The Breast Q patient reported outcome measure covers a range of domains relating to quality of life (psychosocial well-being, physical well-being, and sexual well-being) and relating to satisfaction (satisfaction with breasts, satisfaction with outcome, and satisfaction with care). Of importance, but less so than the outcomes above, were eventual mastectomy rates and re-operation rates. These could be potentially misleading as they can be affected by other factors unrelated to margin width such as decisions to have a mastectomy following genetic testing or be linked to the application of guidelines for further surgery at certain margins in other countries.

1.1.11.2 The quality of the evidence

Invasive breast cancer with or without DCIS

Overall, the outcomes ranged from moderate to very low quality with the main reasons for downgrading being due to risk of bias and imprecision of the evidence. There were no randomised controlled trials meeting the inclusion criteria in the protocol and most included studies were retrospective cohorts. All studies were judged to be at moderate or high risk of bias due to either partial adjustment or no adjustment for the confounders listed in the protocol (see item 16 in the protocol – Appendix A). Much of the evidence was rated as imprecise as the 95% confidence interval crossed the line of no effect (in this case represented by the value of 1.0). Studies with a sample size of less than 500 participants were also downgraded for imprecision as there were likely to be too few participants to reliably detect an effect.

The majority of the outcome data related to local recurrence, with distant recurrence being the second most commonly reported outcome. Very few studies reported data on overall survival, breast cancer specific survival and re-operation rates. Eventual mastectomy rates were not reported by any of the included studies. There was no evidence at all on patient reported outcomes such as Breast Q and health related quality of life questionnaires.

The committee highlighted that Maishman et al. 2017 had very high adjuvant chemotherapy use which is not considered to be normal practice (75.6% had adjuvant chemotherapy and 60.1% had adjuvant hormone therapy). The study included adults 40 years and younger, excluded gene carriers aged 41 to 50 years old, and 62.8% had oestrogen receptor (ER) positive disease. The committee noted that this was a very young population that were likely to have severe/aggressive disease and not be representative of the wider breast cancer population. However, the committee agreed that the study was applicable to a subpopulation of people with breast cancer and they therefore did not exclude it from the evidence base. Instead, they decided to bear this in mind when they looked at the evidence and also considered what the evidence would be without this study.

Some of the studies were conducted a number of years ago going as far back as Peterson et al. 1999, and are likely to include therapies that do not fully reflect current practice.

However, the committee noted that there have been many changes in adjuvant therapy over time, which makes it difficult to pinpoint a certain date when there was a change in practice to use as a cut off for included studies. All studies were therefore included in the analysis. In addition, most studies were not UK-based which means that breast cancer care was not based on NHS guidance or UK practice. However, the committee were not overly concerned about the differences in international practice and guidance for this analysis and so the studies were not downgraded for indirectness.

It was not possible to carry out most of the planned subgroup analyses due to a lack of or very limited data. Most studies included mixed age populations without reporting separate data by age groups. Only 1 study limited their population of interest to adults 40 years and younger (Maishman et al. 2017) and this was a small and carefully selected population which would not necessarily reflect other younger people with breast cancer. Some studies reported the percentage of participants receiving subsequent systemic treatment, but these studies did not tend to report who had what type of subsequent systemic treatment and they did not report the outcome data by whether a person had or did not have these treatments. There was limited data on people who did not have radiotherapy with only 1 study reporting data separately for people with or without radiotherapy (Varghese et al. 2008). Studies did not report the outcomes by any of the characteristics identified in the equalities and health inequalities assessment (people with disabilities, trans people or people who are not binary, pregnant or breastfeeding women, ethnic minorities groups, religious or cultural beliefs, men, people from lower socioeconomic backgrounds, people living in certain regions or rural areas, people with low levels or health literacy, people experiencing homelessness, newly arrived migrants, and people who are in prison).

Data were reported as hazard ratios or as numbers of events. Most studies which reported hazard ratios adjusted for some of the confounding factors that the committee stated as important in the protocol. However, data reported as number of events was unadjusted, resulting in more uncertainty around the true value of the estimate of effect. A limitation was that the studies reporting number of events tended to have smaller sample sizes (less than 500 participants). Studies with a small sample size may not have a high enough number of events to detect a difference between the margins that are compared. Studies also reported different sample sizes between different margins. There were fewer participants with smaller margins compared to larger margins. Unequal sample sizes could have an influence on the statistical power of the study to detect a true effect in this case in the effect of the radial margin on the outcome. In addition, the committee noted that advances in breast cancer care mean that the incidence of local recurrence is now low. The decrease in the number of events is likely to make it harder to see differences between margins in newer studies even when they have reasonably large sample sizes.

Most of the results based on event data had wide confidence intervals and could not differentiate between margin sizes for the different outcomes. Taking this into account and the lack of adjustment for confounding factors in the raw event data, the committee focused their discussions on the hazard ratio outcome data where it was available. They used their expertise to try to determine whether the findings were consistent with each other and their experiences and to try to fill in the gaps in the evidence base.

DCIS only population

Overall, the outcomes for the studies included in the DCIS only population ranged from moderate to very low quality and the main reason for downgrading was the high risk of bias from individual studies and the imprecision in the results. As above, the main reason for classifying the studies as being at high risk of bias was because the reported results were either not adjusted or partially adjusted for confounding factors. In most outcomes assessed, imprecision was serious or very serious, with the 95% confidence intervals crossing the line

of no effect, meaning the evidence could not differentiate between smaller and larger margins for most outcomes.

Although the risk of re-excision was statistically lower for those with a smaller margin compared to a larger margin in the Shaikh et al. 2016 study, the committee were concerned about the quality of the study and therefore did not place much weight on this finding. The study also reported data on local recurrence that could not be used because it was inconsistently reported throughout the paper. The number of events for local recurrence were very high in all margins reported and the numbers of re-excision events were also thought to be very large in proportion to the number of participants.

Many outcomes were reported as the number of events that occurred, which raised some concerns related to the small number of events observed in each group. In all the studies included in the review, there was a much bigger population in the larger margin group compared to the smaller margin group. There was a range of different interventions and comparators for each outcome. This meant there was limited meta-analysis, meaning that most outcomes were based on the results from single studies.

The committee noted that of the studies looking at people with DCIS without invasive breast cancer, only 2 were carried out in the UK, and Ekatah et al. 2017 only had 466 participants. In contrast, Mannu et al. 2020 (which used data from the NHS Breast Screening Programme and the National Cancer Registration and Analysis Service) included data on surgical margins for 16,588 people. Despite the size of this study the number of events in each margin size in the comparisons of interest did not exceed 111, with the numbers of people in each comparison ranging from 411 to as high as 6,656 in Figure 25. The people in this study were diagnosed through screening as opposed to being symptomatic.

The committee discussed the publication year of the evaluated studies, as some of the studies were published a number of years ago. They highlighted that the guidance for treating DCIS in the early 2000s was to take a much larger margin (used to be 5 mm or more) than the current recommendations for 2 mm. Therefore, the results observed would be less relevant to current practice.

Neoadjuvant chemotherapy population

The search terms for this review did not exclude studies with people who had neoadjuvant therapy, and we had planned to exclude them when we were selecting the studies to be included in this review (see item 10 in Appendix A – Review protocols). However, when we only identified 3 studies, we decided to make a protocol deviation to be able to present them to the committee to allow us the possibility of making recommendations on radial margins after breast conserving surgery for this population as well. One additional study was identified (Bhatti et al. 2014) but was not included in the evidence on neoadjuvant therapy because only a third of participants had taken neoadjuvant therapy.

The three studies evaluated the association of surgical margins on disease recurrence in people undergoing breast-conserving surgery after neoadjuvant chemotherapy. Overall, the outcomes for neoadjuvant therapy were rated as low to very low quality due to high risk of bias, and imprecision. With the exception of local recurrence reported as a hazard ratio at 5 years (Figure 30), all outcomes were downgraded once for imprecision due to the 95% confidence intervals crossing the line of no effect. This meant that for most outcomes, the evidence could not differentiate between the risk of recurrence between smaller and larger margins. Similar to the results for people who only had DCIS, most outcomes were reported as the number of events that occurred, which raised some concerns related to the small number of events observed in each group. Different studies reported different interventions and comparators and reported on different outcomes. This meant it was not possible to perform meta-analysis, meaning that all outcomes were based on the results from single studies.

1.1.11.3 Benefits and harms

Invasive breast cancer with or without DCIS

The committee noted that for many of the outcomes the evidence could not differentiate between the smaller and larger margin sizes. The committee were clear that there was an associated degree of uncertainty with the interpretation of the results because this covers 2 scenarios. In the first, there is no difference between the effects of the 2 margin sizes on a particular outcome (i.e., that they are clinically and/ or statistically equivalent). In the second situation, there are differences between the effects of the 2 margin sizes on a particular outcome, but they are not detectable in the individual study or meta-analysis because there are too few people and events to see the difference.

For local recurrence, there were four comparisons between different radial margins (Figure 1). Local recurrence was significantly greater with smaller margins for 2 of the comparisons (0.1 to less than 1 mm compared to equal or greater than 1 mm, and 0.1 to 2 mm compared to greater than 2 mm). Sensitivity analyses were carried out for the comparison between 0.1 mm to 2 mm and 2 mm margins. In one of these analyses the Biglia et al. 2014 study, which had slightly different margin sizes to the other studies in this analysis, was removed. In the other analysis, data from unadjusted studies was removed. The committee noted that both analyses resulted in the results for local recurrence changing from being statistically significant to crossing the line of no effect (Figure 1. 1, and Figure 1. 2). The evidence could not differentiate between the radial margins in the other comparisons (0.1 to 1 mm compared to greater than 2 mm and 1.1 to 2 mm compared to greater than 2 mm). This latter comparison included Maishman et al., 2017 that the committee had previously noted contained a very specific subpopulation of people with invasive breast cancer with or without DCIS. The committee was wary about extrapolating the results from this study to the wider population of people with invasive breast cancer with or without DCIS.

There was limited evidence for locoregional recurrence (Figure 4). Locoregional recurrence was significantly increased with radial margins of 0.1 to 1 mm compared to margins greater than 5 mm and for radial margins of 0.1 to 2 mm compared to greater than 2 mm. The evidence could not differentiate between radial margins of 1.1 to 2 mm compared to greater than 5 mm for this outcome. The committee noted that the evidence for locoregional recurrence was from smaller studies with sample sizes of between 542 and 701 participants. It is very likely that the smaller sample sizes resulted in the wider 95% CIs and greater uncertainty seen in these results.

The evidence for local recurrence and locoregional recurrence was pooled in an additional analysis (Figure 7). The pooled estimates showed greater local/locoregional recurrence in the smaller margin group of radial margins of 0.1 to 2 mm compared to greater than 2 mm, but could not differentiate between comparisons 0.1 to 1 mm compared to greater than 2 mm or for 1.1 to 2 mm compared to greater than 2 mm.

There was very limited evidence for overall survival and breast cancer specific survival and it could not differentiate between smaller margins and larger margins and was mainly reported as event data. In the absence of much data for these outcomes the committee noted that distant recurrence is related to survival and could therefore be used as a proxy for survival outcomes.

The evidence for distant recurrence (Figure 11) showed a significant increase with smaller margins (either 0.1 to 2 mm or 1.1 to 2 mm) compared to larger margins (greater than 2 mm), but the evidence included the study by Maishman et al., 2017 which is not representative of the wider UK breast cancer population undergoing breast conserving surgery. When only the data from Behm et al. 2013 was examined (by looking at the un-

pooled results from this study on the same plot) the evidence could not differentiate between these smaller and larger margins for distant recurrence.

The committee discussed the importance of margin size in relation to the risk of local recurrence and survival. They noted that given the advances in breast cancer care, and improvements in adjuvant systemic treatment, the incidence of local recurrence is now relatively low. The Early breast cancer trialists' collaborative group (EBCTCG) reported that recurrence was significantly reduced with polychemotherapy after 15 years follow up (a 12.3% additional reduction in recurrence with polychemotherapy compared to no chemotherapy). As such, recommending a smaller margin and reducing the number of people who have further surgery is likely to be less of a risk in terms of recurrence than it was previously.

The committee agreed that there should be a balance between clinical outcomes and patient reported outcomes when making decisions about further surgery. However, there was no available evidence on patient reported outcomes or quality of life and the committee had to use their own expertise and experiences to try to fill this gap. The committee contained lay members who were able to bring their experiences and that of people in the patient networks they are involved in to the discussions. In particular, they supported the view of the clinicians that more surgery was not necessarily the best option for an individual even if it could potentially reduce the risk of local recurrence. They agreed with the clinicians that different people will make different decisions about further surgery even if they have the same margins. Factors that influence this decision for the patient include weighing up the benefits of avoiding recurrence by having more surgery against the potential effects on cosmesis and the risks from having additional surgery. The committee agreed that these factors need to be balanced through shared decision making that also takes into account the person's preferences.

The committee also highlighted that hearing that margins are clear can be the first piece of good news in what otherwise feels like a long line of bad news for someone undergoing breast conserving surgery. Clear margins can indicate that this phase of treatment can end, whereas hearing that margins are not clear can have a massive emotional impact. The committee acknowledged that waiting for the results of the pathological report about whether margins are clear can be an incredibly stressful time, and this is something that may be getting worse because waiting times are extending in UK practice.

The committee also highlighted that there is a physical impact from undergoing breast conserving surgery. This can include recovering from anaesthetic, pain, and starting exercises. If people have to have further surgery, then the full cycle of treatment and recovery has to begin again. Other physical impacts could include the increased risk of infection, wound care, and effects on childcare or other care and employment. There could also be delays on other treatments like radiotherapy if there are complications with wound healing. The committee also highlighted that delaying other treatments to allow for additional surgery to achieve clear margins may not always be the best clinical option for an individual. In addition, the importance of appearance after breast conserving surgery could be easy to underestimate. Unlike people who have mastectomy and could later choose to have implants, a person undergoing breast conserving surgery does not know whether the size and the appearance of the operated breast will look different to the other breast. This is likely to be worse if there are repeated re-excisions. This can cause distress and have an emotional impact throughout the person's life. The committee therefore agreed that whatever decision was made it would need to take into account wider factors than just the risk of clinically adverse outcomes associated with a particular margin width.

Drafting the recommendations

In 2018 the committee made a recommendation for a shared decision around further surgery for radial margins greater than 0 but less than 2 mm but noted their uncertainty around the optimal margin size. In the current analyses for invasive cancer with or without DCIS, the committee noted that comparisons between margins of 0.1 to 2 mm and greater than 2 mm showed a greater risk of recurrence when a smaller margin was used. However, they highlighted that when the less than 2 mm margin was broken down further (0.1 to 1 mm and 1.1 to 2 mm), the effects of the smaller margin differed. For local recurrence and for combined local and locoregional recurrence, the evidence could not differentiate between radial margins of 1.1 mm to 2 mm compared to greater than 2 mm. This made the committee less confident that there was a clinically meaningful difference between margins of 1 mm to 2 mm. In contrast, local recurrence was greater for smaller margins when radial margins of 0.1 mm to less than 1 mm were compared to margins greater than 1 mm. This gave the committee more confidence that there was an increased risk of local recurrence with radial margins of 0.1 mm to less than 1 mm. Therefore, they decided that, while it is important to consider further surgery for people who have a tumour within 1 mm of the radial margins, there may be fewer benefits of recommending further surgery for people who have a tumour between 1 mm and 2 mm of the radial margin.

When discussing whether to change the recommendation from 2 mm to 1 mm, the committee noted that advances in breast cancer care mean that the incidence of local recurrence is now relatively low and so although consideration of the risk of local recurrence for an individual is still important, it may have a lower weighting in the decision making around further surgery than in the past. Based on the evidence and their expertise, the committee did not think that recommending a margin of 1 mm, rather than 2 mm, would lead to a substantially increased risk of local recurrence. They also noted that any residual tumour is likely to be cleared by adjuvant treatment. Additionally, they agreed that for many people, a margin of 1 mm is likely to be preferable over a more cautious approach with a margin of 2 mm because of the potential negative effects of further surgery on the individual with breast cancer, as discussed in the benefits and harms section. Taking the above uncertainty into account, the committee agreed that further surgery should be considered for people who had breast-conserving surgery for invasive breast cancer with or without DCIS if tumour cells are present within 1 mm of the radial margins.

Where the tumour is at ink (i.e., the radial margin is 0 mm) the committee retained the 2018 recommendation to offer further surgery. (The committee did not look at the evidence relating to tumour at ink because it was not within the scope of this update as no evidence was identified to change this recommendation during the surveillance process.)

They retained the part of the original 2018 recommendation that covered making a shared decision with the individual making sure they understand the benefits and risks of further surgery and taking into account their preferences as well as their clinical situation (comorbidities, tumour characteristics, the potential use of radiotherapy) with the addition of the potential use of other adjuvant therapies to reflect their usage in current practice. This discussion could include the potential effects of further surgery such as avoiding recurrence, impact on cosmesis, stress of waiting to hear about pathology report on margins, recovery from anaesthetic and pain, risk of infection, wound care, physical activity, childcare and other care, employment, multiple re-operations, delays in adjuvant therapy. They referred to the NICE guidelines on shared decision making and patient experience to help inform these discussions.

DCIS only population

The committee noted that the evidence was more limited for people with DCIS only than for people with invasive breast cancer with or without DCIS and that most of the included

studies had small sample sizes and a small number of events. Mannu et al., (2020) was by far the largest study and presented data by radiotherapy status (Figure 25). The rate ratio results for local recurrence could not differentiate for all comparisons in Mannu et al. (2020) apart from 2 mm versus ≥ 5mm (Figure 26). For people who did not have radiotherapy (-RT), or where the data was pooled irrespective of radiotherapy status, there was a higher rate of local recurrence for the smaller margin (2mm) compared to the larger one (≥ 5mm). This was not seen where people had radiotherapy (+RT). In the unadjusted event data from this study, for margins of 1-2 mm versus ≥ 3 mm -RT (and for the pooled results with the +RT data) the results also favoured the larger margin, but for the same comparisons +RT the results could not differentiate. This could suggest a potential benefit of having larger margins when radiotherapy is not used. However, for 1mm or 3-4mm compared to ≥5 mm the rate ratio results could not differentiate irrespective of radiotherapy status and a similar pattern was seen for the other comparisons in the event data. The committee also noted that the number of events per comparison were still relatively low despite the large sample sizes, leading to uncertainty about how robust these findings are. (The sample sizes for -RT are 27/1092 for 2mm, 56/4080 for ≥5 mm; for +RT 4/444 for 2mm, 9/2184 for ≥5 mm.)

Looking at the effect of margin sizes on local recurrence irrespective of radiotherapy status, a margin of 2 mm was associated with a higher rate of local recurrence than a margin of ≥ 5mm, but the results for 1mm compared to ≥ 5mm could not differentiate (Mannu et al., 20202). The committee noted that the category of ≥ 5mm could include people with very large margins. For the event data, a margin of 1-2 mm had a higher risk of local recurrence than a margin of 3-4mm, but for 1-2 mm or 2 mm compared to 3-4 mm the results could not differentiate.

After considering the evidence base, the committee were not confident that choosing a margin of 1 mm rather than 2 mm would not result in people with DCIS alone having a substantially increased risk of local recurrence. Furthermore, the committee highlighted that the approach for treating people with DCIS alone is different from treating people with invasive breast cancer with or without DCIS. Patients with DCIS, in particular non-high-grade DCIS, may receive no further treatment following surgery. As surgery is potentially the only management then the committee agreed that there needed to be more certainty about completeness of excision for this population group. They therefore agreed to maintain the tumour-free tissue margin for people with DCIS without invasive breast cancer at 2 mm due to a lack of evidence to support decreasing this margin. They did not make a research recommendation for this group because they were aware of new evidence that has yet to be published, but is due to be presented at an upcoming conference, that could inform this decision in the future. This forthcoming evidence will be monitored and assessed for impact when it is published.

Although the committee retained the 2 mm recommendation for people with DCIS, they thought the considerations about the potential negative effects of further surgery that were included in the recommendation for people with invasive breast cancer with or without DCIS, should also be considered for people with DCIS. As such, they included the same list of factors that should be discussed as part of the shared decision-making process.

Neoadjuvant chemotherapy

The committee noted that the number of studies and the quality of evidence for people receiving neoadjuvant therapy was low to very low. Furthermore, the studies were performed outside the UK and evaluated older chemotherapy regimens, which do not reflect current clinical practice in the UK. Considering the limited evidence available, the committee did not feel confident in making a specific recommendation for this population group. However, they noted that although the recommendation for people with invasive breast cancer with or without DCIS was made using evidence that excluded people who had neoadjuvant therapy,

in the absence of any evidence to the contrary the margin and actions in this recommendation could apply to these people as well.

The committee discussed whether a research recommendation would be useful to increase knowledge about the effectiveness of different surgical margins for this group of people. The committee noted that advances in treatments, such as neoadjuvant therapies, had substantially reduced the numbers of people who had local recurrence and locoregional recurrence. They decided against making a research recommendation because they thought that it would be difficult to recruit a sufficient sample size to have enough events to be able to detect a difference in terms of recurrence between margin sizes. Therefore, using similar study designs to those included in this review was unlikely to be feasible for future research on this topic.

1.1.11.4 Cost effectiveness and resource use

No economic evaluations were identified which addressed the cost-effectiveness of using different surgical margins to guide decisions about further breast conserving surgery. Alongside the clinical evidence, the committee therefore considered the type of resources and downstream effects of changes to surgical margins when making their recommendations. The width of the surgical margins when considering further surgery will have an impact on the overall number of lumpectomy procedures for people with breast cancer in the NHS; these are associated with required additional NHS resources, and an emotional and physical impact to the individual. However, local recurrence of the tumour may also have a subsequent impact on both the individual and NHS resources, due the need for further re-treatment.

Based on the clinical evidence for invasive cancer with or without DCIS, the committee recommended that further surgery is considered and a discussion about risks and benefits is had when radial margins are less than 1mm. They noted that, although the existing recommendation was to have this discussion for margins less than 2mm, current clinical practice has largely moved towards using a margin of less than 1mm. The rate of recurrence is very low in this group, and reducing the margin to consider further surgery for a margin of less than 2mm to less than 1mm would have a positive impact on capacity issues of the healthcare system. It is not expected that this recommendation will increase resource use since it reinforces current practice, and it is likely that fewer people will have further surgery given the reduction in margin size.

The committee decided that, based on the uncertainty of effect on local recurrence of people with 1mm to 2mm radial margins with DCIS without invasive cancer, they would continue to recommend considering further surgery when radial margins are within 2mm. No change in resources is expected for this recommendation, as this is what is currently recommended and done in current clinical practice.

1.1.11.5 Other factors the committee took into account

The committee noted that the equality and health inequalities assessment that accompanies this review highlighted a large number of issues that could act as barriers to people accessing further surgery or constrain their decisions about whether to have further surgery. However, they noted that many of these issues were not within the committee's ability to address. For example, problems associated with being able to afford to take time off work and having access to affordable transport to take them to appointments or limited access to oncoplastic services in some areas. Some of the issues related to communication of information in a way that is accessible for people with a range of needs (including those with low health literacy, people who have severe learning disabilities, people who are neurodiverse). To facilitate the decision-making process and ensure that patients are able to fully participate the committee included cross references to relevant sections of some core

NICE guidelines. These were the sections on enabling patients to actively participate in their care in the NICE guideline on patient experience in adult NHS services, and communicating risks, benefits and consequences in the NICE guideline on shared decision making. Some groups, such as people with learning disabilities and autism, may need reasonable adjustments to be made to overcome barriers to access and enable them to make informed decisions. The committee noted that making reasonable adjustments is a legal requirement as stated in the Equality Act 2010. They also noted that there is a newly released Reasonable Adjustment Digital Flag (RADF) and Information Standard. This mandates the identification of people who need reasonable adjustments and the recording, sharing and maintenance of this information with relevant health care providers.

The committee also noted the importance of discussing the person's preferences and asking about their personal circumstances when health professionals explain the benefits and risks of having further surgery. They were aware that, in addition to the risk of recurrence, there are a range of factors that will influence a person's choice over whether to have further surgery. For instance, people who have childcare and other caring responsibilities, or those who will have to take unpaid time off from work might be less likely to choose further surgery than other people with a similar risk of recurrence. The committee also agreed that factors such as having physical or learning disabilities, comorbidities, or being older should not prevent someone from being offered further surgery if they have invasive cancer or DCIS within the recommended margins. However, they acknowledged that these people may need additional support to overcome any barriers they face to taking up the offer if they decide that it is the right option for them. They therefore recommended that the person's circumstances, needs and preferences should form part of the decision-making process to ensure that the realities of people's lives are taken into account and to help identify and minimise the impact of health inequalities, where possible.

The committee noted that the studies did not report information about the histological characteristics of invasive breast cancer (e.g., ductal or lobular). They were therefore unable to make any specific recommendations with this level of detail. The committee highlighted that depending on the characteristics of the tumour it may be more or less resistant to adjuvant therapy or adjuvant therapy may be less likely to be used (in the case of DCIS without invasive cancer) and therefore this needs to be taken into account when discussions around further surgery are taking place. Therefore, they included tumour characteristics in the shared decision-making recommendations for both invasive cancer with or without DCIS and DCIS without invasive cancer.

The committee highlighted the variation in current practice around how different surgeons and multidisciplinary teams apply the current NICE guidance and that in many places a margin of 1 mm is already used as a cut off for further surgery. The committee acknowledged that the Association of Breast Surgery (ABS) published a consensus statement in 2015 advising a 1 mm minimum clear radial margin to be achieved after breast conserving surgery for early invasive breast cancer and for in situ carcinoma of the breast. Many surgeons in the UK are following this consensus statement and the committee's new recommendation for people with invasive breast cancer with or without DCIS is consistent with this.

The committee noted that, in their experience, the existing recommendation about auditing recurrence is not uniformly applied and that the information recorded does not necessarily include the radial margin. They therefore expanded the recommendation to highlight factors that they thought should be recorded to include the collection of local, regional, and distant recurrence rates after treatment as well as data on radial margins and demographics such as socioeconomic status, age and ethnicity. The committee were also aware of a new National Audit of Primary Breast Cancer that may improve recording of this information.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.2 to 1.3.5.

1.1.12 References – included studies

1.1.12.1 Effectiveness

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Maishman, Tom, Cutress, Ramsey I, Hernandez, Aurea et al. (2017) Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study. Annals of surgery 266(1): 165-172

Mannu, Gurdeep S, Wang, Zhe, Broggio, John et al. (2020) Invasive breast cancer and breast cancer mortality after ductal carcinoma in situ in women attending for breast screening in England, 1988-2014: population based observational cohort study. BMJ (Clinical research ed.) 369: m1570

Peterson, M E, Schultz, D J, Reynolds, C et al. (1999) Outcomes in breast cancer patients relative to margin status after treatment with breast-conserving surgery and radiation therapy: the University of Pennsylvania experience. International journal of radiation oncology, biology, physics 43(5): 1029-35

Shaikh, Talha, Li, Tianyu, Murphy, Colin T et al. (2016) Importance of Surgical Margin Status in Ductal Carcinoma In Situ. Clinical breast cancer 16(4): 312-8

Smith, Sally L, Truong, Pauline T, Lu, Linghong et al. (2014) Identification of patients at very low risk of local recurrence after breast-conserving surgery. International journal of radiation oncology, biology, physics 89(3): 556-62

Smitt, Melanie C, Nowels, Kent, Carlson, Robert W et al. (2003) Predictors of reexcision findings and recurrence after breast conservation. International journal of radiation oncology, biology, physics 57(4): 979-85

Solin LJ, Fourquet A, Vicini FA et al. (2005) Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. Cancer 103(6): 1137-1146

Tang, S S K, Rapisarda, F, Nerurkar, A et al. (2019) Complete excision with narrow margins provides equivalent local control to wider excision in breast conservation for invasive cancer. BJS open 3(2): 161-168

Tyler, Susan, Truong, Pauline T, Lesperance, Mary et al. (2018) Close Margins Less Than 2 mm Are Not Associated With Higher Risks of 10-Year Local Recurrence and Breast Cancer Mortality Compared With Negative Margins in Women Treated With Breast-Conserving Therapy. International journal of radiation oncology, biology, physics 101(3): 661-670

Van Zee KJ, Subhedar P, Olcese C et al. (2015) Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. Annals of surgery 262(4): 623-631

Varghese, P, Gattuso, J M, Mostafa, A I H et al. (2008) The role of radiotherapy in treating small early invasive breast cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 34(4): 369-76

Vos, E L, Gaal, J, Verhoef, C et al. (2017) Focally positive margins in breast conserving surgery: Predictors, residual disease, and local recurrence. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 43(10): 1846-1854

1.1.12.2 Economic

No studies were included in the economic review.

Appendices

Appendix A – Review protocols

Review protocol for further surgery after breast-conserving surgery based on tissue margins

ID	Field	Content
1.	Review title	Tumour-free radial margins to minimise the risk of local recurrence after breast-conserving surgery for adults with invasive breast cancer and/or ductal carcinoma in situ (DCIS)
2.	Review question	What is the optimum tumour-free radial margin after breast-conserving surgery for adults with ductal carcinoma in situ (DCIS) and/or invasive breast cancer to minimise the risk of local recurrence and maximise overall survival and patient satisfaction?
3.	Objective	To determine what the optimum tumour-free radial margin is after breast-conserving surgery for adults with ductal carcinoma in situ (DCIS) and/or invasive breast cancer to minimise the risk of local recurrence, maximise overall survival and patient satisfaction and inform decisions about whether further surgery is necessary.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • HTA (Health Technology Assessment) • Embase • MEDLINE ALL • INAHTA • Epistemonikos For the economics review the following databases will be searched:

		• Embase • MEDLINE ALL • Econlit • INAHTA • HTA (Health Technology Assessment) Searches will be restricted by: • Date of last search (January 2017) • English language • Human studies • Abstracts, conference presentations and theses will be excluded. • No publication type limit. Other searches • Citation search - forward citation search using Bundred (2022) paper The full search strategies for MEDLINE database will be published in the final review. Reference: Bundred JR, Michael S, Stuart B, et al. (2022) Margin status and survival outcomes after breast cancer conservation surgery: Prospectively registered systematic review and meta-analysis. BMJ 2022;378:e070346
5.	Condition or domain being studied	Early and locally advanced breast cancer treated with breast conserving surgery where the resulting surgical margins determine the need for additional surgery to reduce the risk of local recurrence and maximise overall survival.
6.	Population	Inclusion: Adults (18 or over) with invasive breast cancer and no distant metastases (M0) and/or DCIS who have undergone breast conserving surgery with or without subsequent radiotherapy Exclusion:

		• People who have had a mastectomy instead of breast conserving surgery • People who have had intraoperative radiotherapy • People who have had neoadjuvant therapy • People with multicentric breast cancer • People who have mastectomy by choice after breast conserving surgery based on their greater genetic risk of breast cancer (e.g., people with BRCA1 or BRCA2 gene mutations)
7.	Exposure	1. Tumour free margin widths of greater than 0 mm and less than 2 mm. 2. If the data from the majority of studies does not fit in category 1, then we will use tumour free margin widths of greater than 0 mm and less than or equal to 2 mm as the exposure. The margins must be assessed by a pathologist.
8.	Comparator	• Tumour free margins of greater than or equal to 2 mm or tumour free margins of greater than 2 mm if option 2 in the exposure box is used (see above). • Any categories of exposure that fall between greater than 0 mm and less than or equal to 2 mm compared to each other.
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Any controlled, non-randomised studies • Cohort studies (prospective and retrospective observational studies) • Systematic reviews of the above studies
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies • Studies with follow up of less than 5 years

		• Cohort studies with less than 100 participants
		• Studies with mixed populations will be excluded if:
		  ○ 25% or more people had neoadjuvant therapy
		  ○ 25% or more people had intraoperative radiotherapy
		• Studies only reporting comparisons including these margins will be excluded:
		  ○ 0 mm at ink
		  ○ greater than or equal to 0 mm from ink (includes 0 mm)

11.	Context	The NICE surveillance review (January 2023) identified new evidence from a systematic review (Bundred et al. 2022). This review concluded that a minimum clear margin of at least 1mm should be aimed for as this was associated with optimum oncological outcomes. This may have an impact on current recommendations which refer to a margin of within 2 mm of the radial margins (greater than 0 mm and less than 2 mm) as the threshold for considering further surgery. Reference: Bundred JR, Michael S, Stuart B, et al. (2022) Margin status and survival outcomes after breast cancer conservation surgery: Prospectively registered systematic review and meta-analysis. BMJ 2022;378:e070346
12.	Primary outcomes (critical outcomes)	• Local recurrence if reported and if not, locoregional recurrence • Distant recurrence • Overall survival • Breast cancer specific survival • Health related quality of life • Breast Q (patient reported outcome measure) **Outcome measures** 1) Hazard ratios (HRs).

		2) Risk ratios (RRs) from numbers at risk and binary outcome data if HRs are not reported.
		3) Health related quality of life and Breast Q will be reported as continuous outcomes.
		
		Minimal important differences:
		Any statistically significant difference will be used for the following outcomes:
		• Local recurrence or locoregional recurrence
		• Distant recurrence
		• Overall survival
		• Breast cancer specific survival
		
		MIDs for the following outcomes are from the literature:
		• Breast Q: 4 points
		• Health-related quality of life (questionnaires):
		  • FACT-G total: 3-7 points
		  • FACT-B total: 7-8 points
		  • TOI (trial outcome index) of FACT-B: 5-6 points
		  • BCS of FACT-B: 2-3 points
		  • SF-36: one-half of an SD
		  • EQ-5D: 0.08 for UK-based scores and 0.07 for VAS scores
		  • EORTC-QLQ-C30: -8 to 12 for global quality of life

13.	Secondary outcomes (important outcomes)	• Eventual mastectomy rates

		• Re-operation rates **Outcome measures** 1) Hazard ratios (HRs). 2) Risk ratios (RRs) from numbers at risk and binary outcome data if HRs are not reported. **Minimal important differences:** Any statistically significant difference will be used for eventual mastectomy rates. The GRADE default value will be used for re-operation rates.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.5).
15.	Risk of bias (quality) assessment	• Risk of bias for cohort and non-randomised studies will be assessed using the ROBINS-E tool (Risk Of Bias In Non-randomized Studies - of Exposures). • Risk of bias for RCTs and systematic reviews will be assessed using the Cochrane Risk of Bias v.2.0 or ROBIS respectively, as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions. Data will be analysed separately for people with: • Invasive breast cancer with or without DCIS • DCIS only

		Where data can be disambiguated it will also be separated into the subgroups identified in section 17 (below). Hazard ratios will be pooled using the generic inverse-variance method. Adjusted, unadjusted and partially adjusted hazard ratios will be pooled. Sensitivity analysis will be carried out to look at the effect of removing partially and unadjusted studies. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials, non-randomised controlled trials and cohort studies (observational studies) will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias. The committee agreed on the following confounding factors for fully adjusted studies: • Age • Tumour stage - (T/N) (only applies to invasive population) • Size – or diameter (applies to the DCIS population) • Grade

		• Lymphovascular involvement/ invasion • Chemotherapy (only applies to invasive population) • Radiotherapy • If not adjusting for these factors, must contain exclusively patients (>95%) receiving chemotherapy/radiotherapy • Oestrogen status • Histological tumour type* (tumour types include DCIS, invasive carcinoma of no special type, mixed invasive tumour, invasive lobular carcinoma)

17.	Analysis of sub-groups	• For people with invasive breast cancer with or without DCIS, or with only DCIS: Locoregional or local recurrence
		For critical outcomes only, where there is significant heterogeneity and disambiguation of the results using the following subgroups reduces this then these analyses will be carried out:
		• For people with invasive breast cancer with or without DCIS or with only DCIS:
		  • People who have had radiotherapy post-surgery compared to people who did not
		  • People who have had re-excisions compared to people who only had one round of breast conserving surgery
		  • Age
		  o <50 years old
		  o 50 to 69 years old
		  o 70 or more years old
		For people with invasive breast cancer with or without DCIS:

		• People with or without subsequent systemic treatment – chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer Abbreviation: oestrogen receptor positive (ER-positive)

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run between 22–23 August 2023. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the terms used for the NG101 NICE guideline. Modifications were made to these original search strategies for the specifications in the review protocol.

Text analysis for additional keywords/subject headings was carried on a set of includes from the 2018 guideline update. PubMedReminer and Medline Ranker were used for the text analysis.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences and clinical trials in Embase and Cochrane Library were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude letters, editorials, news, comments and case reports In Medline ALL were also applied in adherence to standard NICE practice and the review protocol.

The search was limited from January 2017 to August 2023 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters and classifiers

Cost effectiveness searches
The following search filters (precise version) were applied to the search strategies in MEDLINE and Embase to identify cost-utility studies:

Hubbard, W, Walsh N, Hudson T, Heath A, Dietz J, and Rogers G. (2022) Development and validation of paired Medline and Embase search filters for cost-utility studies. Manuscript submitted for publication.

Key decisions

The search strategy was developed to find evidence for the specified population and intervention in the review protocol.

A forward citation was carried out on the following key paper identified in the NICE surveillance report (July 2022):

Bundred, James R et al. (2022) Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. BMJ (Clinical research ed.) vol. 378 e070346

The 2018 update search included a set of outcome terms. These were not included in the 2023 search strategy as outcome terms are often not referred to in abstracts. The inclusion of outcome terms in the strategy could result in relevant records not being picked up.

Effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	22/08/23	Wiley	Issue 7 of 12, July 2023	86
Cochrane Database of Systematic Reviews (CDSR)	22/08/23	Wiley	Issue 8 of 12, August 2023	1
Embase	22/08/23	Ovid	1996 to 2023 August 21	1647
Epistemonikos	22/08/23	Epistemonikos	-	226
MEDLINE ALL	22/08/23	Ovid	1946 to August 21, 2023	1260
HTA (Health Technology Assessment)	22/08/23	CRD	Legacy database	0
International Health Technology Assessment Database (INAHTA)	22/08/23	https://database.inahta.org/	-	1

Main search – Additional methods

Additional method	Date searched	No. of results downloaded
Forwards citation searching	22/08/23	7
Includes from: • Bundred, James R et al. (2022) Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. BMJ (Clinical research ed.) vol. 378 e070346 • NG101 (2018 update)	22/08/23	23

Search strategy history
Database name: Medline ALL

1 exp Breast Neoplasms/ 343489

2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 46668

3 Carcinoma, Lobular/ 6085

4 Carcinoma, Medullary/ 3393

5 Carcinoma, Intraductal, Noninfiltrating/ 10678

6 or/1-5 362537

7 exp Breast/ 53207

8 breast*.ti,ab,kw. 555785

9 7 or 8 565698

10 (breast adj milk).ti,ab,kw. 15604

11 (breast adj tender*).ti,ab,kw. 586

12 10 or 11 16188

13 9 not 12 549510

14 exp Neoplasms/ 3865370

15 13 and 14 358840

16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 413160

17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 36656

18 or/15-17 468493

19 6 or 18 525060

20 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 9424

21 19 or 20 525296

22 Mastectomy, Segmental/ 10182

23 (segmentectom* or post?segmentectom*).ti,ab,kw. 4693

24 (lumpectom* or post?lumpectom*).ti,ab,kw. 3981

25 (quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*).ti,ab,kw. 631

26 Tylectom*.ti,ab. 35

27 ((local* or limit* or sector or segment* or part*) adj2 (excis* or resection*)).ti,ab,kw. 34314

28 WLE.ti,ab,kw. 721

29 ((part* or segment*) adj2 (mammectom* or mastectomy*)).ti,ab,kw. 1117

30 (breast adj2 (conserv* or sparing)).ti,ab,kw. 12154

31 breast conserv*.ti,ab,kw. 11886

32 breast sparing.ti,ab,kw. 91

33 ((conserv* or sparing) adj2 (surg* or therap* or treatment*)).ti,ab,kw. 80049

34 excis* alone.ti,ab,kw. 644

35 or/22-34 124901

36 margin*.ti,ab,kw. 242856

37 "Margins of Excision"/ 4756

38 36 or 37 243448

39 21 and 35 and 38 3941

40 limit 39 to ed=20170130-20230821 1159

41 limit 39 to dt=20170130-20230821 1293

42 40 or 41 1442

43 limit 42 to english language 1405

44 animals/ not humans/ 5113339

45 43 not 44 1403

46 limit 45 to (letter or historical article or comment or editorial or news or case reports) 144

47 45 not 46 1259

48 remove duplicates from 47 1260

Database name: Cochrane Database of Systematic Reviews (CDSR)

1 MeSH descriptor: [Breast Neoplasms] explode all trees 17939

2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 876

3 MeSH descriptor: [Carcinoma, Lobular] this term only 193

4 MeSH descriptor: [Carcinoma, Medullary] this term only 17

5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 270

6 {OR #1-#5} 18181
7 MeSH descriptor: [Breast] explode all trees 1442
8 breast*:ti,ab 58125
9 #7 or #8 58228
10 (breast NEXT milk):ti,ab 2612
11 (breast NEXT tender*):ti,ab 256
12 #10 or #11 2867
13 #9 not #12 55361
14 MeSH descriptor: [Neoplasms] explode all trees 112129
15 #13 and #14 18379
16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 41787
17 (mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 282
18 {OR #15-#17} 42719
19 #6 or #18 43970
20 (duct* carcinoma* in situ or DCIS):ti,ab 850
21 #19 or #20 44042
22 MeSH descriptor: [Mastectomy, Segmental] this term only 699
23 (segmentectom* or post?segmentectom*):ti,ab 300
24 (lumpectom* or post?lumpectom*):ti,ab 713
25 (quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*):ti,ab 103
26 Tylectom*:ti,ab 3
27 ((local* or limit* or sector or segment* or part*) NEAR/2 (excis* or resection*)):ti,ab 1548
28 WLE:ti,ab 181
29 ((part* or segment*) NEAR/2 (mammectom* or mastectomy*)):ti,ab 189
30 (breast NEAR/2 (conserv* or sparing)):ti,ab 2141
31 breast conserv*:ti,ab 2652
32 breast sparing:ti,ab 336
33 ((conserv* or sparing) NEAR/2 (surg* or therap* or treatment*)):ti,ab 8924
34 excis* alone:ti,ab 879
35 {OR #22-#34} 13051
36 margin*:ti,ab 24154
37 MeSH descriptor: [Margins of Excision] this term only 155
38 #36 OR #37 24172
39 #21 AND #35 AND #38 572
40 "conference":pt or (clinicaltrials or trialsearch):so 700381
41 #39 NOT #40 with Publication Year from 2017 to 2023, in Trials 86
42 #39 NOT #40 with Cochrane Library publication date Between Jan 2017 and Aug 2023, in Cochrane Reviews 1

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

1 MeSH descriptor: [Breast Neoplasms] explode all trees 17939

2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 876

3 MeSH descriptor: [Carcinoma, Lobular] this term only 193

4 MeSH descriptor: [Carcinoma, Medullary] this term only 17

5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 270

6 {OR #1-#5} 18181

7 MeSH descriptor: [Breast] explode all trees 1442

8 breast*:ti,ab 58125

9 #7 or #8 58228

10 (breast NEXT milk):ti,ab 2612

11 (breast NEXT tender*):ti,ab 256

12 #10 or #11 2867

13 #9 not #12 55361

14 MeSH descriptor: [Neoplasms] explode all trees 112129

15 #13 and #14 18379

16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 41787

17 (mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 282

18 {OR #15-#17} 42719

19 #6 or #18 43970

20 (duct* carcinoma* in situ or DCIS):ti,ab 850

21 #19 or #20 44042

22 MeSH descriptor: [Mastectomy, Segmental] this term only 699

23 (segmentectom* or post?segmentectom*):ti,ab 300

24 (lumpectom* or post?lumpectom*):ti,ab 713

25 (quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*):ti,ab 103

26 Tylectom*:ti,ab 3

27 ((local* or limit* or sector or segment* or part*) NEAR/2 (excis* or resection*)):ti,ab 1548

28 WLE:ti,ab 181

29 ((part* or segment*) NEAR/2 (mammectom* or mastectomy*)):ti,ab 189

30 (breast NEAR/2 (conserv* or sparing)):ti,ab 2141

31 breast conserv*:ti,ab 2652

32 breast sparing:ti,ab 336

33 ((conserv* or sparing) NEAR/2 (surg* or therap* or treatment*)):ti,ab 8924

34 excis* alone:ti,ab 879

35 {OR #22-#34} 13051

36 margin*:ti,ab 24154

37 MeSH descriptor: [Margins of Excision] this term only 155

38 #36 OR #37 24172

39 #21 AND #35 AND #38 572

40 "conference":pt or (clinicaltrials or trialsearch):so 700381

41 #39 NOT #40 with Publication Year from 2017 to 2023, in Trials 86

42 #39 NOT #40 with Cochrane Library publication date Between Jan 2017 and Aug 2023, in Cochrane Reviews 1

Database name: Embase

1 exp breast cancer/ 512523

2 exp breast carcinoma/ 74869

3 exp medullary carcinoma/ 10526

4 ductal breast carcinoma in situ/ 2253

5 exp breast tumor/ 573463

6 lobular carcinoma/ 3294

7 or/1-6 582620

8 exp breast/ 88777

9 breast*.ti,ab,kw. 685086

10 8 or 9 700151

11 (breast adj milk).ti,ab,kw. 16703

12 (breast adj tender*).ti,ab,kw. 614

13 11 or 12 17312

14 10 not 13 682839

15 exp neoplasm/4658871

16 14 and 15 526355

17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 534708

18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 29461

19 16 or 17 or 18 587926

20 7 or 19 695820

21 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 15630

22 20 or 21 696715

23 partial mastectomy/ 18381

24 lumpectomy/ 5040

25 breast-conserving surgery/ 2574

26 segmentectomy/ 6264

27 local excision/ 3533

28 wide excision/ 7364

29 (segmentectom* or post?segmentectom*).ti,ab,kw. 6365

30 (lumpectom* or post?lumpectom*).ti,ab,kw. 7007

31 (quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*).ti,ab,kw. 796

32 Tylectom*.ti,ab,kw. 10
33 ((local* or limit* or sector or segment* or part*) adj2 (excis* or resection*)).ti,ab,kw. 41087
34 WLE.ti,ab,kw. 1607
35 ((part* or segment*) adj2 (mammectom* or mastectomy*)).ti,ab,kw. 1563
36 (breast adj2 (conserv* or sparing)).ti,ab,kw. 19648
37 breast conserv*.ti,ab,kw. 19473
38 breast sparing.ti,ab,kw. 106
39 ((conserv* or sparing) adj2 (surg* or therap* or treatment*)).ti,ab,kw. 96780
40 excis* alone.ti,ab,kw. 719
41 or/23-40 167254
42 margin*.ti,ab,kw. 296926
43 surgical margin/ 23528
44 42 or 43 303709
45 22 and 41 and 44 7328
46 limit 45 to dc=20170130-20230821 3183
47 limit 46 to english language 3126
48 (conference abstract* or conference review or conference paper or conference proceeding or preprint).db,pt,su. 5377088
49 47 not 48 1710
50 nonhuman/ not (human/ and nonhuman/) 3975145
51 49 not 50 1695
52 (letter or editorial).pt. 1675861
53 51 not 52 1647

Database name: Epistemonikos

(title:((breast* AND (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (duct* carcinoma* in situ OR DCIS)) OR abstract:((breast* AND (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (duct* carcinoma* in situ OR DCIS))) AND (title:((segmentectom* OR (post segmentectom*) OR (post-segmentectom*)) OR (lumpectom* OR (post lumpectom*) OR (post-lumpectom*)) OR (quadrectom* OR quadrantectom* OR (post quadrectom*) OR (post-quadrectom*) OR (post quadrantectom*) OR (post-quadrantectom*)) OR Tylectom* OR ((local* OR limit* OR sector OR segment* OR part*) AND (excis* OR resection*)) OR WLE OR ((part* OR segment*) AND (mammectom* OR mastectomy*)) OR (breast AND (conserv* OR sparing)) OR (breast conserv*) OR (breast sparing) OR ((conserv* OR sparing) AND (surg* OR therap* OR treatment*)) OR (excis* alone)) OR abstract:((segmentectom* OR (post segmentectom*) OR (post-segmentectom*)) OR (lumpectom* OR (post lumpectom*) OR (post-lumpectom*)) OR (quadrectom* OR quadrantectom* OR (post quadrectom*) OR (post-quadrectom*) OR (post quadrantectom*) OR (post-quadrantectom*)) OR Tylectom* OR

((local* OR limit* OR sector OR segment* OR part*) AND (excis* OR resection*)) OR WLE OR ((part* OR segment*) AND (mammectom* OR mastectomy*)) OR (breast AND (conserv* OR sparing)) OR (breast conserv*) OR (breast sparing) OR ((conserv* OR sparing) AND (surg* OR therap* OR treatment*)) OR (excis* alone))) AND (title:(margin*) OR abstract:(margin*))

+ Date limit: 2017-2023

Database name: HTA (Health Technology Assessment)

1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES 1798

2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES 65

3 MESH DESCRIPTOR Carcinoma, Lobular 7

4 MESH DESCRIPTOR Carcinoma, Medullary 7

5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating 13

6 #1 or #2 or #3 or #4 or #5 1820

7 MESH DESCRIPTOR Breast EXPLODE ALL TREES 97

8 breast* 3002

9 #7 or #8 3002

10 (breast NEXT milk) 58

11 (breast NEXT tender*) 14

12 #10 or #11 72

13 #9 not #12 2930

14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 12016

15 #13 and #14 2071

16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 2414

17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)) 7

18 #15 OR #16 OR #17 2453

19 #6 OR #18 2475

20 (duct* carcinoma* in situ or DCIS) 46

21 #19 OR #20 2475

22 MESH DESCRIPTOR Mastectomy, Segmental 73

23 (segmentectom* or post?segmentectom*) 11

24 (lumpectom* or post?lumpectom*) 54

25 (quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*) 4

26 Tylectom* 1

27 ((local* or limit* or sector or segment* or part*) NEAR2 (excis* or resection*)) 82

28 WLE 5

29 ((part* or segment*) NEAR2 (mammectom* or mastectomy*)) 7

30 (breast NEAR2 (conserv* or sparing)) 120

31 breast conserv* 118

32 breast sparing 1

33 ((conserv* or sparing) NEAR2 (surg* or therap* or treatment*)) 772

34 excis* alone 5

35 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 914

36 margin* 999

37 MESH DESCRIPTOR Margins of Excision 0

38 #36 OR #37 999

39 #21 AND #35 AND #38 28

40 * IN HTA 17351

41 #39 AND #40 7

42 * IN HTA FROM 2017 TO 2023 506

43 #41 AND #42 0

Database name: International Health Technology Assessment Database (INAHTA)

(((duct* carcinoma* in situ or DCIS)) OR ((mammar* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).) OR ((breast* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ("Breast Neoplasms"[mhe]))

AND

((breast sparing) OR ((excis* alone) OR (((conserv* or sparing) and (surg* or therap* or treatment*))) OR (breast conserv*) OR ((breast and (conserv* or sparing))) OR (((part* or segment*) and (mammectom* or mastectomy*))) OR (WLE) OR (((local* or limit* or sector or segment* or part*) and (excis* or resection*))) OR (Tylectom*) OR ((quadrectom* or quadrantectom* or "post quadrectomy" or "post quadrectomies" or "post-quadrectomy" or "post-quadrectomies" or "post quadrantectomy" or "post quadrantectomies" or "post-quadrantectomy" or "post-quadrantectomies")) OR ((lumpectom* or "post lumpectomy" or "post lumpectomies" or "post-lumpectomy" or "post-lumpectomies")) OR ((segmentectom* or "post segmentectomy" or "post segmentectomies" or "post-segmentectomy" or "post-segmentectomies")) OR ("Mastectomy, Segmental"[mh])))

AND

(("Margins of Excision"[mh]) OR (margin*))

+ Date limit: 2017-2023

Additional search methods

Source name: Web of Science

Forward citation search using: Bundred, James R et al. (2022) Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. BMJ (Clinical research ed.) vol. 378 e070346

Included records from the above systematic review were also imported into EPPI Reviewer.

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	23/08/23	OVID	1886 to August 10, 2023	0
Embase	23/08/23	Ovid	1996 to 2023 August 22	10
Health Technology Assessment (HTA)	23/08/23	CRD	-	0
International Health Technology Assessment Database (INAHTA)	23/08/23	INAHTA	-	1
MEDLINE ALL	23/08/23	Ovid	1946 to August 22, 2023	8

Search strategy history
Database name: Medline ALL

1 exp Breast Neoplasms/ 343601
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 46687
3 Carcinoma, Lobular/ 6087
4 Carcinoma, Medullary/ 3393
5 Carcinoma, Intraductal, Noninfiltrating/ 10680
6 or/1-5 362664
7 exp Breast/ 53222
8 breast*.ti,ab,kw. 556053
9 7 or 8 565966
10 (breast adj milk).ti,ab,kw. 15611
11 (breast adj tender*).ti,ab,kw. 586
12 10 or 11 16195
13 9 not 12 549771
14 exp Neoplasms/ 3866613
15 13 and 14 358986
16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 413369
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 36660
18 or/15-17 468712
19 6 or 18 525295

20 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 9427
21 19 or 20 525531
22 Mastectomy, Segmental/ 10183
23 (segmentectom* or post?segmentectom*).ti,ab,kw. 4697
24 (lumpectom* or post?lumpectom*).ti,ab,kw. 3983
25 (quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*).ti,ab,kw. 633
26 Tylectom*.ti,ab. 35
27 ((local* or limit* or sector or segment* or part*) adj2 (excis* or resection*)).ti,ab,kw. 34322
28 WLE.ti,ab,kw. 721
29 ((part* or segment*) adj2 (mammectom* or mastectomy*)).ti,ab,kw. 1117
30 (breast adj2 (conserv* or sparing)).ti,ab,kw. 12160
31 breast conserv*.ti,ab,kw. 11891
32 breast sparing.ti,ab,kw. 91
33 ((conserv* or sparing) adj2 (surg* or therap* or treatment*)).ti,ab,kw. 80077
34 excis* alone.ti,ab,kw. 644
35 or/22-34 124945
36 margin*.ti,ab,kw. 242965
37 "Margins of Excision"/ 4760
38 36 or 37 243557
39 21 and 35 and 38 3944
40 Cost-Benefit Analysis/92901
41 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 17467
42 ((incremental* adj2 cost*) or ICER).tw. 17952
43 (cost adj2 utilit*).tw. 6907
44 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2320
45 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 23773
46 (cost and (effect* or utilit*)).ti. 38829
47 or/40-46 114429
48 39 and 47 24
49 limit 48 to dt=20170130-20230823 9
50 limit 48 to ed=20170130-20230823 7
51 49 or 50 9
52 limit 51 to english language 9
53 animals/ not humans/ 5114377
54 52 not 53 9
55 limit 54 to (letter or historical article or comment or editorial or news or case reports) 1
56 54 not 55 8

Database name: Embase

1	exp breast cancer/	512768
2	exp breast carcinoma/	74899
3	exp medullary carcinoma/	10531
4	ductal breast carcinoma in situ/	2263
5	exp breast tumor/	573721
6	lobular carcinoma/	3294
7	or/1-6	582882
8	exp breast/	88813
9	breast*.ti,ab,kw.	685456
10	8 or 9	700528
11	(breast adj milk).ti,ab,kw.	16708
12	(breast adj tender*).ti,ab,kw.	615
13	11 or 12	17318
14	10 not 13	683210
15	exp neoplasm/	4660882
16	14 and 15	526631
17	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	534986
18	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	29465
19	16 or 17 or 18	588223
20	7 or 19	696122
21	(duct* carcinoma* in situ or DCIS).ti,ab,kw.	15639
22	20 or 21	697017
23	partial mastectomy/	18381
24	lumpectomy/	5042
25	breast-conserving surgery/	2581

26	segmentectomy/	6269
27	local excision/	3534
28	wide excision/	7367
29	(segmentectom* or post?segmentectom*).ti,ab,kw.	6367
30	(lumpectom* or post?lumpectom*).ti,ab,kw.	7009
31	(quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*).ti,ab,kw.	796
32	Tylectom*.ti,ab,kw.	10
33	((local* or limit* or sector or segment* or part*) adj2 (excis* or resection*)).ti,ab,kw.	41102
34	WLE.ti,ab,kw.	1607
35	((part* or segment*) adj2 (mammectom* or mastectomy*)).ti,ab,kw.	1563
36	(breast adj2 (conserv* or sparing)).ti,ab,kw.	19656
37	breast conserv*.ti,ab,kw.	19481
38	breast sparing.ti,ab,kw.	106
39	((conserv* or sparing) adj2 (surg* or therap* or treatment*)).ti,ab,kw.	96828
40	excis* alone.ti,ab,kw.	719
41	or/23-40	167324
42	margin*.ti,ab,kw.	297082
43	surgical margin/	23544
44	42 or 43	303865
45	22 and 41 and 44	7330
46	cost utility analysis/	12275
47	(cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw.	29519
48	((incremental* adj2 cost*) or ICER).tw.	30203
49	(cost adj2 utilit*).tw.	10683
50	(cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw.	3091
51	((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw.	35724
52	(cost and (effect* or utilit*)).ti.	52827

53	or/46-52	85121
54	45 and 53	36
55	limit 54 to dc=20170130-20230823	19
56	limit 55 to english language	19
57	(conference abstract* or conference review or conference paper or conference proceeding or preprint).db,pt,su.	5380244
58	56 not 57	10
59	nonhuman/ not (human/ and nonhuman/)	3977017
60	58 not 59	10
61	(letter or editorial).pt.	1676586
62	60 not 61	10

Database name: EconLit

1	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	393
2	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	1
3	(duct* carcinoma* in situ or DCIS).ti,ab,kw.	3
4	or/1-3	395
5	(segmentectom* or post?segmentectom*).ti,ab,kw.	0
6	(lumpectom* or post?lumpectom*).ti,ab,kw.	3
7	(quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*).ti,ab,kw.	0
8	Tylectom*.ti,ab.	0
9	((local* or limit* or sector or segment* or part*) adj2 (excis* or resection*)).ti,ab,kw.	11
10	WLE.ti,ab,kw.	5
11	((part* or segment*) adj2 (mammectom* or mastectomy*)).ti,ab,kw.	0
12	(breast adj2 (conserv* or sparing)).ti,ab,kw.	6

13	breast conserv*.ti,ab,kw.	6
14	breast sparing.ti,ab,kw.	0
15	((conserv* or sparing) adj2 (surg* or therap* or treatment*)).ti,ab,kw.	27
16	excis* alone.ti,ab,kw.	0
17	or/5-16	46
18	margin*.ti,ab,kw.	41500
19	4 and 17 and 18	4
20	limit 19 to english	4
21	limit 20 to yr="2017 -Current"	0

Database name: Health Technology Assessment (HTA)

1	MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES	1798
2	MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES	65
3	MESH DESCRIPTOR Carcinoma, Lobular	7
4	MESH DESCRIPTOR Carcinoma, Medullary	7
5	MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating	13
6	#1 or #2 or #3 or #4 or #5	1820
7	MESH DESCRIPTOR Breast EXPLODE ALL TREES	97
8	breast*	3002
9	#7 or #8	3002
10	(breast NEXT milk)	58
11	(breast NEXT tender*)	14
12	#10 or #11	72
13	#9 not #12	2930
14	MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES	12016
15	#13 and #14	2071
16	(breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))	2414
17	(mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))	7
18	#15 OR #16 OR #17	2453

19	#6 OR #18	2475
20	(duct* carcinoma* in situ or DCIS)	46
21	#19 OR #20	2475
22	MESH DESCRIPTOR Mastectomy, Segmental	73
23	(segmentectom* or post?segmentectom*)	11
24	(lumpectom* or post?lumpectom*)	54
25	(quadrectom* or quadrantectom* or post?quadrectom* or post?quadrantectom*)	4
26	Tylectom*	1
27	((local* or limit* or sector or segment* or part*) NEAR2 (excis* or resection*))	82
28	WLE	5
29	((part* or segment*) NEAR2 (mammectom* or mastectomy*))	7
30	(breast NEAR2 (conserv* or sparing))	120
31	breast conserv*	118
32	breast sparing	1
33	((conserv* or sparing) NEAR2 (surg* or therap* or treatment*))	772
34	excis* alone	5
35	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34	914
36	margin*	999
37	MESH DESCRIPTOR Margins of Excision	0
38	#36 OR #37	999
39	#21 AND #35 AND #38	28
40	* IN HTA	17351
41	#39 AND #40	7
42	* IN HTA FROM 2017 TO 2023	506
43	#41 AND #42	0

Database name: International Health Technology Assessment Database (INAHTA)

(((duct* carcinoma* in situ or DCIS)) OR ((mammar* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).) OR ((breast* AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ("Breast Neoplasms"[mhe]))

AND

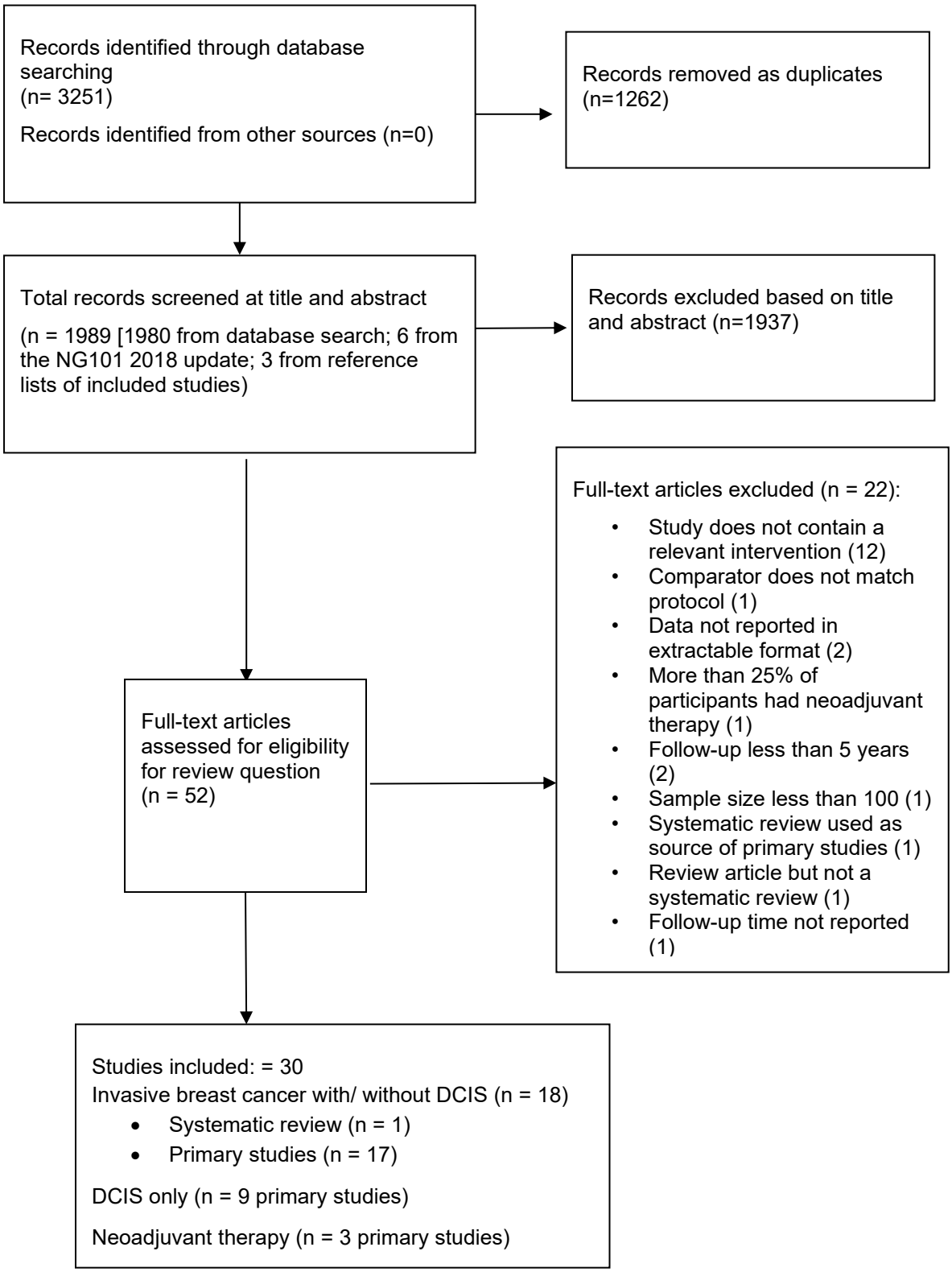
((breast sparing) OR ((excis* alone) OR (((conserv* or sparing) and (surg* or therap* or treatment*))) OR (breast conserv*) OR ((breast and (conserv* or sparing))) OR (((part* or segment*) and (mammectom* or mastectomy*))) OR (WLE) OR (((local* or limit* or sector or segment* or part*) and (excis* or resection*))) OR (Tylectom*) OR ((quadrectom* or quadrantectom* or "post quadrectomy" or "post quadrectomies" or "post-quadrectomy" or "post-quadrectomies" or "post quadrantectomy" or "post quadrantectomies" or "post-quadrantectomy" or "post-quadrantectomies")) OR ((lumpectom* or "post lumpectomy" or "post lumpectomies" or "post-lumpectomy" or "post-lumpectomies")) OR ((segmentectom* or "post segmentectomy" or "post segmentectomies" or "post-segmentectomy" or "post-segmentectomies")) OR ("Mastectomy, Segmental"[mh])))

AND

(("Margins of Excision"[mh]) OR (margin*))

+ Date limit: 2017-2023

Appendix C – Effectiveness of further surgery evidence study selection



Appendix D – Effectiveness of further surgery evidence

Invasive breast cancer with or without DCIS

Systematic review

Bundred, 2022

Bibliographic Reference	Bundred, James R; Michael, Sarah; Stuart, Beth; Cutress, Ramsey I; Beckmann, Kerri; Holleczek, Bernd; Dahlstrom, Jane E; Gath, Jacqui; Dodwell, David; Bundred, Nigel J; Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis.; BMJ (Clinical research ed.); 2022; vol. 378; e070346

Study Characteristics

Study design	Systematic review
Study details	Dates searched 1 January 1980 to 31 December 2021 Databases searched Medline (PubMed), Embase, and Proquest online databases Sources of funding No funding was received for this work. DD received funding from Cancer Research UK (C8225/A21133).
Inclusion criteria	Patients undergoing curative breast conserving surgery for early stage invasive breast cancer (stage I-III) Allowed an estimation of outcomes in relation to margin status Followed up patients for a minimum of 60 months
Exclusion criteria	Patients with ductal carcinoma in situ only Patients treated with neoadjuvant chemotherapy Patients who had a mastectomy
Number of studies included in the	68 studies

systematic review	
Studies from the systematic review that are relevant for use in the current review	• Behm 2013 (locoregional recurrence data was extracted from Behm 2013; distant recurrence data was extracted from Bundred 2022) • Biglia 2014 (local recurrence data was extracted from Biglia 2014) • Bodilsen 2016 (distant recurrence data was extracted from Bodilsen 2016) • Goldstein 2003 (local recurrence and distant recurrence data was extracted from Goldstein 2003) • Kreike 2008 (local recurrence data was extracted from Kreike 2008) • Lupe 2011 (locoregional recurrence, local recurrence, distant recurrence, overall survival and breast cancer specific survival data was extracted from Lupe 2011) • Maishman 2017 (local recurrence and distant recurrence data was extracted from Bundred 2022) • Peterson 1999 (locoregional recurrence, distant recurrence, overall survival, and breast cancer specific survival data was extracted from Peterson 1999; local recurrence data was extracted from Bundred 2022) • Smith 2014 (local recurrence data was extracted from Smith 2014) • Smitt 2003 (local recurrence data was extracted from Smitt 2003) • Tang 2019 (local recurrence data was extracted from Tang 2019) • Tyler 2018 (local recurrence and breast cancer specific survival was extracted from Tyler 2018) • Varghese 2008 (local recurrence data was extracted from Varghese 2008)
Studies from the systematic review that are not relevant for use in the current review	• Adams 2013 (excluded during the 2018 NG101 update, reason: No comparison of different margin widths) • Barbieri 2011 (The margin width >10 mm is the reference variable in the analysis. A margin width of 10 mm was considered to be too wide to compare against <2 mm) • Bellon 2005 (margin width included tumour at ink) • Bernardi 2014 (margin width included tumour at ink) • Besana-Ciani 2008 (excluded during the 2018 NG101 update, reason: Margin width categories inconsistent with protocol) • Bhatti 2014 (More than 25% of participants had neoadjuvant therapy) • Bosma 2016 (margin width included tumour at ink) • Braunstein 2016 (margin width included tumour at ink) • Burke 1995 (margin width included tumour at ink) • Cannon 2013 (margin width included tumour at ink) • Carter 2016 (margin width included tumour at ink) • Clement 2018 (margin width included tumour at ink) • Demirci 2011 (excluded during the 2018 NG101 update, reason: Insufficient presentation of results for analysis) • Dixon 2016 (excluded during the 2018 NG101 update, reason: Margin width categories inconsistent with protocol) • Ewertz 2008 (margin width included tumour at ink) • Freedman 2005 (margin definition only included 2 mm) • Groot 2011 (margin width included tumour at ink) • Hammer 2019 (margin definition only included 1 mm) • Hennigs 2016 (margin width included tumour at ink)

	• Holleczek 2019 (margin width included tumour at ink) • Horiguchi (margin width included tumour at ink) • Jobsen 2014 (margin width included tumour at ink) • Kahlert 2018 (margin width included tumour at ink) • Karasawa 2003 (margin width included tumour at ink) • Karasawa 2005 (margin width included tumour at ink) • Kasumi 2006 (margin width included tumour at ink) • Kim 2017 (margin width included tumour at ink) • Kokubo 2000 (margin width included tumour at ink) • Kunos 2006 (margin width included tumour at ink) • Leong 2004 (excluded during the 2018 NG101 update, reason: Margin width categories inconsistent with protocol) • Liau 2010 (margin width included tumour at ink) • Livi 2007 (margin width included tumour at ink) • Livi 2013 (margin width included tumour at ink) • Mcbain 2003 (margin width included tumour at ink) • Mirza 2002 (margin width included tumour at ink) • Mitsumori 2009 (margin width included tumour at ink) • Neuschatz 2002 (excluded during the 2018 NG101 update, reason: Insufficient presentations of results/margin width categories inconsistent with protocol) • Obedian 1999 (margin width included tumour at ink) • Park 2000 (excluded during the 2018 NG101 update, reason: insufficient presentation of results) • Perez 2010 (excluded during the 2018 NG101 update, reason: Margin width categories inconsistent with protocol) • Pierce 1997 (margin width included tumour at ink) • Pilewskie 2014 (margin width included tumour at ink) • Renton 1996 (only reports margin width at 5 mm) • Russo 2013 (excluded during the 2018 NG101 update, reason: Margin width categories inconsistent with protocol) • Sadek 2015 (margin width included tumour at ink) • Santiago 2004 (excluded during the 2018 NG101 update, reason: insufficient presentation of results) • Spivack 1994 (margin width included tumour at ink) • Takahashi 2016 (margin width included tumour at ink) • Touboul 1999 (excluded during the 2018 NG101 update, reason: insufficient presentation of results) • Voogd 2001 (margin width included tumour at ink) • Whipp 2010 (excluded during the 2018 NG101 update, reason: insufficient presentation of results) • Yoon 2018 (margin width included tumour at ink) • Yoshida 2009 (margin width included tumour at ink)
Additional comments	The first author (James R Bundred) was contacted and the information below was confirmed: • local recurrence data for Peterson 1999 compares ≤2 mm vs >2 mm (we extracted this data from Bundred 2022) • local recurrence data for Voogd 2001 and Yoon 2018 includes tumour at ink (we did not include Voogd 2001 and Yoon 2018)

Critical appraisal ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable *(There were studies only reporting data for radial margins at ink which was not an intervention relevant to the update of NG101 in 2023.)*

Studies included in systematic review by Bundred et al. 2022

Behm, 2013

Bibliographic Reference	Behm, Eirene C; Beckmann, Kerri R; Dahlstrom, Jane E; Zhang, Yanping; Cho, Carolyn; Stuart-Harris, Robin; Craft, Paul; Rezo, Angela; Buckingham, John M; Surgical margins and risk of locoregional recurrence in invasive breast cancer: an analysis of 10-year data from the Breast Cancer Treatment Quality Assurance Project.; Breast (Edinburgh, Scotland); 2013; vol. 22 (no. 5); 839-44

Study details

Study type	Retrospective cohort study
Study location	Australia
Study setting	Breast Cancer Treatment Group established the Breast Cancer Treatment Quality Assurance Project (BCTQAP)
Study dates	July 1997 to June 2007
Inclusion criteria	Inclusion criteria Patients enrolled in the BCTQAP from July 1997 to June 2007 treated by either BCS or mastectomy for IBC and for whom at least 3 years follow-up data were available.
Exclusion criteria	Exclusion criteria Patients with Paget's disease of the breast, phyllodes tumour, invasive breast cancer of special types, bilateral or metachronous breast cancer and those with evidence of distance metastasis at the time of surgery were excluded from the study.
Outcome measures	Locoregional recurrence Defined as local recurrence of breast cancer in the same breast or underlying fascia/muscle, or regional recurrence in ipsilateral axillary lymph

	nodes that had previously been regarded as pathologically and radiologically normal. Distant recurrence Distant recurrence was not defined.
Duration of follow-up	Mean follow-up was 7.9 years (range: 1.4 to 171 months)
Loss to follow-up	There was missing information on grade for 20 participants
Methods of analysis	Data extracted for tumour size, margin distance and LVI were integrated into the existing 10-year BCTQAP dataset. Characteristics of the study group were examined using frequency distributions. Mean follow-up times were derived from dates of diagnosis, progression and death. The rate of recurrence within the study population was determined using actuarial methods. Univariate and multivariate analyses were undertaken using Cox proportional hazards regression. The outcome of interest in these models was time to local recurrence (i.e. time from date of diagnosis to date of disease relapse). If either date was unknown, the date of the first surgical procedure and/or the date of the first treatment following progression were substituted. Time was censored at August 01 2011, or at death or at recurrence, whichever came first. For regression modelling, variables with missing data were collapsed into 'yes' or 'no/not reported'. The exception was for cases with missing grade (n ¼ 20), which were excluded from multivariate analyses. A series of models was undertaken examining the effect of the closest invasive margin distance on risk of local recurrence, for all cases and separately for those treated by BCS or mastectomy, and for those receiving radiotherapy or not. In each of these models, margin clearance was coded as the distance of the closest invasive margin to the nearest mm (rounded) between 0 mm and 5 mm, with >5 mm as the reference category. The effect of any margin distance (rather than just the invasive margin) was also examined in separate analyses, with margin distances derived from the closest invasive or DCIS margin. In each of these models, effects were adjusted for other prognostic factors, including patient age, tumour size and grade of the invasive component, tumour hormone receptor status, nodal status, presence of LVI, surgical approach (except when stratified by surgery type), and whether RT, chemotherapy and endocrine therapy was given. Adjustment was also made for DCIS margin distance as a categorical variable (<2 mm versus >2 mm) in models examining only the invasive margin distance. No evidence of colinearity was observed in any of the models. All analyses were carried out using Stata v11.
Confounding factors used in adjusted models	age, total tumour size, invasive tumour grade, oestrogen/progesterone receptor status, lymphovascular invasion, lymph node involvement, whether hormone therapy and chemotherapy was given, DCIS involvement and whether radiotherapy given
Adjustment	Partially adjusted
Additional comments	• Extracted data for locoregional recurrence was model adjusted hazard ratio with 95% CI (reference group was >5 mm)

	• Extracted data for distant recurrence was taken from Bundred 2022 (figure 2; reference margin was >2 mm).
Radiotherapy status	Mixed population Radiotherapy 63.34% but this % includes both mastectomy and BCS
Age	Mixed population
Subsequent systemic treatment	Mixed population • chemotherapy (43.34% but this % includes both mastectomy and BCS) • hormone therapy (75.95% but this % includes both mastectomy and BCS)
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS 63.6%

Study arms

1 mm (N = 115)

Radial margin: 1 mm. Number of participants is for greater than 0 mm and less than 2 mm. Exact number is not reported for 1 mm.

2 mm (N = 384)

Radial margin: 2 mm. Number of participants is for equal to 2 mm and equal to 5 mm. Exact number is not reported for 2 mm.

>5 mm (N = 586)

Radial margin: greater than 5 mm.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 2300)**
Age	
less than 50 years	n = 626 ; % = 27.2

Characteristic	Study (N = 2300)
50 to 59 years	n = 769 ; % = 33.4
60 to 65 years	n = 535 ; % = 23.3
70 or more years	n = 370 ; % = 16.1
Menopausal status	
Premenopausal	n = 612 ; % = 26.6
Perimenopausal	n = 220 ; % = 9.6
Postmenopausal	n = 1468 ; % = 63.8
Tumour size **Total tumour size including DCIS component**	
less or equal to 5 mm	n = 129 ; % = 5.6
greater than 5 mm to 10 mm	n = 337 ; % = 14.7
greater than 10 mm to 20 mm	n = 890 ; % = 38.7
greater than 20 mm to 50 mm	n = 805 ; % = 35
greater than 50 mm	n = 139 ; % = 6
Tumour grade **Grade of invasive tumour**	
Grade 1	n = 669 ; % = 29.1
Grade 2	n = 894 ; % = 38.9
Grade 3	n = 717 ; % = 31.2
Unknown	n = 20 ; % = 0.9
Tumour ER status **oestrogen receptor (ER)**	
Positive	n = 1870 ; % = 81.3
Negative	n = 417 ; % = 18.1
Unknown	n = 13 ; % = 0.6
Tumour PR status **progesterone receptor (PR)**	
Positive	n = 1601 ; % = 69.6
Negative	n = 683 ; % = 29.7
Unknown	n = 16 ; % = 0.7
Multifocality	
Yes	n = 384 ; % = 16.7
No	n = 1916 ; % = 83.3
DCIS present	

Characteristic	Study (N = 2300)
Yes	n = 1462 ; % = 63.6
No	n = 838 ; % = 36.4
Nodal status	
Positive	n = 837 ; % = 36.4
Negative	n = 1325 ; % = 57.6
Unknown	n = 138 ; % = 6
Lymphovascular invasion	
Yes	n = 573 ; % = 24.9
No	n = 1661 ; % = 72.2
Unknown	n = 66 ; % = 2.9
Surgery type	
Breast conserving surgery	n = 1123 ; % = 48.8
Mastectomy	n = 1177 ; % = 51.2

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns (P*artially adjusted (adjusted factors: age, total tumour size, invasive tumour grade, oestrogen/progesterone receptor status, lymphovascular invasion, lymph node involvement, whether hormone therapy and chemotherapy was given, DCIS involvement and whether radiotherapy given))*
Overall bias	Directness	Directly applicable

Biglia, 2014

Bibliographic Reference	Biglia, N; Ponzone, R; Bounous, V E; Mariani, L L; Maggiorotto, F; Benevelli, C; Liberale, V; Ottino, M C; Sismondi, P; Role of re-excision for positive and close resection margins in patients treated with breast-conserving surgery.; Breast (Edinburgh, Scotland); 2014; vol. 23 (no. 6); 870-5

Study details

Study type	Retrospective cohort study
Study location	Italy

Study setting	Department of Obstetrics and Gynaecology, Hospital
Study dates	Between 2000 and 2009
Inclusion criteria	Inclusion criteria Women with invasive or in situ breast cancer treated with breast conserving surgery and radiotherapy
Intervention(s)	Lumpectomy and radiotherapy
Outcome measures	Local recurrence Local recurrence without definition
Number of participants	1339 participants
Duration of follow-up	Median 47.5 months
Methods of analysis	Qualitative variables were compared by the Pearson's chi square test or with Fisher exact test; quantitative variables were compared by the variance analysis (ANOVA). Normality of the variables distribution was tested by the Kolmogorove Smirnov test. For non-normally distributed variables, a non parametric analysis was performed using U-Mann-Whitney test. Local recurrence free survival (LRFS) and distant recurrence free survival (DRFS) were estimated using the Kaplan Meier method and compared by the log-rank test. Univariate and multivariate analysis were performed in order to investigate which patient and tumour characteristics (age, tumour size, histology, grading, multifocality, histotype, presence of lymphovascular invasion, nodal status, ER and PgR status, oncogene HER-2 and Ki-67 expression) were associated with the risk of having positive margins after primary surgery and if positive resection margins were independent risk factor for the development of local and distant recurrence. Independent variables value was checked with multivariate analysis according to Cox regression model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are calculated. Statistical analysis was performed using the SPSS 15.0 software for Windows. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.
Confounding factors used in adjusted models	age, tumour size, histology, grading, multifocality, histotype, presence of lymphovascular invasion, nodal status, oestrogen and progesterone receptor status, oncogene HER-2 and Ki-67 expression
Adjustment	Partially adjusted
Additional comments	• Data extracted was HR and 95% CI from multivariate analysis (reference margin was >2 mm). • 526 women had intraoperative re-excision during initial surgery. • 142 women had second surgery for positive or close margins. • n=35 with positive margins, n=40 with close margins did not receive second surgery.

Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	Mixed population Study does not report number of people receiving chemotherapy or endocrine therapy. The following information is from the methods section of Biglia 2014: "Patients with intermediate/high risk of relapse according to St Gallen criteria received adjuvant chemotherapy, with Anthracyclines or anthracyclines-taxanes regimens. Since 2006 all patients with HER-2 overexpression were treated with trastuzumab in association to chemotherapy. Patients with positive hormone receptors were prescribed adjuvant endocrine therapy in accordance to their menopausal status."
Invasive breast cancer with or without DCIS	Invasive breast cancer without DCIS (study states as such or that DCIS <25%) DCIS 3.7%

Study arms

≤2 mm (N = 40)

Patients with close margins not undergoing further surgery were included in group C.

>2 mm (N = 1264)

Patients with negative margins ab initio after primary surgery or after further re-excision were included in group A.

Characteristics

Study-level characteristics

Characteristic	Study (N = 1339)
Age	
<50 years	n = 358 ; % = 26.7
> 50 years	n = 981 ; % = 73.3
DCIS present	n = 50 ; % = 3.7
Tumour size	
<= 20mm	n = 921 ; % = 68.8
>20 mm	n = 418 ; % = 31.2

Characteristic	Study (N = 1339)
Tumour grade	
Grade 1	n = 201 ; % = 15
Grade 2	n = 560 ; % = 41.8
Grade 3	n = 578 ; % = 43.2
Histological tumour type	
Infiltrating ductal carcinoma	n = 1072 ; % = 80
Infiltrating lobular carcinoma	n = 200 ; % = 15
Lymphovascular involvement/invasion	
Present	n = 939 ; % = 70.1
Absent	n = 400 ; % = 29.9
Menopausal status	
Premenopausal	n = 435 ; % = 32.5
Postmenopausal	n = 903 ; % = 67.5

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns *(Partially adjusted (adjusted factors: age, tumour size, histology, grading, multifocality, histotype, presence of lymphovascular invasion, nodal status, oestrogen and progesterone receptor status, oncogene HER-2 and Ki-67 expression). Moderate risk of bias due to post-exposure interventions.)*
Overall bias	Directness	Directly applicable

Bodilsen, 2016

Bibliographic Reference	Bodilsen, Anne; Offersen, Birgitte V; Christiansen, Peer; Overgaard, Jens; Pattern of relapse after breast conserving therapy, a study of 1519 early breast cancer patients treated in the Central Region of Denmark 2000-2009.; Acta oncologica (Stockholm, Sweden); 2016; vol. 55 (no. 8); 964-9

Study details

Trial registration number and/or trial name	Danish Breast Cancer Cooperative Group
Study type	Retrospective cohort study
Study location	Denmark
Study setting	Population based regional cohort
Study dates	Between 2000 and 2009
Inclusion criteria	Inclusion criteria • Women <75 years • Diagnosed with unilateral, invasive breast cancer • Treated with breast conserving surgery and radiotherapy • No prior history of cancer
Exclusion criteria	Exclusion criteria • Underwent mastectomy within 2 months of breast conserving surgery • Incomplete data or margin width • Received neoadjuvant radiotherapy • Less than 3 months follow-up
Intervention(s)	Breast conserving surgery (lumpectomy + radiotherapy)
Outcome measures	Distant recurrence Distant recurrence without definition
Number of participants	1519 participants
Duration of follow-up	Median 5.3 years
Methods of analysis	A competing risk approach was used to calculate the cumulative incidence of DM. Competing risk factors were IBTR, RR, new primary breast cancer, other malignancy, and death. DFS was defined as survival time without breast cancer recurrence. Both unadjusted and adjusted hazard rates were calculated using Cox proportional hazards regression. Results are presented with 95% confidence intervals (95% CI), and p-values <0.05 were considered statistical significant. Stata version 12 was used for analyses.
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted

Additional comments	• Extracted data was unadjusted hazard ratio and 95% CI (reference margin was ≥5 mm) • n=178 had re-excision surgery • n=447 had radiotherapy boost
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	with chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer 75% of the total population had adjuvant systemic therapy
Invasive breast cancer with or without DCIS	Invasive breast cancer without DCIS (study states as such or that DCIS <25%) DCIS 11%

Study arms

>0 to 1 mm (N = 33)

≥5 mm (N = 1392)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1519)**
Radiotherapy Boost	n = 447 ; % = 29
Tumour size	
≤ 20mm	n = 1096 ; % = 72
>20mm	n = 421 ; % = 28
Tumour grade	
I to II (including tubular carcinoma)	n = 1012 ; % = 69
III	n = 332 ; % = 23
Special subtypes, not graded	n = 128 ; % = 9
Histological tumour type	
Ductal carcinoma NST	n = 1287 ; % = 25

Characteristic	Study (N = 1519)
Lobular	n = 96 ; % = 6
Special subtypes	n = 128 ; % = 8
Unknown	n = 8 ; % = 0.53
Lymphovascular involvement/invasion	
Yes	n = 174 ; % = 12
No	n = 1324 ; % = 88
Unknown	n = 21 ; % = 1.38

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis and risk of bias due to measurement of the outcome.)*
Overall bias	Directness	Directly applicable

Goldstein, 2003

Bibliographic Reference	Goldstein, Neal S; Kestin, Larry; Vicini, Frank; Factors associated with ipsilateral breast failure and distant metastases in patients with invasive breast carcinoma treated with breast-conserving therapy. A clinicopathologic study of 607 neoplasms from 583 patients.; American journal of clinical pathology; 2003; vol. 120 (no. 4); 500-27

Study details

Study type	Retrospective cohort study
Study location	US
Study setting	Hospital
Study dates	Between 1980 and 1996
Inclusion criteria	Inclusion criteria • Participants with invasive breast carcinoma treated with breast conserving surgery
Intervention(s)	Breast conserving surgery (lumpectomy + radiotherapy)

Outcome measures	Local recurrence Ipsilateral Breast Failure was defined as a distinct invasive carcinoma in the treated breast after the completion of radiation therapy Distant recurrence Distant metastasis without definition
Number of participants	• 583 participants • n=607 tumours
Duration of follow-up	Mean 8.6 years Median 8.7 years
Methods of analysis	Estimated likelihood of events for local recurrence and disease-free survival, overall survival, distant metastasis–free survival, and cause-specific survival were calculated by the Kaplan-Meier method. Associations between factors were analyzed using the Fisher exact test (2-tailed), logistic regression, and linear regression. Associations between clinical, pathologic, and treatment-related variables and clinical events were analyzed using logistic regression and Cox regression. Statistical significance between actuarial outcome and survival curves was calculated with the logrank test. Multivariate analysis was performed using the Cox proportional hazards model. A P value of .05 was considered a statistically significant association. Statistical analysis was performed using Systat, version 10 (SPSS, Chicago, IL).
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	Extracted data was unadjusted percentage rates for local recurrence and distant metastasis at 5 and 12 years. Goldstein reports data for local recurrence and distant metastasis for larger margins that we did not extract because the study reported data comparing to radial margins 2.1 to 3.0 which was a margin closer to the margin listed in the protocol: • Radial margin 3.1 to 5.0 mm • Radial margin 5.1 to 10.0 • Radial margin ≥10 mm

	NOTE: Information obtained from the last surgical excision specimen was the final margin. The status of the final surgical margin was known in 602 cases (99.2%). Of the invasive carcinomas: • 333 (55.3%) had negative final margins • 231 cases (38.4%) had near final margins • 38 (6.3%) had positive final margins Of the 231 carcinomas with near final margins: • 82 (35.5%) had only DCIS near the final margin • 68 (29.4%) had only invasive carcinoma near the final margin • 81 (35.1%) had invasive and in situ carcinoma near the margin Of the 38 carcinomas with positive final margin carcinomas: • 9 (24%) had only DCIS at the final margin • 17 (45%) had only invasive carcinoma at the final margin • 12 (32%) had invasive and in situ carcinoma at the final margin
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	without chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer 17% had adjuvant chemotherapy (n=102 out of 594)
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS 35.5% or less

Study arms

0.1 to 1.0 mm (N = 94)

1.1 to 2.0 mm (N = 45)

2.1 to 3.0 (N = 59)

Characteristics

Study-level characteristics

Characteristic	Study (N = 583)
Age	
> 50 years	n = 102 ; % = 17
<50 years	n = 505 ; % = 83
Tumour size	
≤ 2cm	n = 404 ; % = 67
>2cm	n = 203 ; % = 33
Tumour grade	
Grade 1	n = 241 ; % = 40
Grade 2	n = 194 ; % = 32
Grade 3	n = 137 ; % = 28

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis.)*
Overall bias	Directness	Directly applicable

Kreike, 2008

Bibliographic Reference	Kreike, Bas; Hart, Augustinus A M; van de Velde, Tony; Borger, Jacques; Peterse, Hans; Rutgers, Emiel; Bartelink, Harry; van de Vijver, Marc J; Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up.; International journal of radiation oncology, biology, physics; 2008; vol. 71 (no. 4); 1014-21

Study details

Study type	Retrospective cohort study
Study location	The Netherlands
Study setting	Single cancer institute

Study dates	Between 1979 - 1988
Sources of funding	Grant from Dutch Cancer Society
Inclusion criteria	Inclusion criteria • Participants with type I-II invasive breast cancer treated with breast conserving surgery
Intervention(s)	Breast conserving surgery (lumpectomy + radiotherapy)
Outcome measures	Local recurrence Ipsilateral breast relapse (IBR) that occurred as the first site of failure were counted, censoring those patients with regional or distant failure occurring before the IBR. When the IBR occurred within three months simultaneously with regional or distant failure, this was considered local failure
Number of participants	1024 participants
Duration of follow-up	Median 13.3 years
Methods of analysis	A step-wise proportional hazard Cox regression analysis was used to identify the risk factors associated with an increased risk of IBR. Only IBRs that occurred as the first site of failure were counted, censoring those patients with regional or distant failure occurring before the IBR. When the IBR occurred within three months simultaneously with regional or distant failure, this was considered local failure. Variables that were supplied numerically were used in the analysis in a linear fashion (i.e., age, interval between surgery and the start of RT, interval between the end of whole breast RT and the start of boost RT). All other variables were used as ordinal or nominal variables ordered. A step-wise method for building the Cox regression model was used to overcome the problem of losing power in the analysis because of missing data. A Kaplan-Meier analysis was performed to identify any association between IBR and distant disease-free survival and between IBR and overall survival. Statistical analyses were performed in a similar fashion using Statistical Package for Social Sciences software, version 12 (SPSS, Chicago, IL).
Confounding factors used in adjusted models	Age, vascular invasion, and quantity and type of in situ component
Adjustment	Partially adjusted
Additional comments	Extracted data was hazard ratio and 95% CI from Cox regression model for ipsilateral breast relapse as first event (reference was margin ≥1 mm)

Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	without chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer 17.5% or less with chemotherapy or endocrine therapy
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS 51.3%

Study arms

within 1 mm (N = 161)

It was scored as a doubtful tumour-free margin when the tumour lesion reached within 1 mm from the margin.

≥1 mm (N = 485)

The margin was scored as free of tumour when a border of ≥1 mm of healthy tissue surrounded the tumour.

Characteristics

Study-level characteristics

Characteristic	Study (N = 1024)
Age	
<41 years	n = 223 ; % = 22
41-50 years	n = 344 ; % = 34
<50 years	n = 457 ; % = 45
Tumour size	
0 to 2cm	n = 824 ; % = 80
> 2cm	n = 183 ; % = 18

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns *(Partially adjusted (adjusted factors: age, vascular invasion, and quantity and type of in situ component). Moderate risk of bias due to measurement of exposure and selection of reported result.)*
Overall bias	Directness	Directly applicable

Lupe, 2011

Bibliographic Reference	Lupe, Krystine; Truong, Pauline T; Alexander, Cheryl; Lesperance, Mary; Speers, Caroline; Tyldesley, Scott; Subsets of women with close or positive margins after breast-conserving surgery with high local recurrence risk despite breast plus boost radiotherapy.; International journal of radiation oncology, biology, physics; 2011; vol. 81 (no. 4); e561-8

Study details

Study type	Retrospective cohort study
Study location	Canada
Study setting	Hospitals and cancer centres
Study dates	July 2001 to December 2003
Inclusion criteria	Inclusion criteria • Women with pT1-3, any pN, M0 invasive breast cancer • Treated with breast conserving surgery and radiotherapy (with or without boost)
Exclusion criteria	Exclusion criteria • Women who underwent complete mastectomy • Women who did not receive whole breast radiotherapy • Received partial radiotherapy or any other nonstandard radiotherapy technique • Margin or disease state undetermined
Intervention(s)	Breast conserving surgery + whole breast radiotherapy (with or without boost)
Outcome measures	Locoregional recurrence Regional recurrence without definition

	Local recurrence Local recurrence defined as the first site of recurrence in the ipsilateral breast Distant recurrence Distant recurrence without definition Overall survival Overall survival without definition Breast cancer specific survival Breast cancer specific survival without definition
Number of participants	2264 participants
Duration of follow-up	Median 5.2 years
Methods of analysis	Clinicopathologic characteristics were compared between cohorts with negative, close, and positive margins using chi-square tests. Kaplan-Meier (KM) and log-rank statistics were used to estimate and compare 5-year recurrence and survival outcomes according to margin status and clinicopathologic characteristics. Multivariable analysis of LR in the entire cohort was performed using Cox regression modeling. Because of the limited number of LR events in the data set, we were not able to include a large number of variables in the Cox modeling. Our variable selection was guided by Harrell's regression modeling principles, which advocated the use of substantive knowledge and experience over automated stepwise techniques. The selection of variables in our Cox regression modeling was thus based on clinical and statistical judgment as well as prior published work on prognostic factors for local recurrence. With the small number of LR events, we were not able to restrict the multivariable analysis to only patients with close or positive margins and exclude those with negative margins. To account for heterogeneous distributions of prognostic variables in the negative compared with close and positive margin cohorts, a 2:1 matched analysis was performed. For each case in the close or positive margin group (n = 284), two matches were selected from the negative margin reference group. Cases were matched sequentially for the number of positive nodes, grade, LVI status, age, T size, ER status, histology, use of RT boost, and use of systemic therapy. Matching proceeded with software that first attempted to match participants on all nine variables. If the required matches were found, they were selected and removed from the reference group. If there was no match in the reference group for all nine variables, the last variable in the list was dropped and a match on the remaining eight variables was sought. The program proceeded iteratively in this fashion until the required number of matches was found. Kaplan-Meier (KM) survival curves were generated for the close/positive margin cases and negative margin controls and compared

	using log-rank statistics. All statistical tests were two-sided, with significance established at $p < 0.05$. Statistical computations were performed using SPSS version 17.0 and R 2.8.1.
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	Extracted data was percentage rates and standard error of local recurrence, regional recurrence, distant recurrence, breast cancer specific survival and overall survival.
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	with chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer systemic therapy 84.6%
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS 28.8% in people with margin <2 mm

Study arms

<2 mm (N = 222)

Defined as close margin

≥2 mm (N = 1980)

Defined as negative margin

Characteristics

Arm-level characteristics

Characteristic	<2 mm (N = 222)	≥2 mm (N = 1980)
Age		
< 45 years	n = 33 ; % = 14.9	n = 242 ; % = 12.2
Tumour grade		
grade III	n = 71 ; % = 32	n = 569 ; % = 28.7
Histological tumour type		

Characteristic	<2 mm (N = 222)	≥2 mm (N = 1980)
T2	n = 78 ; % = 35.1	n = 508 ; % = 25.7
Lymphovascular involvement/invasion	n = 62 ; % = 27.9	n = 321 ; % = 16.2

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis and risk of bias from measurement of the outcome.)*
Overall bias	Directness	Directly applicable

Maishman, 2017

Bibliographic Reference	Maishman, Tom; Cutress, Ramsey I; Hernandez, Aurea; Gerty, Sue; Copson, Ellen R; Durcan, Lorraine; Eccles, Diana M; Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study.; Annals of surgery; 2017; vol. 266 (no. 1); 165-172

Study details

Trial registration number and/or trial name	Prospective Study of Outcomes in Sporadic versus Hereditary breast cancer (POSH)
Study type	Prospective cohort study
Study location	UK
Study setting	Multicentre, hospital
Study dates	Between 2000 to 2008
Sources of funding	Cancer Research UK, University Hospital Southampton NHS Foundation Trust
Inclusion criteria	Inclusion criteria • Women aged 18-40 years at breast cancer diagnosis • Diagnosed in the UK between 2000 and 2008
Exclusion criteria	Exclusion criteria • Metastatic disease at presentation

Intervention(s)	Breast conserving surgery with or without radiotherapy
Outcome measures	Local recurrence Ipsilateral local-recurrence interval was defined as time from date of diagnosis to date of local recurrence (either an ipsilateral recurrence or ipsilateral new primary, whichever event occurred first after breast conserving surgery or chest-wall recurrence after mastectomy) Distant recurrence Distant disease-free interval was defined as time from breast cancer diagnosis to distant metastases or death from breast cancer; deaths from other causes were censored at the time of death
Number of participants	1395
Duration of follow-up	Median 7.3 years
Methods of analysis	Summary statistics were used to describe the cohort and key characteristics were compared by surgical type using Pearson x2 tests or Mann-Whitney U tests. All reported P-values were 2-sided. Study endpoints were in breast ipsilateral local-recurrence interval (LRI), distant disease-free interval (DDFI), and overall survival (OS). LRI was defined as time from date of diagnosis to date of local recurrence (either an ipsilateral recurrence or ipsilateral new primary, whichever event occurred first after BCS or chest-wall recurrence after mastectomy). The local-recurrence event was counted as an event if the date of the non-event (death from breast cancer, distant metastases, ipsilateral local axillary recurrence, ipsilateral regional nodes recurrence, and/or contralateral recurrence, if/where applicable) was >3 months after the date of the local-recurrence event. If the date of the non-event was 3 months after the local recurrence event then the patient was censored at the date of non-event. Deaths from other cancers after local recurrence did not affect the event. DFFI was defined as time from breast cancer diagnosis to distant metastases or death from breast cancer; deaths from other causes were censored at the time of death. OS was defined as time from breast cancer diagnosis to death from any cause. Nelson-Aalen cumulative-hazard plots were used to describe LRI and Kaplan-Meier plots were used to describe DDFI and OS. Univariable analyses (UVA) and multivariable analyses (MVA) were carried out using Cox proportional-hazards models, or Flexible Parametric Survival Models (FPSMs) for models which involved time-varying hazards. Covariates included in the MVA models included age at diagnosis (fitted as a continuous variable), tumor size, focality, nodal (N) stage, histological grade, ER and HER2 tumor status, adjuvant radiotherapy, adjuvant hormone therapy, and surgical margins, regardless of significance. Patients treated with neoadjuvant chemotherapy were included in UVA but excluded from all MVA because of difficulties in classifying pathological T and N staging for these patients. For each FPSMs, we explored varying degrees of freedom for the baseline-hazard rate and time-dependent effect to obtain the best model fit. All

	analyses were performed using STATA v13.1 (StataCorp, College Station, TX, USA) on records with complete data (levels of missing data were reported).
Confounding factors used in adjusted models	Age, T stage, N stage, histology, boost dose radiotherapy, focality
Adjustment	Partially adjusted
Additional comments	• Extracted data for distant recurrence and local recurrence was taken from Bundred 2022 (figure 2 and figure 3; respectively; reference margin was >2 mm). • Study reported on cohorts of women who received a mastectomy or those receiving breast conserving surgery. Only data for the breast conserving surgery population was extracted. • 24.5% of margin status data is missing • 11.1% had neoadjuvant chemotherapy
Radiotherapy status	Radiotherapy 96.0% had adjuvant radiotherapy
Age	Less than 50 years old median age 36 years (range 19 to 40 years)
Subsequent systemic treatment	with chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer 75.6% had adjuvant chemotherapy and 60.1% had adjuvant hormone therapy
Invasive breast cancer with or without DCIS	DCIS percentage not reported DCIS percentage not reported only that invasive + in situ was reported for tumour size

Study arms

0.1 to 2 mm (N = 375)

0.1 to 1 mm (N = 234)

1.1 to 2 mm (N = 234)

>2 mm (N = 563)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1395)
Mean age (SD) Median (IQR)	36 (34 to 38)
Family history	
Yes	n = 640 ; % = 48.1
No	n = 690 ; % = 51.9
Missing	n = 65 ; % = 4.7
Race	
White	n = 1284 ; % = 93.2
Black	n = 44 ; % = 3.2
Asian	n = 41 ; % = 3
Other	n = 9 ; % = 0.7
Missing	n = 17 ; % = 1.2
Chemotherapy	n = 155 ; % = 11.1
Tumour grade	
Grade 1	n = 93 ; % = 6.8
Grade 2	n = 429 ; % = 31.3
Grade 3	n = 848 ; % = 61.9
Missing	n = 25 ; % = 1.8
Histological tumour type	

Characteristic	Study (N = 1395)
Ductal	n = 44 ; % = 3.2
Lobular	n = 24 ; % = 1.7
Ductal and lobular	n = 24 ; % = 1.7
Other	n = 97 ; % = 7
Lymphovascular involvement/invasion	
Absent	n = 784 ; % = 59.9
Present	n = 524 ; % = 40.1
Missing	n = 87 ; % = 6.2

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns (*Partially adjusted (adjusted factors: Age, T stage, N stage, histology, boost dose radiotherapy, focality))*
Overall bias	Directness	Directly applicable *(11.1% had neoadjuvant chemotherapy)*

Peterson, 1999

Bibliographic Reference	Peterson, M E; Schultz, D J; Reynolds, C; Solin, L J; Outcomes in breast cancer patients relative to margin status after treatment with breast-conserving surgery and radiation therapy: the University of Pennsylvania experience.; International journal of radiation oncology, biology, physics; 1999; vol. 43 (no. 5); 1029-35

Study details

Study type	Prospective cohort study
Study location	US
Study setting	Single Centre
Study dates	Between 1977 to 1992
Sources of funding	National Cancer Institute Grants
Inclusion criteria	Inclusion criteria • Women with clinical stage 1 and 2 invasive breast cancer

	• Treated with breast conserving surgery and radiation therapy
Intervention(s)	Breast conserving surgery + radiotherapy (with or without boost)
Outcome measures	Locoregional recurrence “Any local-regional failure” was defined as a local and/or regional failure that occurred at any time during follow-up regardless of distant disease status. Regional failure was defined as a failure that occurred in the ipsilateral axillary, supraclavicular, infraclavicular, and/or internal mammary nodal regions Local recurrence Local failure was defined as a failure that occurred within the treated breast Distant recurrence Freedom from distant metastases. Distant failure was defined as a failure that was beyond local or regional disease Overall survival Overall survival without definition Breast cancer specific survival Cause-specific survival without definition
Number of participants	1021 participants
Duration of follow-up	Median 6.1 years
Methods of analysis	Survival curves were determined using the Kaplan-Meier method. The Mantel-Cox test was used for statistical comparison between curves.
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	Extracted data for local recurrence was taken from Bundred 2022 (figure 3; reference margin was >2 mm). Percentage rates were extracted for locoregional recurrence, distant recurrence, overall survival and breast cancer specific survival from Peterson 1999
Radiotherapy status	Radiotherapy
Age	Mixed population

Subsequent systemic treatment	Mixed population 37% or less with chemotherapy or hormone therapy
Invasive breast cancer with or without DCIS	DCIS percentage not reported DCIS percentage not reported only that both invasive carcinoma and ductal carcinoma in situ (but not lobular carcinoma in situ) were considered for the determination of margin status

Study arms

≤2 mm (N = 96)

Margins were considered focally close if one or two foci of tumour were 2 mm or less from the post-surgically applied inked margin.

>2 mm (N = 518)

A surgical margin was diagnosed as negative if all tumour was >2 mm from the surgical margin.

Characteristics

Arm-level characteristics

Characteristic	≤2 mm (N = 96)	>2 mm (N = 518)
Age		
≤ 35 years	n = 6 ; % = 6	n = 39 ; % = 8
36-50 years	n = 32 ; % = 33	n = 191 ; % = 37
≥ 51 years	n = 75 ; % = 60	n = 288 ; % = 55
Tumour size		
≤ 1cm	n = 19 ; % = 20	n = 81 ; % = 16
1.1 to 2cm	n = 28 ; % = 29	n = 162 ; % = 31
2.1 to 3cm	n = 20 ; % = 21	n = 96 ; % = 19
3.1 to 4cm	n = 9 ; % = 9	n = 24 ; % = 5
4.1 to 5cm	n = 1 ; % = 1	n = 4 ; % = 1
Unknown	n = 19 ; % = 20	n = 151 ; % = 29
Histological tumour type		
Ductal	n = 88 ; % = 92	n = 463 ; % = 89
Lobular	n = 4 ; % = 4	n = 18 ; % = 3

Characteristic	≤2 mm (N = 96)	>2 mm (N = 518)
Other	n = 4 ; % = 4	n = 37 ; % = 7
Menopausal status		
Premenopausal	n = 26 ; % = 27	n = 187 ; % = 36
Perimenopausal	n = 10 ; % = 10	n = 33 ; % = 6
Postmenopausal	n = 60 ; % = 63	n = 298 ; % = 58

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Very high risk *(Unadjusted analysis; critical risk of bias due to measurement of the exposure (27.7% missing margin data); and serious/critical risk of bias due to missing data used as part of analysis inappropriately.)*
Overall bias	Directness	Directly applicable

Smith, 2014

Bibliographic Reference	Smith, Sally L; Truong, Pauline T; Lu, Linghong; Lesperance, Mary; Olivotto, Ivo A; Identification of patients at very low risk of local recurrence after breast-conserving surgery.; International journal of radiation oncology, biology, physics; 2014; vol. 89 (no. 3); 556-62

Study details

Study type	Retrospective cohort study
Study location	Canada
Study setting	Hospital
Study dates	Between 1989 to 2006
Inclusion criteria	Inclusion criteria • Women => 50 years • pT1 pN0 invasive breast cancer • Treated with breast conserving surgery and whole breast radiotherapy
Exclusion criteria	Exclusion criteria • In situ breast cancer

	• Node positive disease • Unknown nodal disease • Distant metastases • Treatment with mastectomy • No adjuvant whole breast radiotherapy
Intervention(s)	Breast conserving surgery with radiotherapy (with or without boost)
Outcome measures	Local recurrence Local recurrence defined as the first site of tumor recurrence in the ipsilateral breast
Number of participants	5974 participants
Duration of follow-up	Median 8 years
Methods of analysis	Multivariable analyses using the Cox proportional hazards model was used to determine factors associated with LR and LRR risk. Recursive partitioning analysis (RPA) of the time to LR was conducted to identify groups with an LR risk 1.5% at 5 years. Because clinical practice shifted to the use of sentinel lymph node biopsy alone during the treatment era, the number of lymph nodes removed was not included in this portion of the analysis. All patients received whole-breast RT. Due to concerns about reliability of boost RT information in the dataset, the variable of boost RT was not included in the analysis. Five- and 10-year risks of LR and LRR were estimated using Kaplan Meier methods, and the associated standard errors were computed for the groups identified with 5-year LR and LRR 1.5%. Statistical analyses were performed using R software survival.
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	Extracted data was number of events of local recurrence
Age	Mixed population
Subsequent systemic treatment	Mixed population 47.8% without systemic therapy
Invasive breast cancer with or without DCIS	Invasive breast cancer without DCIS (study states as such or that DCIS <25%) DCIS was excluded

Study arms

<2 mm (N = 201)

Defined as close margin <2 mm. This does not include positive. Positive margin was defined as tumour touching ink. Close and positive margins were combined as positive/close but that combination is not relevant to us.

≥2 mm (N = 5397)

Defined as negative margin ≥2 mm.

Characteristics

Study-level characteristics

Characteristic	Study (N = 5974)
Mean age (SD) Median (IQR)	63 (50 to 91)
Tumour grade	
Grade 1	n = 1929 ; % = 32.3
Grade 2	n = 2709 ; % = 45.3
Grade 3	n = 1166 ; % = 19.5
Unknown	n = 170 ; % = 2.8
Histological tumour type	
Ductal	n = 5515 ; % = 92.3
Lobular	n = 423 ; % = 7.1
Other	n = 36 ; % = 0.6
Lymphovascular involvement/invasion	
Present	n = 614 ; % = 10.3
Absent	n = 5181 ; % = 86.7
Unknown	n = 179 ; % = 3
Menopausal status	
Premenopausal	n = 498 ; % = 8.3
Postmenopausal	n = 5395 ; % = 90.3
Unknown	n = 81 ; % = 1.4

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis and risk of bias due to selection of participants.)*
Overall bias	Directness	Directly applicable

Smitt, 2003

Bibliographic Reference	Smitt, Melanie C; Nowels, Kent; Carlson, Robert W; Jeffrey, Stefanie S; Predictors of reexcision findings and recurrence after breast conservation.; International journal of radiation oncology, biology, physics; 2003; vol. 57 (no. 4); 979-85

Study details

Study type	Retrospective cohort study
Study location	US
Study setting	Hospital
Study dates	Between 1972 to 1996
Inclusion criteria	Inclusion criteria • Women with stage 1 or 2 invasive breast cancer • Treated with breast conserving surgery and radiation
Intervention(s)	Breast conserving surgery with radiotherapy (with or without boost)
Outcome measures	Local recurrence Local recurrence without definition
Number of participants	397 participants
Duration of follow-up	The mean follow-up for surviving patients without local or distant recurrence is 6 years (median 5 years). The mean follow-up for the patients with non-negative margins is 7.5 years.
Methods of analysis	The actuarial probability of freedom from local recurrence as a first failure was calculated using the Kaplan-Meier method. Analysis of potential prognostic factors was performed using Cox regression analysis (SPSS, Inc., Chicago, IL). Factors were included in the forward conditional Cox multivariate analysis if the univariate p value was <=0.05. For variables found to have independent prognostic value (p 0.05) by multivariate analysis, the hazard ratio (HR) with the 95% confidence interval (CI) was calculated. Association between patient

	characteristics was determined with the chi-square test, and significance of correlations was assessed with Pearson's coefficient.
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	Extracted data was crude recurrence rather than 6-year actuarial recurrence because overall survival was not reported to back calculate number of events from people who survived at 6 years.
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	Mixed population 242 participants did not receive systemic therapy (45% of n=535)
Invasive breast cancer with or without DCIS	DCIS percentage not reported DCIS percentage not reported only that margin status was classified on the initial and reexcision specimens as positive when invasive or in situ disease was seen at an inked surgical margin

Study arms

≤2 mm (N = 55)

Margin was defined as close when tumour cells were ≤2 mm from the ink. Close margin did not include tumour at ink. Tumour at ink was a separate category called positive (n=28).

≥2 mm (N = 342)

Margin was defined as negative if tumour was ≥2 mm from the inked margin.

Characteristics

Study-level characteristics

Characteristic	Study (N = 535)
Age	
<50 years	n = 197 ; % = 36.8
> 50 years	n = 338 ; % = 63.2

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis and risk of bias due to post-exposure interventions and serious risk of bias due to 20% missing margin data.)*
Overall bias	Directness	Directly applicable

Tang, 2019

Bibliographic Reference	Tang, S S K; Rapisarda, F; Nerurkar, A; Osin, P; MacNeill, F; Smith, I; Johnston, S; Ross, G; Mohammed, K; Gui, G P H; Complete excision with narrow margins provides equivalent local control to wider excision in breast conservation for invasive cancer.; BJS open; 2019; vol. 3 (no. 2); 161-168

Study details

Study type	Retrospective cohort study
Study location	UK
Study setting	Single centre
Study dates	Between 1997 to 2007
Sources of funding	Joint BASO - Association of Cancer Surgery and Royal College of Surgeons Cancer Research UK
Inclusion criteria	Inclusion criteria • Women with invasive breast cancer treated with breast conserving surgery
Exclusion criteria	Exclusion criteria • Initial surgery performed at different hospital • Did not receive radiotherapy
Intervention(s)	Breast conserving surgery + radiotherapy
Outcome measures	Local recurrence A true local recurrence was determined by the presence of a subsequent carcinoma of similar biology (grade and receptor status) within the same quadrant of the breast as the first presenting carcinoma

Number of participants	1045 participants
Duration of follow-up	Median 89 months
Methods of analysis	The Cox proportional hazard regression model was used to compare the hazards of patients in each group, using univariable models. A two-sided 5 per cent α level was used to assess statistically significant difference in the models. A multivariable model was used to identify the independent predictors of local recurrence and disease-free survival. Variables found to be significant at P ≤0·200 in the univariable model were included in a forward stepwise method, which was used to fit the multivariable model. SPSS® version 16.0 (IBM, Armonk, New York, USA) was used for statistical analysis. The Kaplan–Meier method was used to calculate the time to local recurrence and disease-free survival from the date of wide local excision. Diagnosis of local recurrence in the ipsilateral breast was the defining event for time to local recurrence; axillary recurrence, supraclavicular fossa (SCF) recurrence, metastasis and death without local recurrence were censored as independent events. For disease-free survival, defining events included local recurrence, axillary recurrence, SCF recurrence, metastasis and death from any cause. Patients who were alive and disease-free or lost to follow-up were censored at the date of their last follow-up or upon discharge.
Confounding factors used in adjusted models	age, tumour size, grade, oestrogen receptor status and final node grouping
Adjustment	Partially adjusted
Additional comments	Extracted data was hazard ratio and 95% CI from Cox multivariable analysis of local recurrence (reference was margin ≥1 mm)
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	Not reported
Invasive breast cancer with or without DCIS	Invasive breast cancer without DCIS (study states as such or that DCIS <25%) DCIS was not reported only that a database of patients with invasive breast cancer treated by breast conserving surgery

Study arms

<1 mm (N = 110)

Defined as close (less than 1mm but no ink on tumour).

≥1 mm (N = 798)

Defined as clear (1mm or more).

Characteristics

Study-level characteristics

Characteristic	Study (N = 1045)
Age	
< 50 years	n = 346 ; % = 33.1
≥ 50 years	n = 699 ; % = 66.9
Tumour size	
≤2cm	n = 667 ; % = 63.8
>2cm	n = 372 ; % = 35.6
Tumour grade	
Grade 1	n = 160 ; % = 15.3
Grade 2	n = 463 ; % = 44.3
Grade 3	n = 420 ; % = 40.2
Lymphovascular involvement/invasion	
No	n = 699 ; % = 66.9
Yes	n = 333 ; % = 31.9

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns *(Partially adjusted (adjusted factors: age, tumour size, grade, oestrogen receptor status and final node grouping). Moderate risk of bias due to post-exposure interventions.)*
Overall bias	Directness	Directly applicable

Tyler, 2018

Bibliographic Reference	Tyler, Susan; Truong, Pauline T; Lesperance, Mary; Nichol, Alan; Baliski, Chris; Warburton, Rebecca; Tyldesley, Scott; Close Margins Less Than 2 mm Are Not Associated With Higher Risks of 10-Year Local Recurrence and Breast Cancer Mortality Compared With Negative Margins in Women

Treated With Breast-Conserving Therapy.; International journal of radiation oncology, biology, physics; 2018; vol. 101 (no. 3); 661-670

Study details

Study type	Retrospective cohort study
Study location	Canada
Study setting	Hospital, population based single-province
Study dates	Between 2001 and 2011
Inclusion criteria	Inclusion criteria • Women with pT1-T3, pN0-N3, M0 invasive breast cancer • Treated with breast conserving surgery + radiotherapy
Exclusion criteria	Exclusion criteria • Ductal carcinoma in situ • Neoadjuvant chemotherapy • Partial breast radiotherapy
Intervention(s)	Breast conserving surgery + radiotherapy (with or without boost)
Outcome measures	Local recurrence Local recurrence defined as initial recurrence within the ipsilateral breast Breast cancer specific survival Breast cancer specific survival defined as death due to breast cancer
Number of participants	10,863 participants
Duration of follow-up	Median 8 years (10 year follow-up in plan)
Methods of analysis	The outcomes evaluated were LR, defined as initial recurrence within the ipsilateral breast, and BCSS, defined as death due to breast cancer. Clinicopathologic and treatment characteristics were compared between cohorts stratified by margin status (negative, close, or positive) using c2 tests. Competing-risk cumulative incidence analyses were performed to provide estimates and comparisons of 10-year rates of LR and BCSS stratified by margin status and clinicopathologic characteristics. Competing-risk analysis was used as this statistical method analyzes LR in clinical scenarios in which death is considered a competing event. To compare cumulative incidences of LR and BCSS in the entire cohort, Gray tests were performed. Multivariable analysis of LR and BCSS in the entire cohort was performed with competing-risk Fine and Gray modeling. Harrell's regression modeling principles advocated for use of experience and substantive knowledge over automated stepwise techniques.

	Accordingly, our selection of variables for inclusion in the multivariable modeling was guided by previously published work on prognostic factors for LR. The variables were margin status, age, grade, lymphovascular invasion (LVI), number of positive nodes, use of boost RT, use of systemic therapy, and breast cancer subtype. Given the heterogeneous distribution of prognostic variables in the negative margin cohort versus the close or positive margin cohort, a 1:1 matched analysis was performed. For each case in the close or positive margin cohort with known data for all prognostic variables, 1 match was selected from the reference negative margin cohort. Case matching was sequential, based on age at diagnosis, T category, number of involved nodes, histology, grade, LVI, estrogen receptor status, RT boost use, and systemic therapy use. Data on margin location were available in a subset of 2381 cases referred from January 1, 2010, to December 31, 2011. Descriptive analysis was performed in this cohort. All analyses were 2-sided with significance established at P < .05. Analysis was performed using SPSS software (version 17.0) and the R package (version 3.3.2). The study was approved by the institutional review board.
Confounding factors used in adjusted models	age, grade, lymphovascular invasion, number of positive nodes, use of boost radiotherapy, use of systemic therapy, and breast cancer subtype
Adjustment	Partially adjusted
Additional comments	Extracted data was hazard ratio and 95% CI from competing-risk multivariable analysis of local recurrence and breast cancer specific survival (reference was margin ≥2 mm)
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	Mixed population <52% had hormone therapy and <17% chemotherapy
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS percentage not reported only that the database lacked information regarding whether the pathologic disease representing the close or positive margins was invasive or in situ disease

Study arms

<2 mm (N = 1310)

Close margins were defined as tumour <2 mm from a margin but not touching ink.

≥2 mm (N = 9241)

Negative margins were defined as tumour ≥2 mm from the inked resection margin.

Characteristics

Arm-level characteristics

Characteristic	<2 mm (N = 1310)	≥2 mm (N = 9241)
Age		
< 45 years	n = 151 ; % = 11.5	n = 931 ; % = 10.1
≥ 45 years	n = 1159 ; % = 88.5	n = 8310 ; % = 89.9
Tumour grade		
pT1	n = 871 ; % = 66.5	n = 6819 ; % = 73.8
pT2	n = 423 ; % = 32.3	n = 2353 ; % = 25.5
pT3	n = 16 ; % = 1.2	n = 69 ; % = 0.7
Histological tumour type		
Ductal	n = 1200 ; % = 91.6	n = 8575 ; % = 92.8
Lobular	n = 105 ; % = 8	n = 618 ; % = 6.7
Other	n = 5 ; % = 0.4	n = 48 ; % = 0.5
Lymphovascular involvement/invasion		
No	n = 989 ; % = 75.5	n = 7608 ; % = 82.3
Yes	n = 290 ; % = 22.1	n = 1419 ; % = 15.4
Unknown	n = 31 ; % = 2.4	n = 214 ; % = 2.3
Menopausal status		
Premenopausal or perimenopausal	n = 385 ; % = 29.4	n = 2621 ; % = 28.4
Postmenopausal	n = 910 ; % = 69.5	n = 6539 ; % = 70.8
Unknown	n = 15 ; % = 1.1	n = 81 ; % = 0.9

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns (*Partially adjusted (adjusted factors: age, grade, lymphovascular invasion, number of positive nodes, use of boost radiotherapy, use of systemic therapy, and breast cancer subtype))*

Section	Question	Answer
Overall bias	Directness	Directly applicable

Varghese, 2008

Bibliographic Reference	Varghese, P; Gattuso, J M; Mostafa, A I H; Abdel-Rahman, A T; Shenton, K C; Ryan, D A; Jones, J L; Wells, C A; Mair, G; Kakkar, A K; Carpenter, R; The role of radiotherapy in treating small early invasive breast cancer.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2008; vol. 34 (no. 4); 369-76

Study details

Study type	Retrospective cohort study
Study location	UK
Study setting	Hospital
Study dates	January 1990 to December 2004
Inclusion criteria	Inclusion criteria • Early breast cancer with invasive tumours <=1cm (T1b or lower) • Treated with breast conserving surgery
Exclusion criteria	Exclusion criteria • Required mastectomy to clear margins
Intervention(s)	Breast conserving surgery + radiotherapy
Outcome measures	Local recurrence Ipsilateral breast tumour recurrence was defined as reappearance of invasive tumour or DCIS in the treated breast
Number of participants	173 participants
Duration of follow-up	Median 9 to 11 years
Loss to follow-up	• Breast conserving surgery alone = 2 • Breast conserving surgery + radiotherapy = 3
Methods of analysis	Data was collected on tumour characteristics (age, grade, tumour size, presence of EIC, hormonal receptor status, use of RT and adjuvant endocrine therapy). This was tested for significance as univariate

	predictors for IBTR, regional and distant metastasis. Univariate analysis was done by the Pearson chi-squared test. Fisher's exact test was employed if any of the expected frequencies were less than five. All the P values reported were two-tailed. Relative risk (RR) and 95% confidence interval (CI) was calculated for the parameters. Multivariate logistic regression was used only if significant factors of IBTR were found on univariate analysis. Actuarial curves for IBTR, and survival were calculated using Kaplan Meier methods. A patient was censored from the calculation of IBTR at the time of last follow up, when lost to follow up, distant disease was detected and/or death occurred. Statistical analysis was performed using the SPSS 12.0 program (SPSS, Chicago, IL, USA).
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	Data was extracted separately for: • participants with only breast conserving surgery (relative risk and 95% CI for local recurrence; reference was margin ≥1 mm) • participants with breast conserving surgery and radiotherapy (number of events of local recurrence) Unclear if groups were balanced at baseline
Radiotherapy status	Mixed population Study reported data separately for participants with only breast conserving surgery and for participants with breast conserving surgery and radiotherapy
Age	Mixed population
Subsequent systemic treatment	with chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer >75% had hormonal therapy
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS 41.7%

Study arms

within 1 mm (N = 9)

A close margin required the presence of tumour cells within 1 mm of the inked margin.

≥1 mm (N = 152)

A negative/clear margin implied at least 1 mm of normal parenchyma between the tumour and the inked margin and no in-situ or invasive carcinoma within the shaved margin blocks.

Characteristics

Study reported baseline characteristics separately for breast conserving surgery alone (n=94) or breast conserving surgery with radiotherapy (n=79)

Characteristic	Breast conserving surgery alone (n=94)	Breast conserving surgery with radiotherapy (n=79)
Age		
< 50 years	n = 4	n = 13
50 to 60 years	n = 44	n = 39
50 to 60 years	n = 34	n = 24
> 70 years	n = 12	n = 3
Tumour size		
< 3 mm	n = 5	n = 3
3 to 5 mm	n = 15	n = 3
> 5 to 10 mm	n = 74	n = 73
Tumour type		
Infiltrating ductal carcinoma	n = 55	n = 59
Infiltrating lobular carcinoma	n = 3	n = 5
Tubular	n = 20	n = 7
Others	n = 16	n = 8
Associated DCIS	n = 43	n = 33
Lymphovascular involvement/invasion	n = 1	n = 3
Grade		
1	n = 54	n = 31
2	n = 30	n = 28
3	n = 7	n = 17
Not available	n = 3	n = 3
Oestrogen receptor		
Positive	n = 38	n = 16

Characteristic	Breast conserving surgery alone (n=94)	Breast conserving surgery with radiotherapy (n=79)
Not available	n = 54	n = 58
Number of operations		
1	n = 72	n = 56
> 1	n = 22	n = 23
Hormonal treatment	n = 74	n = 63

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis and risk of bias due to post-exposure interventions and selection of the reported results.)*
Overall bias	Directness	Directly applicable

Additional studies found by the systematic search carried out by NICE in 2023

Chae, 2022

Bibliographic Reference	Chae, Sumin; Min, Sun Young; Association of Surgical Margin Status with Oncologic Outcome in Patients Treated with Breast-Conserving Surgery.; Current oncology (Toronto, Ont.); 2022; vol. 29 (no. 12); 9271-9283

Study details

Study type	Retrospective cohort study
Study location	South Korea
Study setting	Cancer center
Study dates	Between 2003 - 2009
Inclusion criteria	Inclusion criteria • Women with newly diagnosed breast cancer treated with breast conserving surgery
Exclusion criteria	Exclusion criteria • Carcinoma in situ • Metastatic disease

	• Did not undergo re-excision • Re-excision after adjuvant therapy • Missing data
Intervention(s)	Breast conserving surgery with close/positive margins
Outcome measures	Locoregional recurrence Locoregional recurrence was defined as an invasive or non-invasive relapse in the ipsilateral breast and axillary lymph nodes
Number of participants	542 participants
Duration of follow-up	Median 72 months
Methods of analysis	Kaplan-Meier for recurrence rates Log-rank test for univariate analysis Cox-proportional hazard models for multivariate analysis
Confounding factors used in adjusted models	Tumour size, Nodal status, multifocality, hormone receptor, HER2, and adjuvant radiotherapy.
Adjustment	Partially adjusted
Additional comments	• Extracted data for locoregional recurrence was multivariable hazard ratio with 95% CI (reference group was ≤2 mm) • 4.4% of participants had neoadjuvant chemotherapy
Radiotherapy status	Radiotherapy 95.8% had adjuvant radiotherapy
Age	Mixed population
Subsequent systemic treatment	Mixed population • adjuvant chemotherapy (n=278 [51.3%]) • adjuvant hormone therapy (n=429 [79.2%]) • adjuvant HER2 targeted therapy (n=65 [12.0%])
Invasive breast cancer with or without DCIS	DCIS percentage not reported

Study arms

≤2 mm (N = 114)

Patients who did not undergo re-excision for close (≤2 mm) margins were classified into group A.

>2 mm (N = 428)

Patients with negative (>2 mm) margins after the initial breast conserving surgery and those who underwent re-excision for positive or close margins to obtain negative margins were classified into group B.

Characteristics

Study-level characteristics

Characteristic	Study (N = 542)
Age	
≤ 40 years	n = 52 ; % = 9.6
41 to 60 years	n = 343 ; % = 63.3
≥ 61 years	n = 147 ; % = 27.1
Radiotherapy	n = 519 ; % = 95.8
Neoadjuvant chemotherapy	n = 24 ; % = 4.4
Tumour size	
≤ 2cm	n = 384 ; % = 70.8
> 2cm	n = 158 ; % = 29.2
Tumour grade	
Grade I	n = 150 ; % = 27.7
Grade II	n = 201 ; % = 37.1
Grade III	n = 154 ; % = 28.4
Unknown	n = 37 ; % = 6.8

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns *(Study partially adjusted (adjusted for tumour size, Nodal status,*

Section	Question	Answer
		multifocality, hormone receptor, HER2, and adjuvant radiotherapy))
Overall bias	Directness	Directly applicable *(4.4% had neoadjuvant chemotherapy)*

Guinot, 2018

Bibliographic Reference	Guinot, Jose Luis; Tortajada, Maria Isabel; Santos, Miguel Angel; Moreno, Araceli; Fernandez, Jesus; Pena, Marina; Gozalbo, Francisco; Oliver, Laura; Boso, Cristina; Santamaria, Paula; Gimenez, Julia; ARRibas, Leoncio; Can invasive breast carcinoma with close or positive margins be managed without a new surgery?.; The breast journal; 2018; vol. 24 (no. 6); 1024-1027

Study details

Study type	Prospective cohort study
Study location	Spain
Study setting	Single cancer center
Study dates	Between 1996 to 2011
Sources of funding	Grant from Elekta company
Inclusion criteria	Inclusion criteria • Breast cancer patients with breast conserving surgery • Positive or close surgical margins <5mm
Exclusion criteria	Exclusion criteria • Refused re-excision for margins
Intervention(s)	Breast conserving surgery and radiotherapy with or without boost
Outcome measures	Breast cancer specific survival Actuarial cause specific survival without definition
Number of participants	248
Duration of follow-up	Mean 127 months

Methods of analysis	Kaplan-Meier for actuarial analysis
Confounding factors used in adjusted models	Unadjusted
Adjustment	Unadjusted
Additional comments	Data extracted for breast cancer specific survival (reported as actuarial cause specific survival) was event rate in percentage for each margin group at longest follow-up: 15 years (unadjusted data). Data was not extracted from Kaplan Meir curves (Actuarial breast local control) to estimate hazard ratio and 95% CI because the quality of the graph was not good to digitise and get reliable data from it. Local recurrence could not be back calculated to number of events because the study did not report overall survival by margins which is needed for the calculation because the study used the actuarial method for local recurrence.
Radiotherapy status	Radiotherapy
Age	Mixed population
Subsequent systemic treatment	Not reported
Invasive breast cancer with or without DCIS	Mixed population (invasive breast cancer and DCIS ≥25% to <75%, or study reports as mixed population without reporting DCIS percentage) DCIS 60%

Study arms

≤2 mm (N = 76)

>2 to <5 mm (N = 52)

Characteristics

Study-level characteristics

Characteristic	Study (N = 248)
Age	
≤ 50 years	n = 90 ; % = 36.3

Characteristic	Study (N = 248)
51 to 70 years	n = 134 ; % = 54
>70 years	n = 24 ; % = 9.7
Tumour grade	
T1	n = 180 ; % = 72.6
T2	n = 62 ; % = 25
T3	n = 6 ; % = 2.4

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis. Study does not report how margins were assessed and whether a pathologist assessed the margins.)*
Overall bias	Directness	Directly applicable

Kuru, 2020

Bibliographic Reference	Kuru, Bekir; Yuruker, Savas; Sullu, Yurdanur; Gursel, Bilge; Ozen, Necati; Does a Close Surgical Margin for Ductal Carcinoma In Situ Associated with Invasive Breast Carcinoma Affect Breast Cancer Recurrence?.; Journal of investigative surgery : the official journal of the Academy of Surgical Research; 2020; vol. 33 (no. 7); 627-633

Study details

Study type	Retrospective cohort study
Study location	Turkey
Study setting	Single cancer center
Study dates	Between 2009 and 2017
Inclusion criteria	Inclusion criteria • T1 and T2 invasive breast cancer • Treated with breast conserving surgery
Exclusion criteria	Exclusion criteria

	• Neoadjuvant chemotherapy
Intervention(s)	Breast conserving surgery and radiotherapy
Outcome measures	Local recurrence Reported as local recurrence-free survival. Ipsilateral breast tumor recurrence which was defined as the appearance of breast cancer in the ipsilateral breast following breast conserving surgery.
Number of participants	628
Duration of follow-up	Median 56 months
Loss to follow-up	7 participants
Methods of analysis	• Kaplan-Meier method for recurrence-free survival • Log-rank test for comparisons • Cox proportional hazards model for multivariate analysis
Confounding factors used in adjusted models	Unadjusted
Adjustment	Unadjusted
Additional comments	Extracted data for local recurrence free survival was event rate in percentage for each margin group at 5 years.
Radiotherapy status	Radiotherapy All patients received whole breast irradiation, with or without irradiation of peripheral lymphatics within the first 6 months after surgery.
Age	Mixed population
Subsequent systemic treatment	with chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer Patients with positive axillary lymph node (ALN) and patients who had negative ALN but were oestrogen receptor (ER) negative or progesterone receptor (PR) negative received adjuvant chemotherapy. All patients who were ER (positive) and/or PR (positive) received adjuvant hormonotherapy, and patients with HER2 (positive) tumours had trastuzumab treatment.
Invasive breast cancer with or without DCIS	Invasive breast cancer with DCIS (study states as such or that DCIS ≥75%) DCIS 100% (all participants had DCIS)

Study arms

within 2 mm (N = 119)

A close surgical margin was defined as no ink on tumour but invasive or in situ cancer cells within 2mm of the inked edge of the surgical specimen.

≥2 mm (N = 321)

A negative margin was defined as a margin with “no ink on tumour,” that is, no tumour cells on the inked edge of the surgical specimen.

Characteristics

Arm-level characteristics

Characteristic	within 2 mm (N = 119)	≥2 mm (N = 321)
Median age (range)	51 years (27 to 80)	52 years (28 to 83)
Tumour size (Median (range))	2.0 cm (0.3 to 5.0)	2.3 cm (1.5 to 5.0)
Tumour grade		
1	n = 11 ; % = 9	n = 21 ; % = 6
2	n = 73 ; % = 61	n = 176 ; % = 55
3	n = 35 ; % = 29	n = 124 ; % = 39
Histological tumour type		
Invasive ductal	n = 111 ; % = 93	n = 309 ; % = 96
Invasive lobular	n = 8 ; % = 7	n = 12 ; % = 4
Lymphovascular involvement/invasion		
Absent	n = 77 ; % = 65	n = 183 ; % = 57
Present	n = 42 ; % = 35	n = 138 ; % = 43

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis)*
Overall bias	Directness	Directly applicable

Vos, 2017

Bibliographic Reference	Vos, E L; Gaal, J; Verhoef, C; Brouwer, K; van Deurzen, C H M; Koppert, L B; Focally positive margins in breast conserving surgery: Predictors, residual disease, and local recurrence.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2017; vol. 43 (no. 10); 1846-1854

Study details

Study type	Retrospective cohort study
Study location	The Netherlands
Study setting	University hospital
Study dates	Between 2005 and 2014
Inclusion criteria	Inclusion criteria • Breast conserving surgery for invasive breast cancer or ductal carcinoma in situ • T1-T3 disease • No neoadjuvant chemotherapy
Exclusion criteria	Exclusion criteria Stage T4 disease
Intervention(s)	Breast conserving surgery +/- re-excision
Outcome measures	Re-operation rates Re-excision was define as a subsequent breast conserving surgery where breast tissue was excised performed by an oncological surgeon in the same breast within 6 months of primary surgery
Number of participants	499
Duration of follow-up	Median 57 months
Methods of analysis	• Chi-square test • Logistic regression • Cox proportional hazards model
Confounding factors used in adjusted models	Unadjusted analysis
Adjustment	Unadjusted

Additional comments	Extracted data were percentages of people with/without reoperations (re-excision by breast conserving surgery) from histograms. Data was not extracted for eventual mastectomies (re-excision by mastectomy) because there were 14 eventual mastectomies from which 8 (51%) were preventative mastectomies in BRCA mutation carriers. It was also unclear in which margins these preventative mastectomies happened.
Radiotherapy status	Not reported
Age	Mixed population
Subsequent systemic treatment	Not reported
Invasive breast cancer with or without DCIS	Invasive breast cancer without DCIS (study states as such or that DCIS <25%) Re-operation rates were reported separately for invasive breast cancer

Study arms

Invasive <2 mm (N = 118)

Close margin was defined as tumour less than 2 mm width from the inked margin.

Invasive ≥2 mm (N = 178)

Negative margin was defined as tumour at 2 mm width or more from the inked margin.

DCIS <2 mm (N = 43)

Close margin was defined as tumour less than 2 mm width from the inked margin.

≥2 mm (N = 34)

Negative margin was defined as tumour at 2 mm width or more from the inked margin.

Characteristics

Arm-level characteristics

Characteristic	Invasive <2 mm (N=118)	Invasive ≥2 mm (N = 178)	DCIS <2 mm (N = 43)	DCIS ≥2 mm (N = 34)
Age				
> 60 years	n = 36 ; % = 30.5	n = 58 ; % = 32.6	n = 7 ; % = 16.3	n = 11 ; % = 32.4
51 to 60 years	n = 40 ; % = 33.9	n = 56 ; % = 31.5	n = 18 ; % = 41.9	n = 8 ; % = 23.5
≤ 50 years	n = 42 ; % = 35.6	n = 64 ; % = 36	n = 18 ; % = 41.9	n = 15 ; % = 44.1
Tumour size Median (IQR)	13 (18 to 19)	13 (8 to 18)	18 (10 to 37)	10 (6 to 17)
Tumour grade				
Grade 1	n = 22 ; % = 18.6	n = 51 ; % = 28.7	n = 5 ; % = 11.6	n = 12 ; % = 35.3
Grade 2	n = 52 ; % = 44.1	n = 69 ; % = 38.8	n = 18 ; % = 41.9	n = 10 ; % = 29.4
Grade 3	n = 44 ; % = 37.3	n = 58 ; % = 32.6	n = 20 ; % = 46.5	n = 12 ; % = 35.3
Histological tumour type				
Ductal	n = 97 ; % = 82.2	n = 157 ; % = 88.2	n = 0 ; % = 0	n = 0 ; % = 0
Lobular	n = 11 ; % = 9.3	n = 6 ; % = 3.4	n = 0 ; % = 0	n = 0 ; % = 0
Other	n = 10 ; % = 8.5	n = 14 ; % = 7.9	n = 0 ; % = 0	n = 0 ; % = 0
Unknown	n = 0 ; % = 0	n = 1 ; % = 0.6	n = 0 ; % = 0	n = 0 ; % = 0
Lymphovascular invasion				
No	n = 56 ; % = 47.5	n = 79 ; % = 44.4	n = 0 ; % = 0	n = 0 ; % = 0
Yes	n = 23 ; % = 19.5	n = 32 ; % = 18	n = 0 ; % = 0	n = 0 ; % = 0
Unknown	n = 39 ; % = 33.1	n = 67 ; % = 37.6	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis. Study does not report actual number of participants undergoing radiotherapy (post-exposure intervention).)*
Overall bias	Directness	Directly applicable

Ductal carcinoma in situ only

Dick, 2011

Bibliographic Reference	Dick AW; Sorbero MS; Ahrendt GM; Hayman JA; Gold HT; Schiffhauer L; Stark A; Griggs JJ; Comparative effectiveness of ductal carcinoma in situ management and the roles of margins and surgeons.; Journal of the National Cancer Institute; 2011; vol. 103 (no. 2)

Study details

Study type	Retrospective cohort study
Study location	US
Study setting	Tumour registries from based on a population dataset from Monroe County (MC) (New York) and the tumor registry of the Henry Ford Health System (HFHS, Detroit, MI)
Study dates	1985 and 2000
Sources of funding	National Cancer Institute at the National Institutes of Health (R01 CA922444- 01A1 to A.W.D., M.S.S., G.M.A., J.A.H., H.T.G., L.S., A.Z., and J.J.G.).
Inclusion criteria	Inclusion criteria Women diagnosed with DCIS
Exclusion criteria	Exclusion criteria Patients with a history of cancer before the study period were excluded, as were those with microinvasive disease
Outcome measures	Local recurrence Ipsilateral recurrence - the time from the final surgical treatment until the first ipsilateral event, death, or the last date of follow-up.
Number of participants	994
Duration of follow-up	The median follow-up was 5 years with a maximum of 18 years.

Methods of analysis	A bivariate analysis approach was used to assess the relationship between dichotomous outcomes (ipsilateral event vs. no event). Pearson x2 tests of independence were used for each dichotomous covariate defined for the multivariable model. Standard discrete-time duration models were used to estimate the relationship between time to ipsilateral breast tumour recurrence and the clinical and nonclinical factors.
Confounding factors	Age, race, number of comorbid conditions, historic subtype, multifocality, treatment, year, census level per cent black, census level per cent below poverty, insurance status and type, histologic subtype, mammographic tumour size, presence of extensive ductal carcinoma in situ, nuclear grade, menopausal status, calcifications, tamoxifen use, and method of detection
Adjustment	Partially adjusted
Additional comments	The outcome was ipsilateral recurrence and presented as ipsilateral event-free survival, using relative risk as a measure.
Radiotherapy status	No radiotherapy 36.8% of patients received radiotherapy
Age	Mixed population

Study arms

Within 2 mm (N = 250)

Close

≥2 mm (N = 550)

Negative

Characteristics

Study-level characteristics

Characteristic	Study (N = 800)
Age	
<40	n = 53 ; % = 5.3
40 to 49	n = 230 ; % = 23.1
50 to 64	n = 350 ; % = 35.2
≥ 65	n = 361 ; % = 36.3
Race	
White	n = 789 ; % = 79.4

Characteristic	Study (N = 800)
Black	n = 152 ; % = 15.3
Asian	n = 10 ; % = 1
Other	n = 43 ; % = 4.3
Comorbidities	
0 comorbidities	n = 339 ; % = 34.1
1 comorbidities	n = 330 ; % = 33.2
≥ 2 comorbidities	n = 325 ; % = 32.7
Family history of breast cancer	
Yes	n = 201 ; % = 20.2
No	n = 672 ; % = 67.6
Unknown	n = 121 ; % = 12.2
Menopausal status	
Premenopausal	n = 241 ; % = 24.2
Perimenopausal	n = 38 ; % = 3.8
Postmenopausal	n = 637 ; % = 64.1
Unknown	n = 78 ; % = 7.8

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns *(There is concern about the risk of bias due to confounding, as the study did not adjust for all confounding factors. Multivariate analysis was adjusted for age, race, number of comorbidities, histologic subtype, multifocality, treatment, year, census level per cent black, census level per cent below poverty, insurance status and type, histologic subtype, mammographic tumour size, presence of extensive ductal carcinoma in situ, nuclear grade, menopausal status, calcifications, tamoxifen use, and method of detection..)*
Overall bias	Directness	Directly applicable

Ekatah, 2017

Bibliographic Reference	Ekatah, Gregory E; Turnbull, Arran K; Arthur, Laura M; Thomas, Jeremy; Dodds, Christine; Dixon, J Michael; Margin width and local recurrence after breast conserving surgery for ductal carcinoma in situ.; European journal of surgical oncology : the journal of the European Society of

Surgical Oncology and the British Association of Surgical Oncology; 2017; vol. 43 (no. 11); 2029-2035

Study details

Study type	Retrospective cohort study
Study location	UK
Study setting	Single cancer center
Study dates	Between 2000 and 2010
Inclusion criteria	Inclusion criteria • Women with pure ductal carcinoma in situ • Treated with breast-conserving surgery
Exclusion criteria	Exclusion criteria • Microinvasive cancers
Intervention(s)	Breast conserving surgery with or without radiotherapy
Outcome measures	Local recurrence Actuarial IBTR rates
Number of participants	466 participants
Duration of follow-up	Median 7.2 years
Methods of analysis	Actuarial survival and relapse rates were calculated using the Kaplan-Meier method. The log rank test was used for statistical comparison between curves. A proportional hazards regression model was used to assess the independent significance of variables. The odds ratio and 95% confidence intervals were calculated. Tests of significance for odds ratio were calculated. The analysis on margin width relates only to the distance to the nearest radial margin.
Confounding factors	Age, tumour grade, tumour size, radiotherapy, comedo necrosis, ER status, hormone treatment and margin width
Adjustment	Partially adjusted
Additional comments	Outcomes measured were rates of ipsilateral breast tumour recurrence (IBTR) and described as actuarial IBTR rates, rates for invasive IBTR, and DCIS IBTR rates.
Radiotherapy status	Mixed population 292 (62.7%) patients received whole breast radiotherapy

Study arms

<1mm (N = 10)

1-2mm (N = 94)

>2mm (N = 362)

Characteristics

Study-level characteristics

Characteristic	Study (N = 466)
Median age (IQR)	60 (35 to 94)
Radiotherapy	n = 292 ; % = 58.5

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	Some concerns *(There is concern regarding the risk of bias due to confounding, as the study did not adjust for all confounding factors. Multivariate analysis was adjusted for tumour grade, radiotherapy, tumour size, age, comedo necrosis, ER status, hormone treatment and margin width.)*
Overall bias	Directness	Directly applicable

Fregatti, 2019

Bibliographic Reference	Fregatti, Piero; Gipponi, Marco; Depaoli, Francesca; Murelli, Federica; Guenzi, Marina; Bonzano, Elisabetta; Ceppi, Marcello; Friedman, Daniele; No Ink on Ductal Carcinoma In Situ: A Single Centre Experience.; Anticancer research; 2019; vol. 39 (no. 1); 459-466

Study details

Study type	Prospective cohort study
Study location	Italy
Study setting	Hospital/breast surgery unit
Study dates	2000-2016
Inclusion criteria	Inclusion criteria Patients with DCIS without any histologic evidence of micro invasion who underwent BCS with or without post-operative RT
Intervention(s)	
Outcome measures	Local recurrence Ipsilateral breast tumor recurrence (IBTR)
Number of participants	388
Duration of follow-up	Median 90 months (range=12-189 months)
Loss to follow-up	
Methods of analysis	Univariate analysis and multivariate Cox regression were used to correlate clinical and pathologic factors in patients with or without IBTR. The univariate analysis of the recurrence and survival outcomes was performed using the Kaplan–Meier estimation method and log-rank test.
Confounding factors	The study has reported the multivariate regression outcomes, however, we haven't used multivariate analysis because it compares positive vs. negative margins. Values were adjusted for tumour grade, radiotherapy, tumour size, age, comedo necrosis, ER status, hormone treatment and margin width
Adjustment	Unadjusted
Additional comments	The outcome was measured as ipsilateral breast tumour recurrence. Data was extracted as number of events of recurrence.
Radiotherapy status	Mixed population Post-operative whole breast radiation: 255/388 (65.7%)
Age	Mixed population

Study arms

0.1-0.9 mm (N = 46)

Close/Negative

1.0-1.9 mm (N = 14)

Close/Negative

≥2 mm (N = 310)

Negative

Characteristics

Study-level characteristics

Characteristic	Study (N = 388)
Age	
33 to 49	n = 97 ; % = 25
50 to 58	n = 97 ; % = 25
59 to 68	n = 97 ; % = 25
69 to 91	n = 97 ; % = 25
DCIS subtype	
Din 1 C	n = 53 ; % = 13.7
Din 2	n = 195 ; % = 50.3
Din 3	n = 127 ; % = 32.7
Unknown	n = 13 ; % = 3.4
Radiotherapy	
Yes	n = 255 ; % = 65.7
No	n = 110 ; % = 28.4
Unknown	n = 13 ; % = 3.4
Tumour size	
<2 cm	n = 261 ; % = 67.3
2.1 to 5 cm	n = 111 ; % = 28.6
>5 cm	n = 16 ; % = 4.1

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted analysis. The study has reported the multivariate regression outcomes, however, we haven't used multivariate analysis because it compares positive vs. negative margins.)*
Overall bias	Directness	Directly applicable

Livingston-Rosanoff, 2021

Bibliographic Reference	Livingston-Rosanoff, Devon; Trentham-Dietz, Amy; Hampton, John M; Newcomb, Polly A; Wilke, Lee G; Does margin width impact breast cancer recurrence rates in women with breast conserving surgery for ductal carcinoma in situ?.; Breast cancer research and treatment; 2021; vol. 189 (no. 2); 463-470

Study details

Study type	Prospective cohort study
Study location	US
Study setting	Population based cohort/in hospital
Study dates	Between 1997 to 2006, with follow-up through 2016
Sources of funding	National Cancer Institute
Inclusion criteria	Inclusion criteria • Women diagnosed with ductal carcinoma in situ • Completed baseline interview
Exclusion criteria	Exclusion criteria • Unknown diagnosis date • No publicly available phone number • Unable to complete phone interview
Intervention(s)	Breast conserving surgery with margin width measured
Outcome measures	Locoregional recurrence Locoregional recurrence was defined based on participant self-report on biennial follow-up surveys since 85.5% of self-reports were confirmed through a review of medical reports or the Wisconsin state cancer registry; records were not found or available for 14.5% of the self-

	reported diagnoses due to participant or facility refusal to provide records.
Number of participants	559 participants
Duration of follow-up	Up to 19 years
Methods of analysis	LRR was defined based on participant self-report on biennial follow-up surveys since 85.5% of self-reports were confirmed through a review of medical reports or the Wisconsin state cancer registry; records were not found or available for 14.5% of the self-reported diagnoses due to participant or facility refusal to provide records. Descriptive statistics were calculated for baseline characteristics. Each participant's residential address at time of initial diagnosis was geocoded and linked to census tracts (2000 U.S Census). Each address was assigned a value for the percentage of census tract classified as urban, and categorised as urban (100% urban), urban/rural mixed (1%- 99% urban), or rural (0% urban). Rural–Urban Commuting Area Codes were used to characterise hospital reporting facilities as rural or urban. Academic medical centres included the Medical College of Wisconsin hospitals and the University of Wisconsin Hospital and Clinics. Univariate Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals for potential covariates of interest in relation to risk of LRR. Covariates considered included: age at diagnosis (dichotomised into<50y and≥50y), menopausal status, family history of breast cancer, nuclear grade, tumour size, presence of necrosis, ER/PR status, radiation therapy, receipt of endocrine therapy, and duration of endocrine therapy. Age at diagnosis was converted to a bivariate variable as it better reflects how clinicians think of treatment in breast cancer. Covariates that were significant in univariate analyses were included in multivariable models. Models were also constructed that only included participants with known negative margins with adjustments for age and receipt of radiation treatment. These models were constructed to allow direct comparisons between our cohort and the cohort. Statistical analyses were performed in SAS version 9.4.
Confounding factors	Age, menopausal status, and duration of endocrine therapy
Adjustment	Partially adjusted – locoregional recurrence outcome only adjusted for age.
Additional comments	The margin width >2 mm is the reference variable in the multivariable analysis. We carried out a data transformation to invert the reference margin width to present the outcome
Radiotherapy status	Radiotherapy Adjuvant radiation: 294/368 (79.9%)
Age	Mixed population

Study arms

<2 mm (N = 71)

>2 mm (N = 301)

Characteristics

Study-level characteristics

Characteristic	Study (N = 559)
Age	
< 50 years	n = 144 ; % = 26
> 50 years	n = 415 ; % = 74
Family history of breast cancer	
No	n = 413 ; % = 74
Yes	n = 123 ; % = 22
Unknown	n = 23 ; % = 4
Menopausal status	
Premenopausal	n = 172 ; % = 31
Postmenopausal	n = 338 ; % = 61
Unknown	n = 49 ; % = 9
Tumour size	
≤ 1 cm	n = 267 ; % = 48
> 1 cm	n = 147 ; % = 26
Unknown	n = 145 ; % = 26

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(There is concern about the risk of bias due to confounding, as the study did not adjust for all confounding factors. Furthermore, there are some concerns related to the missing data and the outcomes were collected based on patient surveys and not clinical reports.)*

Section	Question	Answer
Overall bias	Directness	Directly applicable

MacDonald, 2005

Bibliographic Reference	MacDonald HR; Silverstein MJ; Mabry H; Moorthy B; Ye W; Epstein MS; Holmes D; Silberman H; Lagios M; Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins.; American journal of surgery; 2005; vol. 190 (no. 4)

Study details

Study type	Retrospective cohort study
Study location	US
Study setting	Cancer Center
Study dates	Between 1972 to 2004
Inclusion criteria	Inclusion criteria • Pure ductal carcinoma in situ • Treated with local wide excision alone • Margin width measured
Intervention(s)	Wide local excision alone
Outcome measures	Local recurrence The outcome studied was the time to local recurrence, which was calculated from the date of diagnosis to the date of local recurrence. Because of the difficulty of accurately differentiating between a true local recurrence and a new cancer in another quadrant of the breast, all ipsilateral breast cancer events were scored as local recurrences.
Number of participants	445 participants
Duration of follow-up	Median 57 months
Methods of analysis	Kaplan-Meier estimates of the probabilities of remaining free of local recurrence were calculated at 5 and 8 years. The Greenwood formula was used to calculate the standard errors. Both univariate and multivariate Cox regression analyses were performed for surgical margin, age at diagnosis, tumor size, nuclear grade, and the presence of comedo necrosis. The proportional hazard assumption was checked using Schoenfeld residuals. The partial likelihood ratio test based on the

	Cox model was used to calculate P values (all 2-sided)
Confounding factors	Age, nuclear grade, tumour size, necrosis
Adjustment	Partially adjusted but local recurrence data was based on univariate analysis.
Additional comments	The outcome was measured as local recurrence. The data from the multivariate analysis was not extracted because it was for 0 vs 10mm and we were not interested in that comparison. We extracted the total number and number of events of local recurrence to calculate the RR.
Radiotherapy status	No radiotherapy
Age	Mixed population

Study arms

0.1-1.9 mm (N = 53)

1.0-1.9 mm (N = 20)

2.0-2.9 mm (N = 82)

Characteristics

Baseline characteristics were not reported for the entire study population. Instead, patients were grouped by age, tumour size, nuclear grade, tumour margin and presence of necrosis.

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High *(There is concern about the risk of bias due to confounding, as the study did not adjust forconfounding factors for the outcome of interest.)*

Section	Question	Answer
Overall bias	Directness	Directly applicable

Mannu, 2020

Bibliographic Reference	Mannu, Gurdeep S; Wang, Zhe; Broggio, John; Charman, Jackie; Cheung, Shan; Kearins, Olive; Dodwell, David; Darby, Sarah C; Invasive breast cancer and breast cancer mortality after ductal carcinoma in situ in women attending for breast screening in England, 1988-2014: population based observational cohort study.; BMJ (Clinical research ed.); 2020; vol. 369; m1570

Study details

Study type	Retrospective cohort study
Study location	UK
Study setting	Dataset from the National Cancer Registration and Analysis Service (NCRAS)
Study dates	April 2000 to March 2014
Sources of funding	Funding was provided by Cancer Research UK (grant C8225/A21133), the National Institute for Health Research Oxford Biomedical Research Centre, and the UK Medical Research Council (grant MCU137686858).
Inclusion criteria	Inclusion criteria Screen detected DCIS in England April 2000 to March 2014
Exclusion criteria	Exclusion criteria Any woman recorded as having an invasive cancer (other than non-melanoma skin cancer) before her diagnosis of DCIS, as well as women registered with invasive breast cancer or death from breast cancer or recorded as receiving chemotherapy within six months of diagnosis of DCIS. Bilateral DCIS. Unilateral DCIS, no surgery recorded.
Outcome measures	Local recurrence Incidence of ipsilateral invasive breast cancer
Number of participants	35,024 participants for the whole study 16,588 participants with data on final surgical margin distance
Duration of follow-up	Follow-up was reported separately for people receiving or not radiotherapy: • Breast conserving surgery with radiotherapy (n=5,368)

	○ 0 to 4 years (n=3,428, 63.9%) ○ 5 to 9 years (n=1,316, 24.5%) ○ 10 to 14 years (n=624, 11.6%) • Breast conserving surgery without radiotherapy (n=15,188) ○ 0 to 4 years (n=5,939, 39.1%) ○ 5 to 9 years (n=5,898, 38.8%) ○ 10 to 14 years (n=3,351, 22.1%)
Loss to follow-up	Not reported
Methods of analysis	Cumulative observed risks of invasive breast cancer and death from breast cancer and cumulative rates of invasive breast cancer were calculated by considering women from six months after their DCIS diagnosis until the earliest of diagnosis of invasive breast cancer or death, loss to follow-up, or 31 December 2014. Cumulative expected risks were calculated similarly, using cancer incidence rates for England and mortality rates for England and Wales in five year age groups and single calendar years. Competing risks of death from other causes were taken into account by using 2014 death rates for England and Wales. Confidence intervals for cumulative risks, observed and cumulative rates, and ratios of observed to expected rates were based on the Poisson distribution. Poisson regression was also used for analyses requiring adjustments and tests for interactions. However, information was missing for some women for the variables tumour size, DCIS grade, oestrogen receptor status, and tumour laterality. Omitting these women from the analysis may lead to loss of precision and possible bias. Therefore, analyses were done including these variables in two different ways. Firstly, the missing values for each variable were assigned to a separate category. Secondly, analyses were done using multiple imputation for the missing values. This takes account of any correlations between the missing variable and variables that are known. It also allows for the uncertainty arising from the missing variables in standard errors and significance tests. Results from the two different methods were virtually identical, and those presented in the paper are based on multiple imputation. Stata statistical software version 15.1 and R version 3.2.2 were used for analyses.
Confounding factors	Rate ratios were adjusted for year of DCIS diagnosis, age at DCIS diagnosis, English region, time since DCIS diagnosis, DCIS size, DCIS grade, and laterality of DCIS.
Adjustment	Unadjusted event data and adjusted rate ratios (partial adjustment for confounding factors of interest).
Additional comments	• The study reported the number of people with follow-up times from 0-4 years to >20 years. Results for local recurrence with different margin sizes were not stratified by follow-up time. • Unadjusted event data (number of cases of ipsilateral invasive breast cancer/ population of women) was used to allow comparisons between margins other than ≥ 5mm. • For the comparison involving margins of ≥ 2 mm event data for margins of 2 mm, 3 to 4 mm and ≥ 5 mm were pooled. For the ≥ 3 mm comparison event data for margins of 3 to 4 mm and ≥ 5 mm were pooled.

	• Adjusted rate ratios were also extracted but these only compared smaller margins to those ≥ 5mm. • For women who had more than one operation, the final margin distance was calculated by the study authors as the sum of the final closest margin distances recorded for each operation. • Information on final margin distance was available only from 2007 onwards.
Radiotherapy status	Mixed population • Breast conserving surgery with radiotherapy (n=5,368) • Breast conserving surgery without radiotherapy (n=15,188)
Age	Mixed population Age ranged from less than 55 years to 65 years and older

Study arms

1 mm (N = 1413)

2 mm (N = 1536)

3 to 4 mm (N = 2168)

≥5 mm (N = 6264)

Characteristics

Study reported baseline characteristics separately for breast conserving surgery with radiotherapy (n=5,638) or breast conserving surgery without radiotherapy (n=15,188)

Characteristic	Breast conserving surgery with radiotherapy (n=5,638)	Breast conserving surgery without radiotherapy (n=15,188)
Years of screening		
April 2000 to Dec 2004	n = 669; % = 12.5	n = 3617; % = 23.8
Jan 2005 to Dec 2009	n = 1313; % = 24.5	n = 5908; % = 38.9
Jan 2010 to March 2014	n = 3386; % = 63.1	n = 5663; % = 37.3

Characteristic	Breast conserving surgery with radiotherapy (n=5,638)	Breast conserving surgery without radiotherapy (n=15,188)
Age at DCIS diagnosis, years		
Less than 55	n = 1611; % = 30.0	n = 4577; % = 30.1
55 to 59	n = 1122; % = 20.9	n = 3107; % = 20.5
60 to 64	n = 1183; % = 22.0	n = 3446; % = 22.7
65 and more	n = 1452; % = 27.0	n = 4058; % = 26.7
Tumour size, mm		
10 or less	n = 1595; % = 29.7	n = 7085; % = 46.6
11 to 20	n = 2147; % = 40.0	n = 4820; % = 31.7
21 to 50	n = 1551; % = 28.9	n = 3056; % = 20.1
51 and more	n = 75; % = 1.4	n = 227; % = 1.5
DCIS grade		
Low/intermediate	n = 1375; % = 25.6	n = 8019; % = 52.8
High	n = 3993; % = 74.4	n = 7169; % = 47.2
Oestrogen receptor status and endocrine treatment		
ER+, no endocrine	n = 3585; % = 66.8	n = 9947; % = 65.5
ER+, endocrine	n = 569; % = 10.6	n = 2747; % = 18.1
ER-	n = 1214; % = 22.6	n = 2494; % = 16.4
Laterality of DCIS		
Left	n = 2802; % = 52.2	n = 7821; % = 51.5
Right	n = 2566; % = 47.8	n = 7367; % = 48.5

ER+ = oestrogen receptor positive; ER- = oestrogen receptor negative

Critical appraisal ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk for unadjusted event data *(Unadjusted data was used, lack of information about post-exposure interventions and missing data.)* Moderate risk for adjusted rate ratio data as this was not adjusted for the full list of confounders in the review protocol.
Overall bias	Directness	Directly applicable for the subgroup of people without radiotherapy as the majority of people had a follow up time of 5 or more years. Partially applicable for the subgroup of people with radiotherapy because 64% of people had a follow-up time of 0 to 4 years and the protocol specified at least 5 years.

Shaikh, 2016

Bibliographic Reference	Shaikh, Talha; Li, Tianyu; Murphy, Colin T; Zaorsky, Nicholas G; Bleicher, Richard J; Sigurdson, Elin R; Carlson, Robert; Hayes, Shelly B; Anderson, Penny; Importance of Surgical Margin Status in Ductal Carcinoma In Situ.; Clinical breast cancer; 2016; vol. 16 (no. 4); 312-8

Study details

Trial registration number and/or trial name	Fox Chase Cancer Centre
Study type	Retrospective cohort study
Study location	US
Study setting	Hospital
Study dates	Between 1989 and 2014
Sources of funding	National Cancer Institute Grant
Inclusion criteria	Inclusion criteria • Women diagnosed with DCIS • Underwent breast conversing surgery • Received adjuvant whole breast radiotherapy • Received tumour bed boost

Exclusion criteria	Exclusion criteria • Invasive breast cancer • Underwent mastectomy • Received hypofractionated radiotherapy • Male patients • Metastatic disease
Intervention(s)	Breast-conserving surgery + whole breast radiotherapy + tumour bed boost
Outcome measures	Re-operation rates A patient was considered to have undergone re-excision if they were found to have a close or positive margin after surgery, and were recommended to undergo re-excision to obtain negative margins.
Number of participants	498 participants
Duration of follow-up	Median 8.3 years (range 3 months to 27 years)
Methods of analysis	Study end points included LC, regional control, distant control, cause-specific survival (CSS), disease-free survival and overall survival. LC was defined as a recurrence of invasive or non-invasive breast cancer in the ipsilateral breast. The differences of patient and tumor characteristics between the study groups were compared using the c2 test for categorical variables and Wilcoxon test for continuous variables. Variables analysed included margin status, re-excision, age, dose, hormonal therapy, comedo subtype, and grade. The univariate analysis on the recurrence and survival outcomes was done using the Kaplan-Meier estimation method and log rank test. Multivariate analysis was performed using a Cox proportional hazard model.
Confounding factors	Unadjusted analysis
Adjustment	Unadjusted
Additional comments	The outcomes comparing close (>0 - ≤2 mm) vs. negative (>2 mm) margin widths were calculated using the Kaplan-Meier curves, which are unadjusted values. Multivariate analysis describes results comparing the following margin widths: 0-1 mm, 1-2 mm, and >2 mm. Outcomes are presented as local control rates, which should be interpreted as a decrease in the risk of ipsilateral breast tumour recurrence.
Radiotherapy status	Radiotherapy

	All patients received radiotherapy (n: 498)
Age	50 to 69 years old Median (range): 58 years (30-91)

Study arms

> 0 ≤ 2 mm (N = 87)

Close

> 2 mm (N = 400)

Negative

Characteristics

Study-level characteristics

Characteristic	**Study (N = 498)**
Median age (IQR)	58 (30 to 91)
Tumour size (cm) Median (IQR)	0.8 (0.1 to 5)

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	**Question**	**Answer**
Overall bias	Risk of bias judgement	High *(There is concern about the risk of bias due to confounding, as the study did not adjust for confounding factors.*
Overall bias	Directness	Directly applicable

Solin, 2005

Bibliographic Reference	Solin LJ; Fourquet A; Vicini FA; Taylor M; Olivotto IA; Haffty B; Strom EA; Pierce LJ; Marks LB; Bartelink H; McNeese MD; Jhingran A; Wai E; Bijker N; Campana F; Hwang WT; Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast.; Cancer; 2005; vol. 103 (no. 6)

Study details

Study type	Retrospective cohort study
Study location	Canada, France, The Netherlands, US
Study setting	Hospital
Study dates	Between 1973 to 1995
Sources of funding	Breast Cancer Research Foundation Grant
Inclusion criteria	Inclusion criteria • Women with unilateral mammographically detected DCIS • Clinically occult disease • No concurrent invasive carcinoma • Treatment conserving surgery + whole breast radiotherapy
Exclusion criteria	Exclusion criteria • Invasive breast cancer • Bilateral disease • Palpable mass or nipple discharge • Prior breast cancer • Concurrent breast cancers except nonmelanoma skin cancer • Whole breast radiotherapy dose < cGy4000 • Adjuvant systemic therapy
Intervention(s)	Breast-conserving surgery and whole breast radiotherapy
Outcome measures	Local recurrence A local failure was scored for a failure that occurred within the treated breast. All local failures, including the first and subsequent events and including DCIS and invasive local failures, were included in the calculation of any local failure. Local only first failure was defined as a local failure that occurred in the breast as the first and only site of failure without any other prior or concurrent event (i.e., regional failure, distant failure, contralateral breast carcinoma, or second malignant neoplasm). The location of the local failure was scored according to the method of Recht et al. 1985.
Number of participants	1003 participants
Duration of follow-up	Median 8.5 years
Methods of analysis	The Kaplan–Meier method was used to calculate actuarial curves for survival, freedom from distant metastases, local control, and contralateral breast carcinoma. The period measured was calculated from the start of definitive breast irradiation, not at the time of diagnosis

	of DCIS. The log-rank test was used for statistical comparisons between groups. A multivariate Cox proportional hazards regression model was used to evaluate the independent prognostic significance of the variables. Excluded from the model were potential prognostic variables for which a large fraction of the patients had incomplete information.
Confounding factors	Age at the time of treatment, final pathology margin status, mammographic findings, institution at which the patient was treated, date of treatment, location of the primary tumor, and total radiation dose
Adjustment	Partially adjusted for hazard ratio data. Unadjusted for event data.
Additional comments	The negative margin is the reference variable in the multivariable analysis. We carried out a data transformation to invert the reference margin width to present the outcome. Eight of the 10 participating institutions used 2 mm to differentiate between negative margins (> 2 mm or ≥ 2 mm) and close margins (≤ 2 mm or < 2 mm). One institution used 2–3 mm for this differentiation, and 1 institution used 3 mm.
Radiotherapy status	Radiotherapy All women underwent breast-conserving surgery followed by definitive breast irradiation.
Age	Mixed population

Study arms

< 2 mm or ≤ 2 mm (N = 158)

Close

> 2 mm or ≥ 2 mm (N = 599)

Negative

Characteristics

Study-level characteristics

Characteristic	Study (N = 1003)
Age	
20 to 29 years	n = 2 ; % = 0.2
30 to 39 years	n = 59 ; % = 6
40 to 49 years	n = 317 ; % = 32

Characteristic	Study (N = 1003)
50 to 59 years	n = 304 ; % = 30
60 to 69 years	n = 223 ; % = 22
70 to 79 years	n = 92 ; % = 9
80 to 89 years	n = 6 ; % = 0.6
Menopausal status	
Premenopausal	n = 324 ; % = 32
Postmenopausal	n = 541 ; % = 54
Perimenopausal	n = 36 ; % = 4
Unknown	n = 102 ; % = 10
Tumour size	
≤ 2cm	n = 350 ; % = 35
2.1 to 5cm	n = 73 ; % = 7
> 5cm	n = 2 ; % = 0.2
Unknown	n = 578 ; % = 58

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(There is concern regarding the risk of bias due to confounding, as the study did not adjust for all confounding factors for one outcome (local recurrence HR data), and one outcome (local recurrence event data) was unadjusted. Furthermore, there is a concern related to exposure measurement, where one institution used 2–3 mm to differentiate between negative margins (> 2 mm or ≥ 2 mm) and close margins (≤ 2 mm or < 2 mm) and another institution used 3mm for this differentiation.)*
Overall bias	Directness	Directly applicable

Van Zee, 2015

Bibliographic Reference	Van Zee KJ; Subhedar P; Olcese C; Patil S; Morrow M; Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years.; Annals of surgery; 2015; vol. 262 (no. 4)

Study details

Study type	Retrospective cohort study
Study location	US
Study setting	Single cancer centre
Study dates	Between 1978 to 2010
Sources of funding	NIH/NCI Cancer center support grant
Inclusion criteria	Inclusion criteria • Women with DCIS treated with breast-conserving surgery
Exclusion criteria	Exclusion criteria • Synchronous or metachronous bilateral DCIS (included once per breast)
Intervention(s)	Breast-conserving surgery with or without radiotherapy
Outcome measures	Locoregional recurrence The outcome of interest was any recurrence, defined as ipsilateral breast recurrence of DCIS or invasive cancer, ipsilateral axillary nodal recurrence without ipsilateral breast recurrence, or in one case, distant recurrence consistent with a breast primary carcinoma but without the presence of any ipsilateral recurrence or contralateral diagnosis of breast carcinoma.
Number of participants	2996 participants
Duration of follow-up	Median 75 months
Methods of analysis	Time to event was defined as the interval between definitive surgery and date of first recurrence. 10- year Kaplan-Meier recurrence estimates were calculated by margin width for the entire cohort as well as for the subsets with and without RT, and log rank tests were used. A multivariable Cox model was created to evaluate the association of margin width with recurrence while controlling for other variables. Interaction between RT and margin width was assessed, and separate models were created for the subsets with and without RT. The proportionality of hazards was checked for all Cox models and found to be appropriate. Statistical analysis was performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).
Confounding factors	Age, family history, presentation, nuclear grade, number of excisions, endocrine therapy, year of surgery
Adjustment	Partially adjusted for some outcomes but the outcome of interest was unadjusted event data.

Additional comments	The results described compare margins ≤2 mm (close) and >2-10 mm. The results are presented as ten-year recurrence rates by margin width and by receipt of radiation. Hazard ratio of radiation vs. no radiation, controlling for age, family history, presentation, nuclear grade, number of excisions, endocrine therapy, and year of surgery.
Radiotherapy status	Mixed population 53% of women received radiotherapy
Age	Mixed population ≤50 years: 845 (28.2%) > 50 years: 2,151 (71.8%)

Study arms

≤ 2 mm (N = 449)

Close

>2–10 mm (N = 888)

Characteristics

Study-level characteristics

Characteristic	Study (N = 2996)
Age	
> 50 years	n = 2151 ; % = 71.8
<50 years	n = 85 ; % = 28.2
Family history	
No	n = 1816 ; % = 60.6
Yes	n = 1136 ; % = 37.9
Unknown	n = 44 ; % = 1.5
Menopausal status	
Pre/perimenopausal	n = 1038 ; % = 34.6

Characteristic	Study (N = 2996)
Postmenopausal	n = 1946 ; % = 65
Unknown	n = 12 ; % = 0.4

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(There is concern related to the risk of bias due to confounding, as the study did not adjust for all confounding factors and the outcome of interest was unadjusted. Furthermore, there are some concerns related to the missing data and the exposure measurement due to the negative margin width being >2–10mm, which includes cases with margins described as widely clear. the outcomes were collected based on patient surveys and not clinical reports. There is a concern related to exposure measurement due to the negative margin width being >2–10mm, which includes cases with margins described as widely clear.)*
Overall bias	Directness	Directly applicable

Neoadjuvant therapy

Choi, 2018

Bibliographic Reference	Choi, Jungeun; Laws, Alison; Hu, Jiani; Barry, William; Golshan, Mehra; King, Tari; Margins in Breast-Conserving Surgery After Neoadjuvant Therapy.; Annals of surgical oncology; 2018; vol. 25 (no. 12); 3541-3547

Study details

Study type	Retrospective cohort study
Study location	US
Study setting	Medical center
Study dates	Between 2002 to 2014
Inclusion criteria	Inclusion criteria • Stage I-III breast cancer • => 18 years old • Received neoadjuvant chemotherapy • Underwent breast conserving surgery

	• Received whole breast irradiation
Exclusion criteria	Exclusion criteria • Neoadjuvant endocrine therapy alone
Intervention(s)	Breast conserving surgery with whole breast radiotherapy
Outcome measures	Local recurrence Local recurrence was defined as ipsilateral breast tumour recurrence.
Number of participants	382 participants
Duration of follow-up	Median 57 months (range 10-148 months)
Methods of analysis	Descriptive statistics were used to characterize the cohort's baseline features. Survival analysis was performed using Kaplan–Meier methods, with time zero defined as date of diagnosis. Patients who later chose to pursue prophylactic mastectomy were censored at the time of this operation. Univariate and multivariate Cox proportional hazards regression analyses were performed to determine the relationship between margin width and the primary outcomes, and a sensitivity analysis was performed excluding patients with a breast pCR. Patients with a positive margin were included in the close margin group for analysis due to small sample size. The impact of pCR on LRFS, DFS, and OS among four receptor subtypes was further studied by univariate Cox proportional hazards model. All statistical analysis was performed using R version 3.3.1.
Confounding factors	Age, presenting cT stage, receptor status, post-NAC pathologic nodal status, overall pCR, margin status
Adjustment	Unadjusted (as only raw event data available for margins of interest)
Radiotherapy status	Radiotherapy
Age	50 to 69 years old
Subsequent systemic treatment	Mixed population 382 patients were identified and among 188 HR+ patients, 170 (90.4%) received adjuvant endocrine therapy

Study arms

1.1 to 2 mm (N = 103)

> 2 mm (N = 174)

Characteristics

Study-level characteristics

Characteristic	Study (N = 382)
Median age (IQR)	51 (22 to 79)
Tumour size (cm) Median (IQR)	3 (0.6 to 11)
Tumour grade	
Grade 1	n = 5 ; % = 1.3
Grade 2	n = 87 ; % = 22.8
Grade 3	n = 284 ; % = 74.3
Unknown	n = 6 ; % = 1.6
Tumour histology	
Ductal	n = 359 ; % = 94
Lobular	n = 6 ; % = 1.6
Mixed	n = 17 ; % = 14.5

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted data used for our review)*
Overall bias	Directness	Directly applicable *(All participants had neoadjuvant chemotherapy)*

Lin, 2020

Bibliographic Reference	Lin, Joseph; Lin, Kuo-Juei; Wang, Yu-Fen; Huang, Ling-Hui; Chen, Sam Li-Sheng; Chen, Dar-Ren; Association of surgical margins with local recurrence in patients undergoing breast-conserving surgery after neoadjuvant chemotherapy.; BMC cancer; 2020; vol. 20 (no. 1); 451

Study details

Study type	Retrospective cohort study
Study location	Taiwan
Study setting	Hospital
Study dates	Between 2008 and 2018

Inclusion criteria	Inclusion criteria • Untreated operable breast cancer • Received neoadjuvant chemotherapy • Underwent breast-conserving surgery • Received radiotherapy
Exclusion criteria	Exclusion criteria • Stage IV breast cancer • Bilateral breast cancer • Lost to follow-up • Died without surgery • Ongoing neoadjuvant chemotherapy
Intervention(s)	Breast conserving surgery and radiotherapy
Outcome measures	Locoregional recurrence Defined as recurrence tumour in the ipsilateral breast parenchyma or metastatic disease in the internal mammary, ipsilateral axillary, infraclavicular or supraclavicular nodes.
Number of participants	161 participants
Duration of follow-up	Median 47 months (range 25-87 months)
Methods of analysis	Clinicopathological characteristics were compared by Mann–Whitney U test for medians and chi-square test for proportions. Kaplan–Meier (KM) survival curves were generated to compare the survival outcomes according to the margin status, and two-sided log rank test was used to test the significant difference between survival experiences. Statistical analysis was performed using MedCalc statistical software version 18.5 (MedCalc Software bvba, Ostend, Belgium), and a significance level of 5% was used in all analyses.
Confounding factors	Age, lymph node status (positive vs. negative), histological grade, receptor status, Ki-67 index, pCR status and surgical margin distance
Adjustment	Unadjusted (as only raw event data available for margins of interest)
Additional comments	Data extracted were number of events of locoregional recurrence.
Radiotherapy status	Radiotherapy 100%
Age	Mixed population
Subsequent systemic treatment	without chemotherapy (for all ER positive or negative tumours) and/or endocrine therapy for people with ER-positive breast cancer

Study arms

≥1mm < 2mm (N = 21)

≥2mm (N = 112)

Characteristics

Arm-level characteristics

Characteristic	≥1mm < 2mm (N = 21)	≥2mm (N = 112)
Mean age (SD)	46.3 (10.1)	47.5 (10.4)
Tumour size		
T1 (≤ 2cm)	n = 1 ; % = 4.8	n = 14 ; % = 12.5
T2 (>2cm, ≤5cm)	n = 18 ; % = 85.7	n = 90 ; % = 80.4
T3 (>5cm)	n = 2 ; % = 9.5	n = 8 ; % = 7.1
Tumour grade		
Grade 1	n = 1 ; % = 5	n = 12 ; % = 11.8
Grade 2	n = 13 ; % = 65	n = 48 ; % = 47.1
Grade 3	n = 5 ; % = 25	n = 42 ; % = 41.2
Missing	n = 1 ; % = 5	n = 0 ; % = 0

Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	High risk *(Unadjusted data used for our analysis)*
Overall bias	Directness	Directly applicable *(All participants had neoadjuvant chemotherapy)*

Rouzier, 2001

Bibliographic Reference	Rouzier, Roman; Extra, Jean-Marc; Carton, Mathieu; Falcou, Marie-Christine; Vincent-Salomon, Anne; Fourquet, Alain; Pouillart, PieRRe; Bourstyn, Edwige; Primary Chemotherapy for Operable Breast Cancer: Incidence and Prognostic Significance of Ipsilateral Breast Tumor Recurrence After Breast-Conserving Surgery; Journal of Clinical Oncology; 2001; vol. 19 (no. 18); 3828-3835

Study details

Study type	Retrospective cohort study
Study location	France
Study setting	Cancer centre
Study dates	January 1985 to December 1994
Inclusion criteria	Inclusion criteria • Women with T1-T3 invasive breast cancer • Treated with neoadjuvant chemotherapy followed by lumpectomy and radiation therapy
Exclusion criteria	Exclusion criteria • Inflammatory, bilateral, or T4 breast tumours • Metastatic disease
Outcome measures	Local recurrence Ipsilateral breast tumor recurrence (IBTR), measured from the date of first treatment to the time of last follow-up visit or IBTR. Only patients with histologically or cytologically confirmed recurrences in the ipsilateral breast were scored as having IBTR. Distant recurrence Distant metastasis was measured from the date of first treatment to the time of last follow-up visit or distant metastasis. Patients with radiographic and/or clinical evidence of metastatic disease were scored as having distant metastasis.
Number of participants	257 participants
Duration of follow-up	Median 93 months (range 14 - 178 months)
Methods of analysis	Kaplan-Meier estimates were used to calculate the IBTR-free and metastases-free survival rates. The statistical significance of the difference between survival distributions was determined by means of the log-rank test. Clinical and pathologic factors tested by univariate and multivariate analysis included patient age, initial clinical tumor size, SBR

	grade, ER status, S-phase fraction, clinical regression, clinical tumour size at surgery, pathologic tumour size, pathologic residual disease, margin status, initial clinical lymph node status, pathologic nodal status, chemotherapy regimen, and radiation boost. The influence of tumour characteristics on outcome was assessed in multivariate analysis by using the Cox proportional hazards model in a forward stepwise procedure. Variables with k subgroups were coded with k-1 dummy variables, yielding a nonlinear relation between two subsequent subgroups when k was more than 2. For the metastasis-free survival rate, two separate models were constructed: one without IBTR and a second including IBTR as a time-dependent covariate. All significance tests were two-tailed, and differences were considered to be statistically significant at P <0.05. The Cox proportional hazards model was used to compute relative risks (RRs) and 95% confidence intervals to examine the effects of prognostic variables. All analyses were done with the Biomedical Package (BMDP; Statistical Solutions, Cork, Ireland).
Confounding factors	For local recurrence (age, initial clinical tumour size, histologic grade according to Scarff, Bloom, and Richarson (SBR) method, oestrogen status, S-phase fraction, clinical regression, clinical tumour size at surgery, pathologic tumour size, pathologic residual disease, initial clinical lymph node status, pathologic nodal status, chemotherapy regimen, and radiation boost).
Adjustment	Partially adjusted for local recurrence, unadjusted analysis for distant recurrence
Additional comments	All the patients but one were given postoperative radiotherapy to the breast. Local recurrence data was extracted as RR and 95% CI from the Cox regression model. Distant recurrence data was extracted from event data.
Radiotherapy status	Radiotherapy 100
Age	Mixed population
Subsequent systemic treatment	Mixed population 25/257 (9.7%) patients received one to five adjuvant courses of chemotherapy

Study arms

≤2mm (N = 45)

>2mm (N = 173)

Characteristics

Study-level characteristics

Characteristic	Study (N = 257)
Age	
≤ 40 years	n = 60 ; % = 23.3
>40 years	n = 197 ; % = 76.7
Tumour size	
≤ 2cm	n = 190 ; % = 74
>2 cm	n = 67 ; % = 26

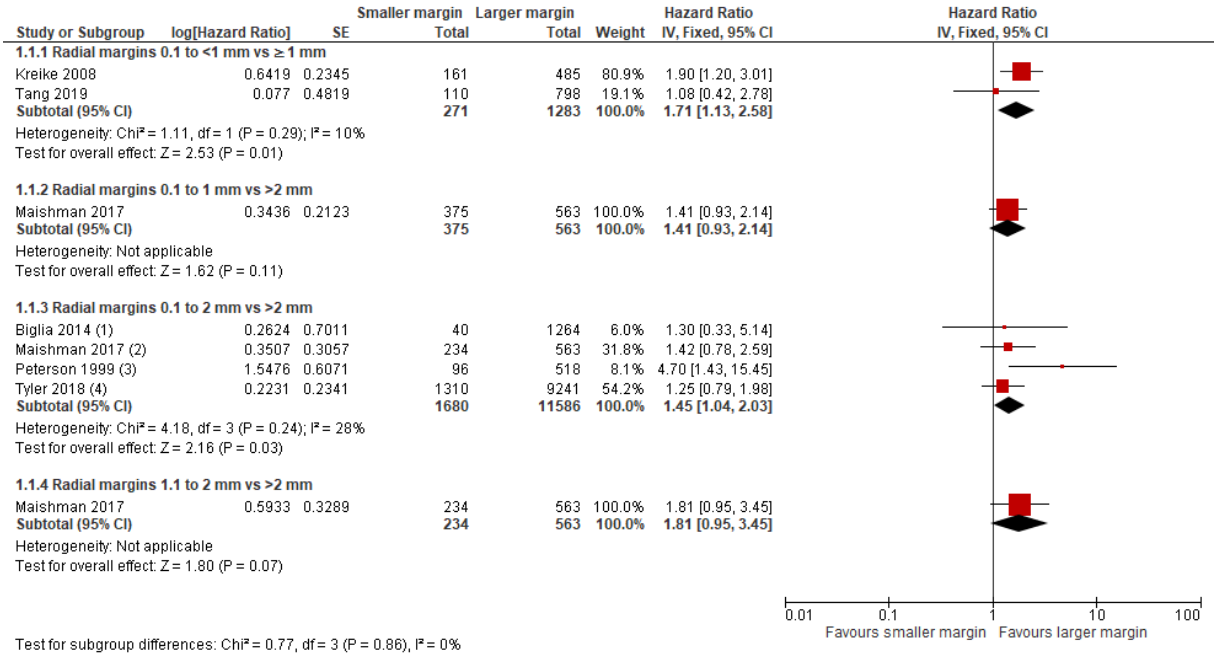
Critical appraisal: ROBINS-E: a tool for non-randomised studies of exposure

Section	Question	Answer
Overall bias	Risk of bias judgement	*Some concerns for local recurrence as partially adjusted, high risk of bias for* distant recurrence as unadjusted.
Overall bias	Directness	Directly applicable *(All participants had neoadjuvant chemotherapy)*

Appendix E – Forest plots

Invasive breast cancer with or without DCIS

Figure 1 - Local recurrence – Hazard ratios at 10 years follow-up

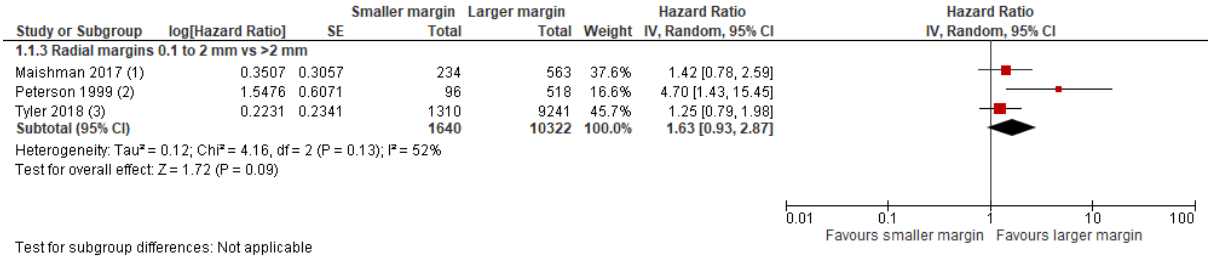


Test for subgroup differences: Chi² = 0.77, df = 3 (P = 0.86), I² = 0%

Footnotes

(1) Radial margins 0.1 to <2 mm vs ≥2 mm
(2) Radial margins 0.1 to 2 mm vs >2 mm
(3) Radial margins 0.1 to 2 mm vs >2 mm
(4) Radial margins 0.1 to 2 mm vs >2 mm

Figure 1. 1 - Local recurrence – Hazard ratios at 10 years follow-up up – sensitivity analysis for subgroup 1.1.3 without Biglia 2014 (larger margin includes 2 mm)



Test for subgroup differences: Not applicable

Footnotes

(1) Radial margins 0.1 to 2 mm vs >2 mm
(2) Radial margins 0.1 to 2 mm vs >2 mm
(3) Radial margins 0.1 to 2 mm vs >2 mm

Figure 1. 2 - Local recurrence – Hazard ratios at 10 years follow-up up – sensitivity analysis for subgroup 1.1.3 without Peterson 1999 (unadjusted analysis)

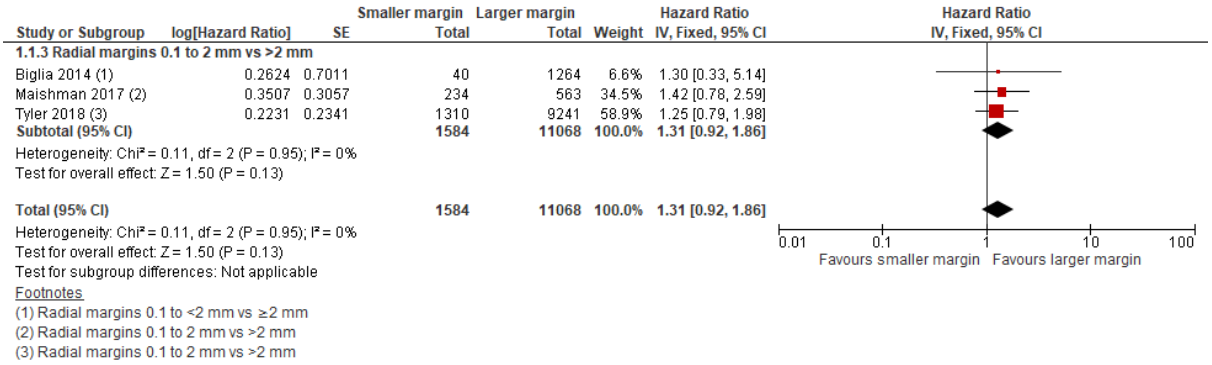


Figure 2 Local recurrence – Event data at 5 years follow-up

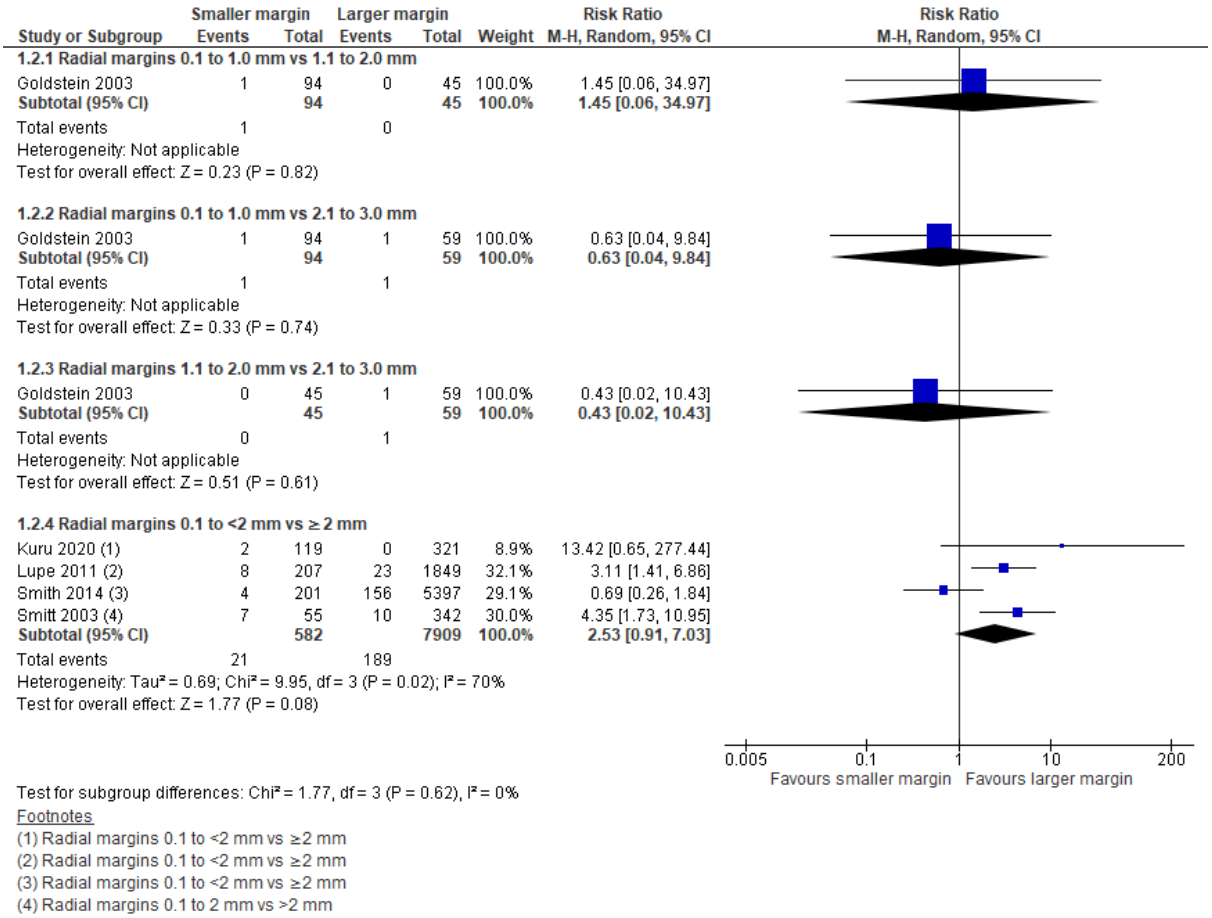
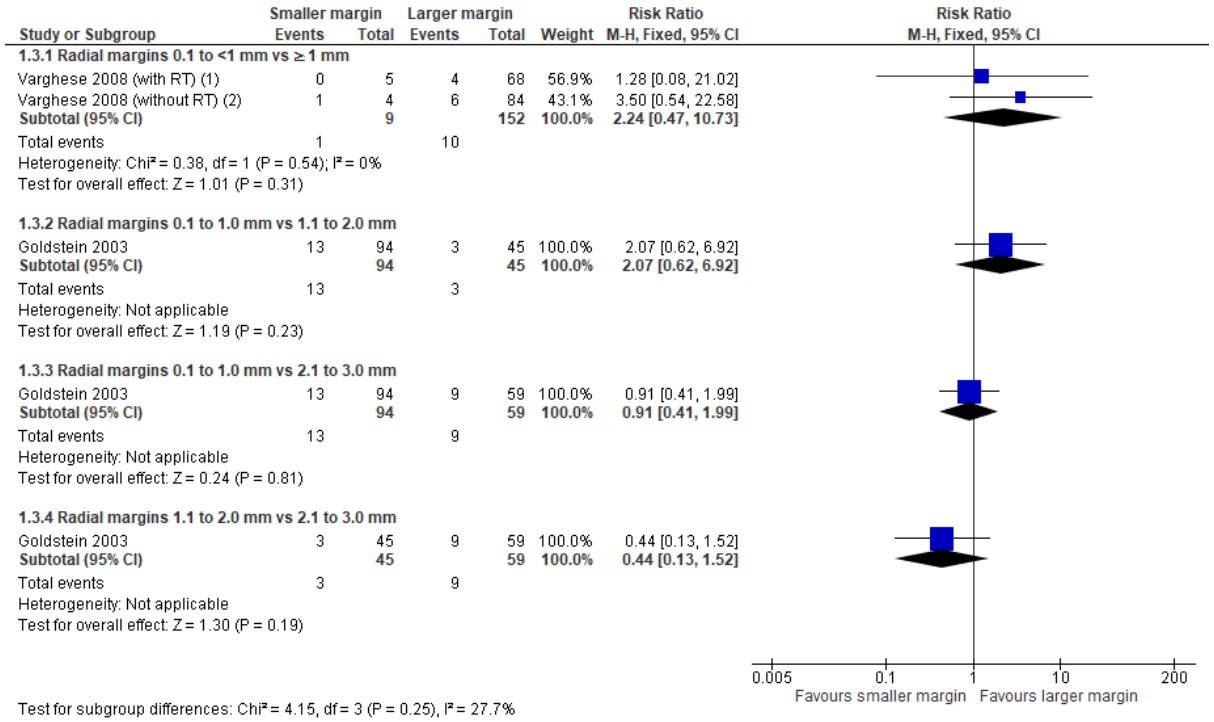


Figure 3 Local recurrence – Event data at 10 years follow-up



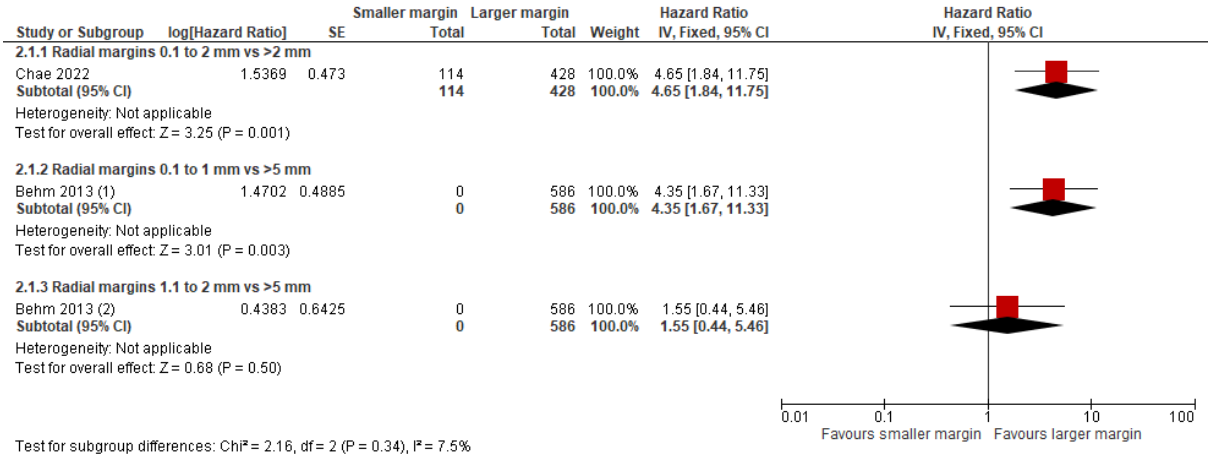
Test for subgroup differences: Chi² = 4.15, df = 3 (P = 0.25), I² = 27.7%

Footnotes

(1) Varghese 2008 reported number of events and totals

(2) Varghese 2008 reported RR and 95% CI

Figure 4 Locoregional recurrence – Hazard ratios at 10 years follow-up



Test for subgroup differences: Chi² = 2.16, df = 2 (P = 0.34), I² = 7.5%

Footnotes

(1) Sample size for the smaller margin was not reported

(2) Sample size for the smaller margin was not reported

Figure 5 Locoregional recurrence – Event data at 5 years follow-up

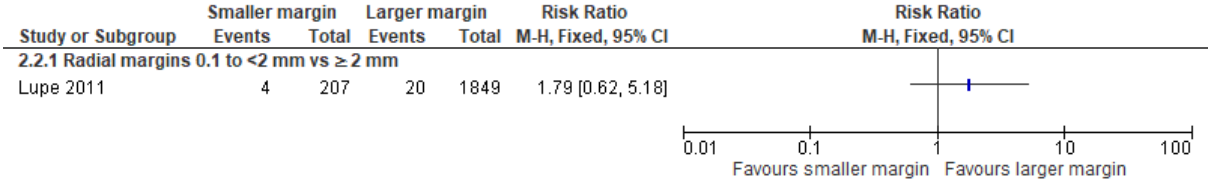


Figure 6 Locoregional recurrence – Event data at 10 years follow-up

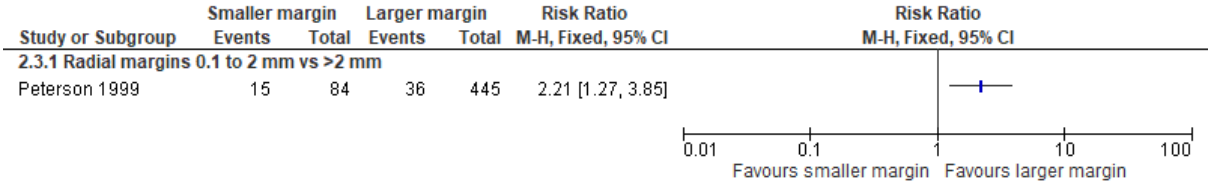
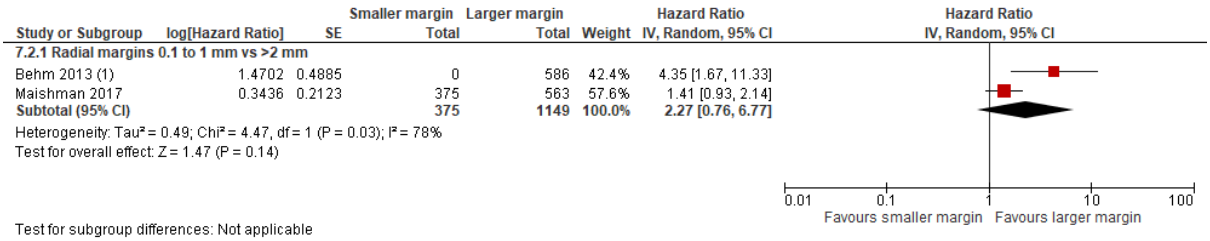


Figure 7 Pooled data combining local and locoregional recurrence – Hazard ratios at 10 years follow-up – data is presented in separate plots because each subgroup needed a different effect model (fixed or random)

Radial margins 0.1 to 1 mm vs >2 mm

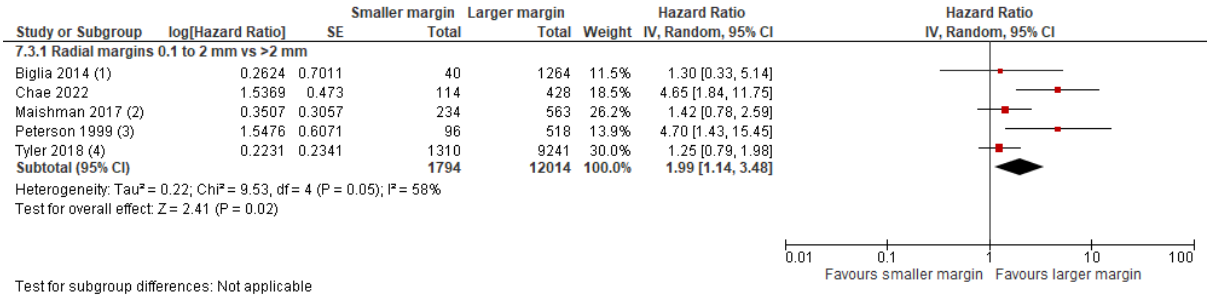


Test for subgroup differences: Not applicable

Footnotes

(1) Radial margins 0.1 to 1 mm vs >5 mm; sample size for the smaller margin was not reported

Radial margins 0.1 to 2 mm vs >2 mm

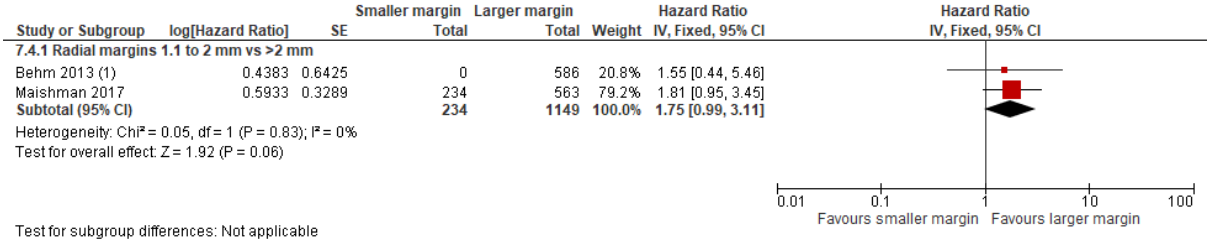


Test for subgroup differences: Not applicable

Footnotes

(1) Radial margins 0.1 to <2 mm vs ≥2 mm
(2) Radial margins 0.1 to 2 mm vs >2 mm
(3) Radial margins 0.1 to 2 mm vs >2 mm
(4) Radial margins 0.1 to 2 mm vs >2 mm

Radial margins 1.1 to 2 mm vs >2 mm

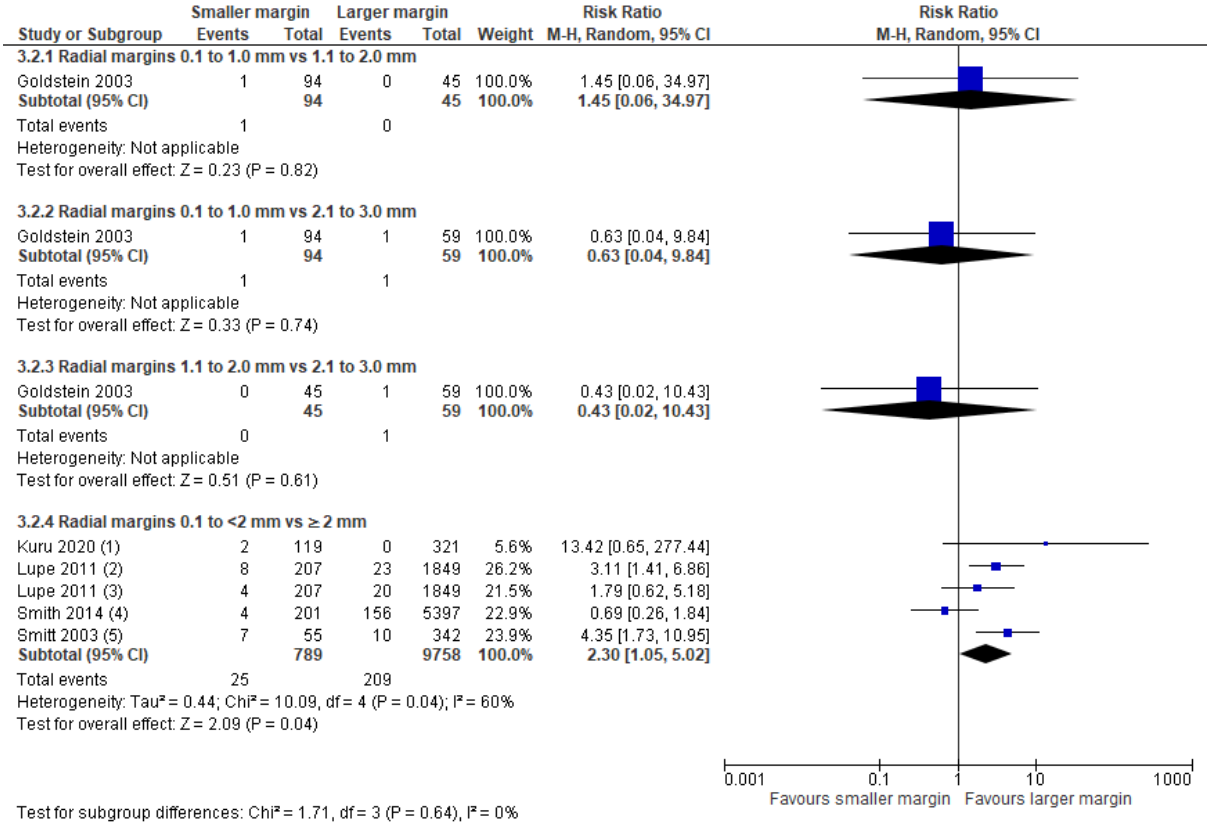


Test for subgroup differences: Not applicable

Footnotes

(1) Radial margins 0.1 to 1 mm vs >5 mm; sample size for the smaller margin was not reported

Figure 8 Pooled data combining local and locoregional recurrence – Event data at 5 years follow-up



Test for subgroup differences: Chi² = 1.71, df = 3 (P = 0.64), I² = 0%

Footnotes

(1) Radial margins 0.1 to <2 mm vs ≥2 mm

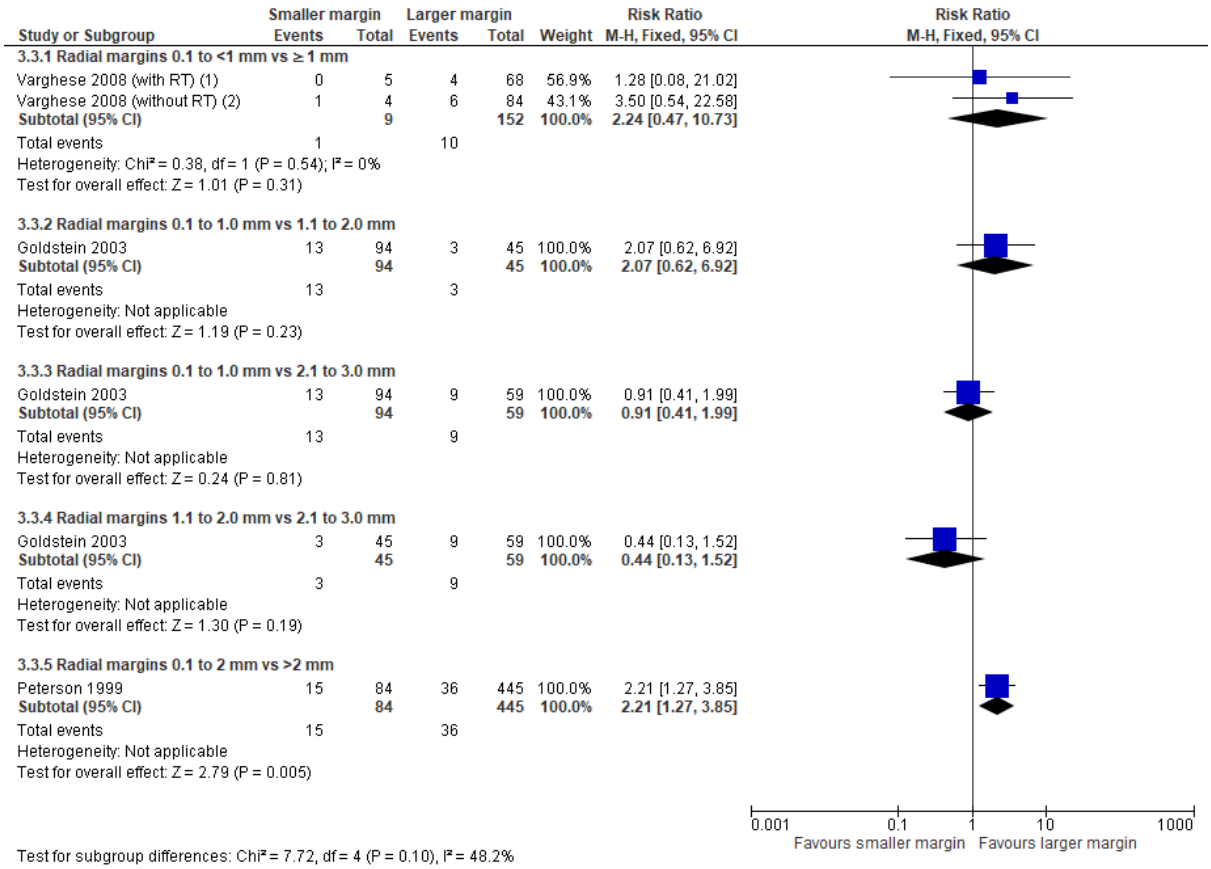
(2) Radial margins 0.1 to <2 mm vs ≥2 mm

(3) Data reported separately for locoregional recurrence

(4) Radial margins 0.1 to <2 mm vs ≥2 mm

(5) Radial margins 0.1 to 2 mm vs >2 mm; actual follow-up was 6 years

Figure 9 Pooled data combining local and locoregional recurrence – Event data at 10 years follow-up



Test for subgroup differences: Chi² = 7.72, df = 4 (P = 0.10), I² = 48.2%

Footnotes

(1) Varghese 2008 reported number of events and totals

(2) Varghese 2008 reported RR and 95% CI

Figure 10 Distant recurrence – Hazard ratios at 5 years follow-up

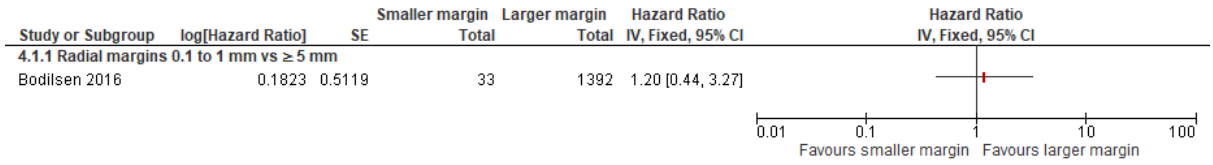


Figure 11 Distant recurrence – Hazard ratios at 10 years follow-up

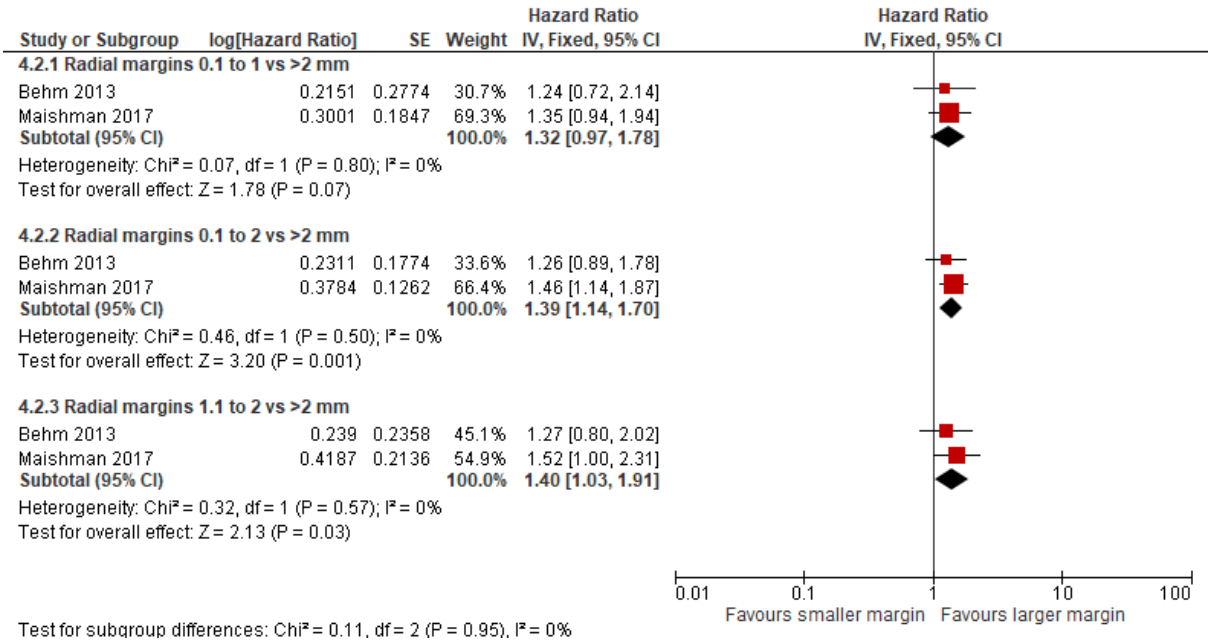


Figure 12 Distant recurrence – Event data at 5 years follow-up

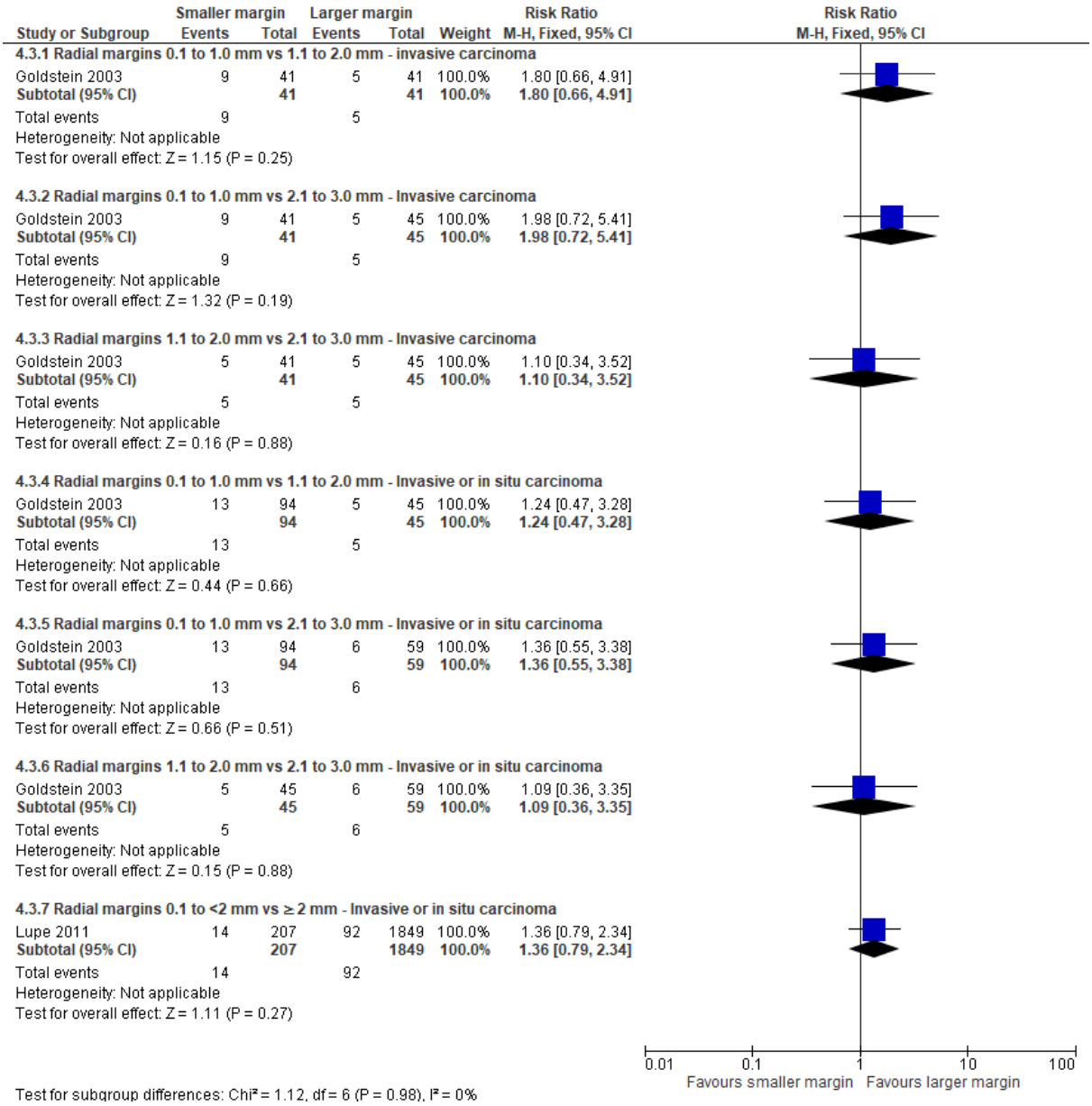
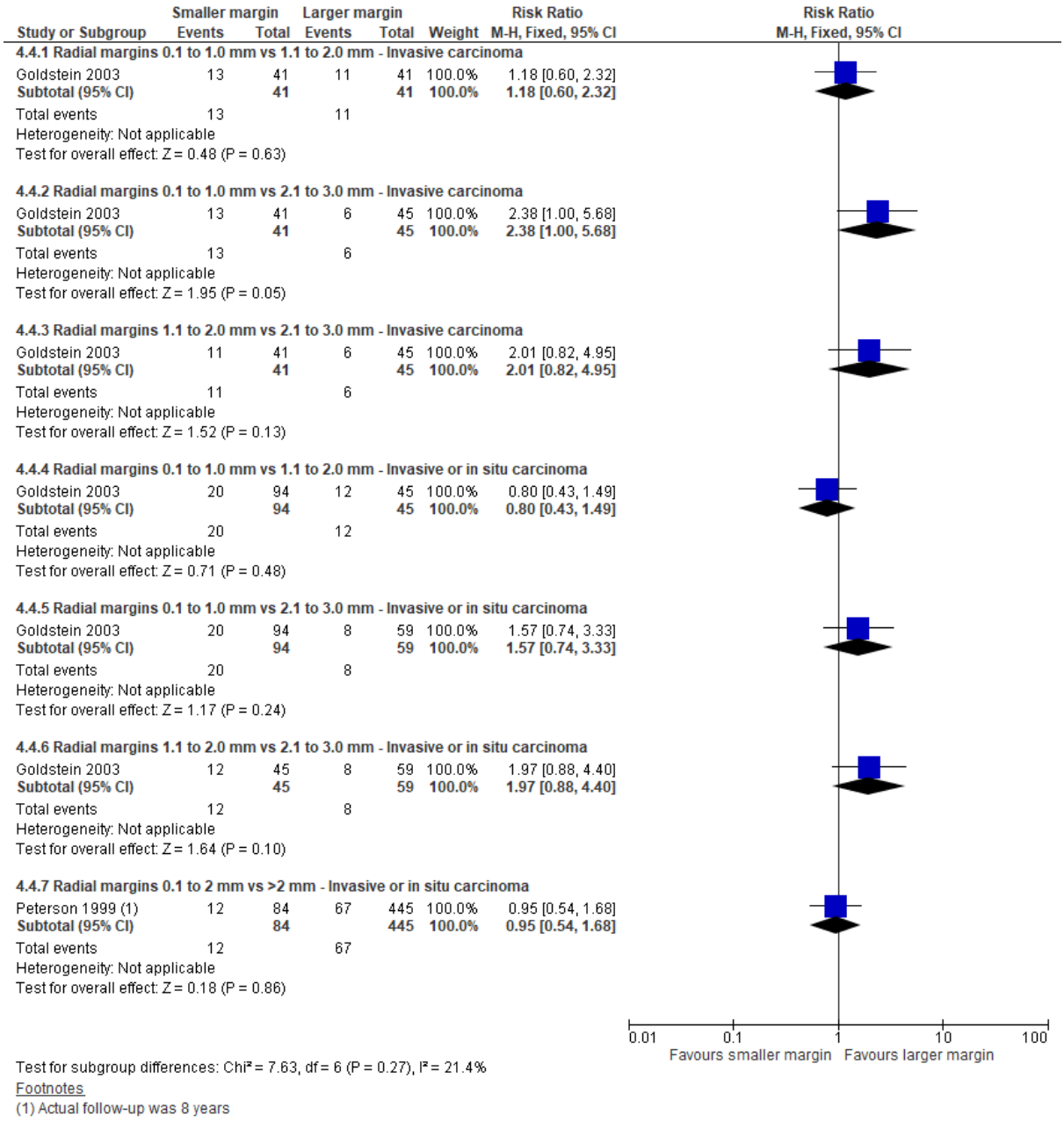


Figure 13 Distant recurrence – Event data at 10 years follow-up



Test for subgroup differences: Chi² = 7.63, df = 6 (P = 0.27), I² = 21.4%

Footnotes

(1) Actual follow-up was 8 years

Figure 14 Overall survival – Event data at 5 years follow-up

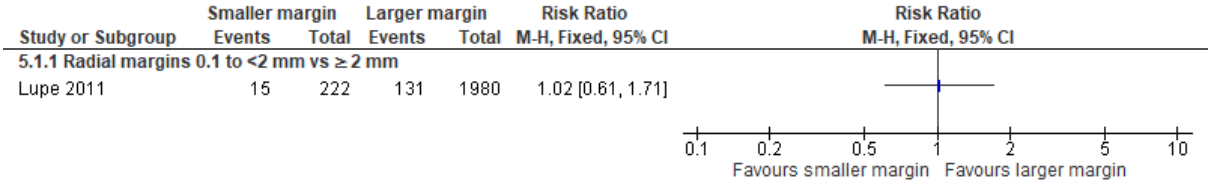


Figure 15 Overall survival – Event data at 10 years follow-up

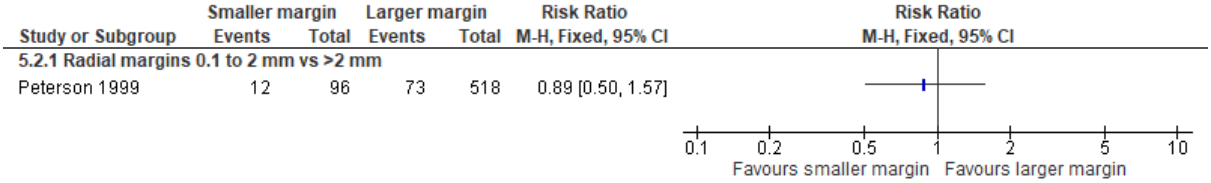


Figure 16 Breast cancer specific survival – Hazard ratios at 10 years follow-up

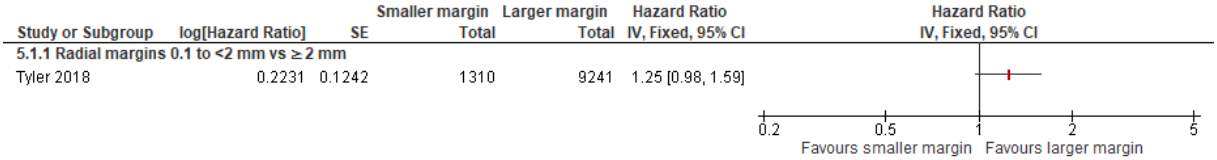


Figure 17 Breast cancer specific survival – Event data at 5 years follow-up

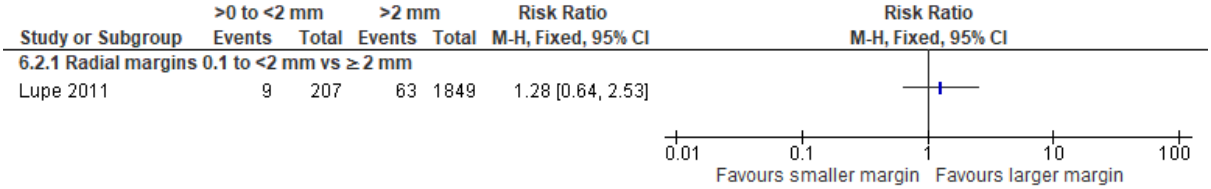


Figure 18 Breast cancer specific survival – Event data at 10 years follow-up

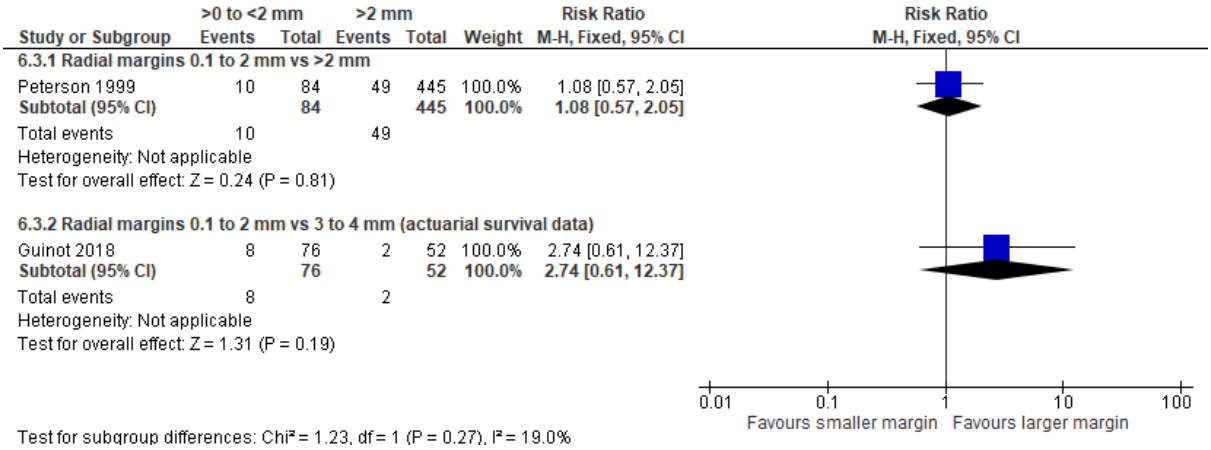
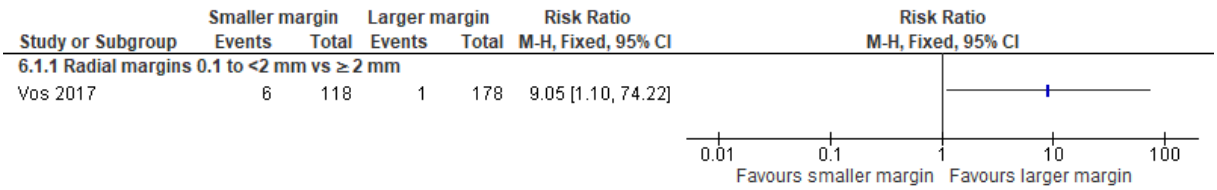
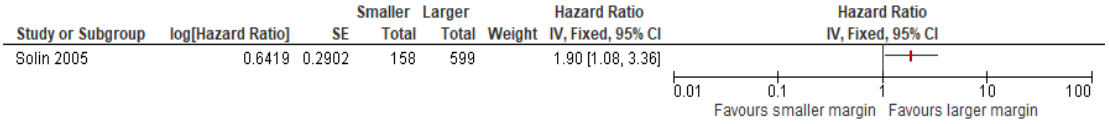


Figure 19 Re-operation rates – Event data at 5 years follow-up



Ductal carcinoma in situ

Figure 20 Local recurrence – Hazard ratios at 5 years follow-up*



*** Local recurrence - 0.1 to 1.9 mm vs. ≥2 mm - 5 years**

Figure 21 Local recurrence – Event data at 5 years follow-up

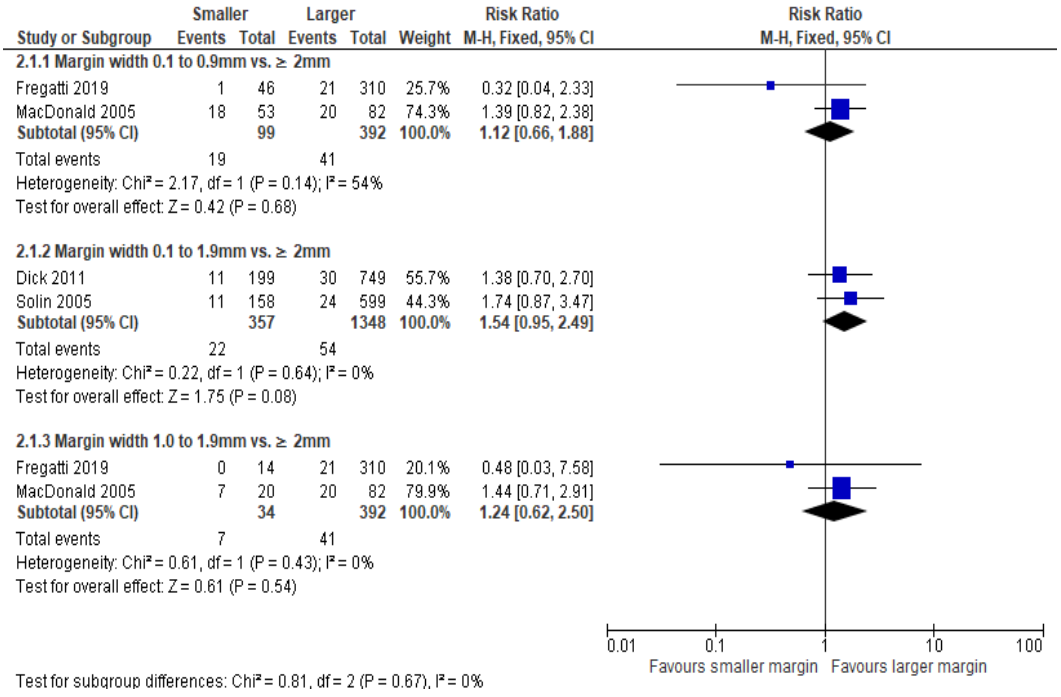


Figure 22 Local recurrence – Event-data at 10 years follow-up

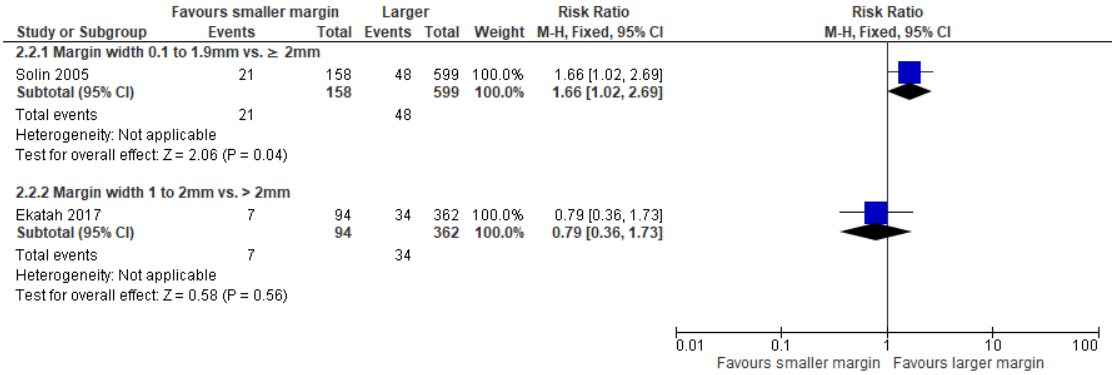
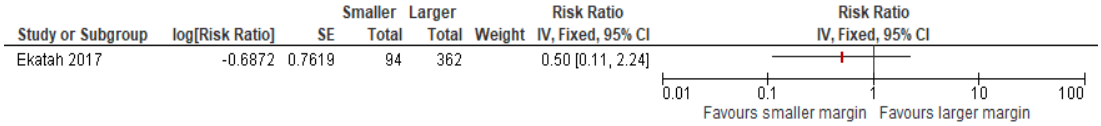


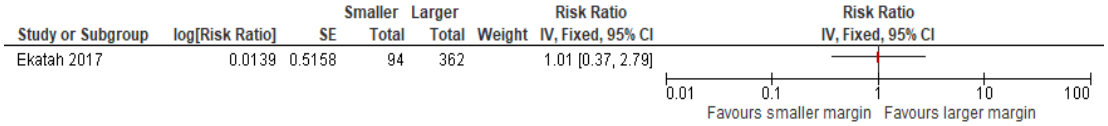
Figure 23 Local recurrence for invasive* – Event data 10 years follow-up**



* 466 patients with DCIS were included in the study. There were 44 in breast tumour recurrences in the 466 patients of which 27 were DCIS and 17 were invasive cancer.

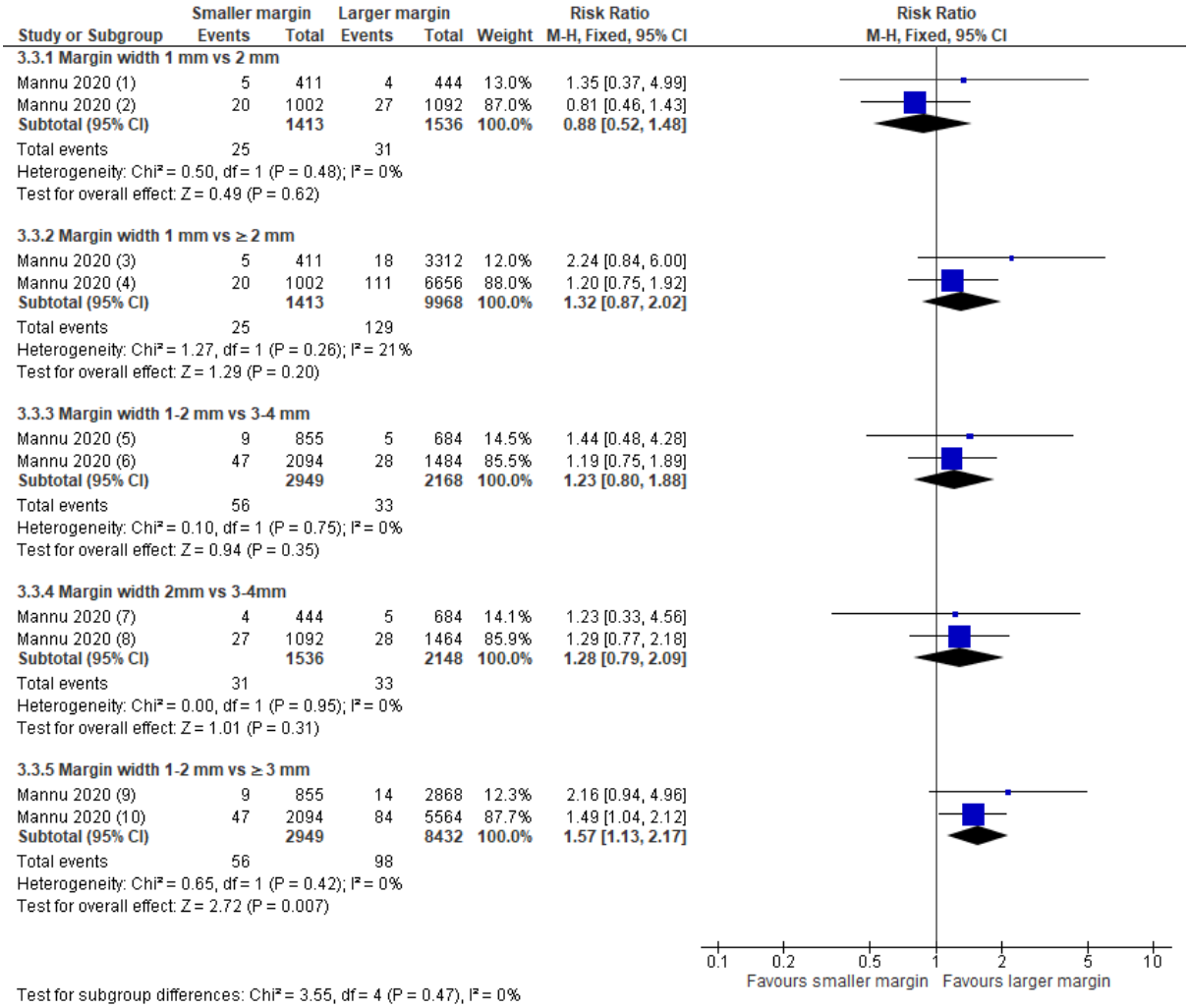
**** Margin width assessed was 1 to 2 mm vs. >2 mm**

Figure 24 Local recurrence for DCIS – Event data 10 years follow-up*



**** Margin width assessed was 1 to 2 mm vs. >2 mm**

Figure 25 Local recurrence (invasive breast cancer) – Event data at 0 to 14 years follow-up

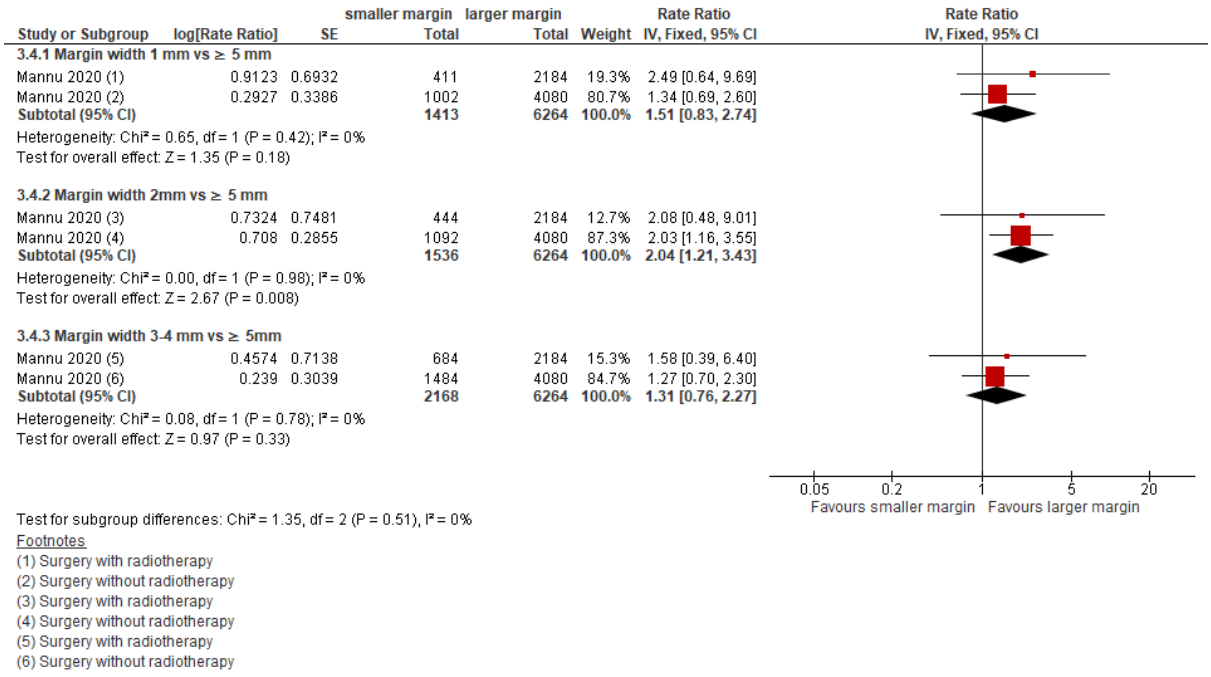


Test for subgroup differences: Chi² = 3.55, df = 4 (P = 0.47), I² = 0%

Footnotes

(1) Surgery with radiotherapy
(2) Surgery without radiotherapy
(3) Surgery with radiotherapy
(4) Surgery without radiotherapy
(5) Surgery with radiotherapy
(6) Surgery without radiotherapy
(7) Surgery with radiotherapy
(8) Surgery without radiotherapy
(9) Surgery with radiotherapy
(10) Surgery without radiotherapy

Figure 26 Local recurrence (invasive breast cancer) – Rate ratios at 0 to 14 years follow-up

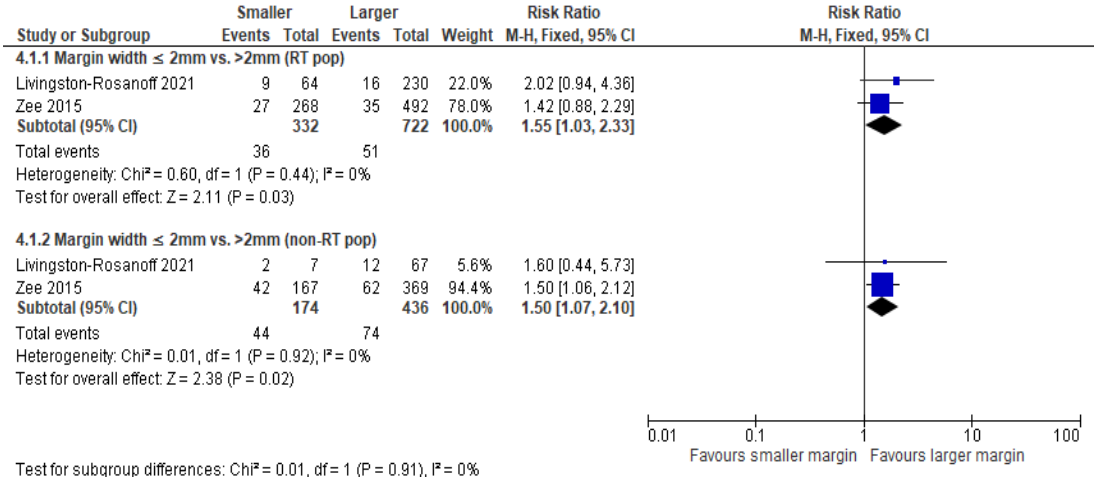


Test for subgroup differences: Chi² = 1.35, df = 2 (P = 0.51), I² = 0%

Footnotes

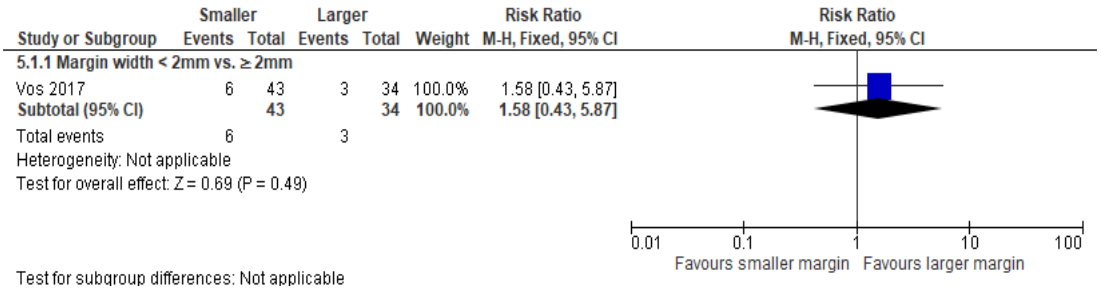
(1) Surgery with radiotherapy
(2) Surgery without radiotherapy
(3) Surgery with radiotherapy
(4) Surgery without radiotherapy
(5) Surgery with radiotherapy
(6) Surgery without radiotherapy

Figure 27 Loco-regional recurrence – Event data at 10 years follow-up



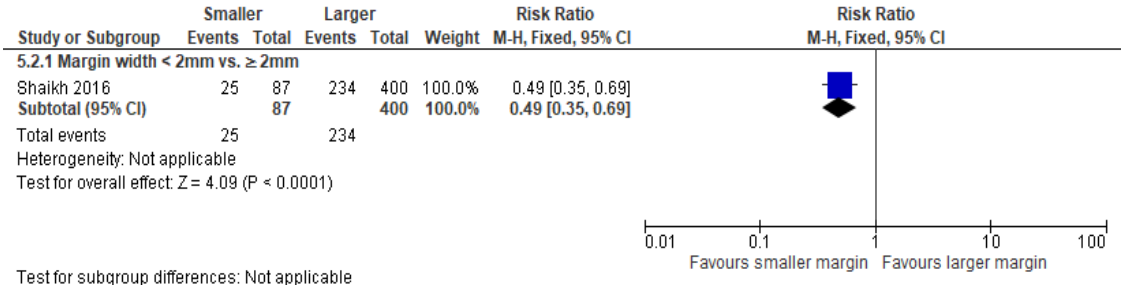
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%

Figure 28 Re-operation rates – Event data at 5 years follow-up



Test for subgroup differences: Not applicable

Figure 29 Re-operation rates – Event data at 10 years follow-up



Neoadjuvant therapy

Figure 30 Local recurrence – Hazard ratio at 10 years follow-up

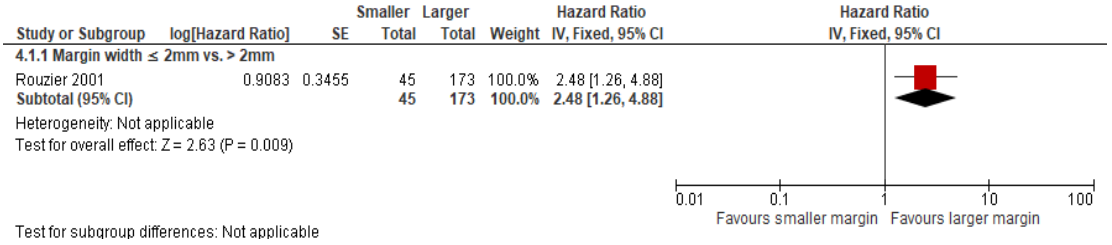


Figure 31 Local recurrence – Event data at 5 years follow-up

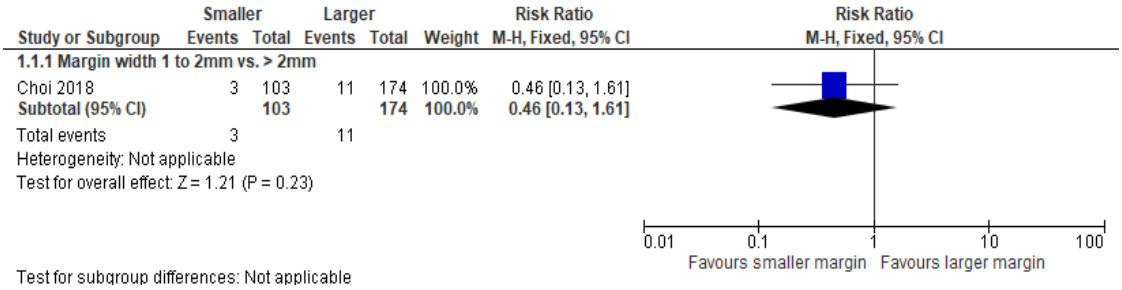


Figure 32 Distant recurrence - Event data at 5 years follow-up

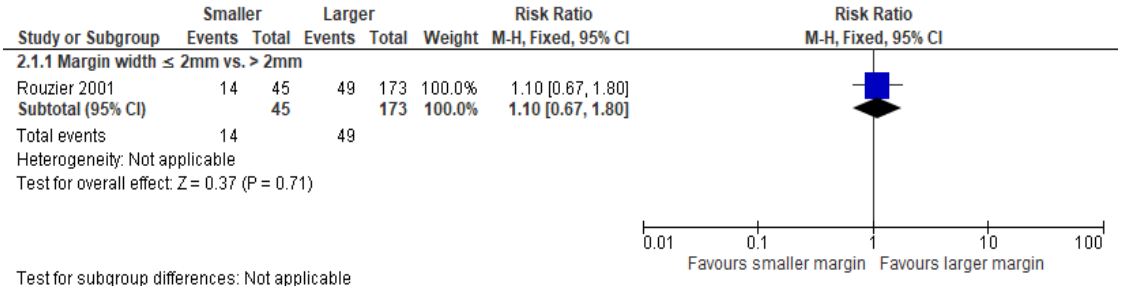


Figure 33 Distant recurrence - Event data at 10 years follow-up

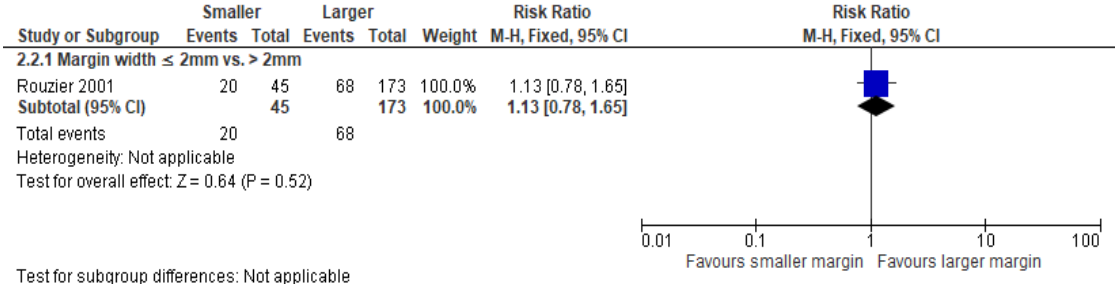
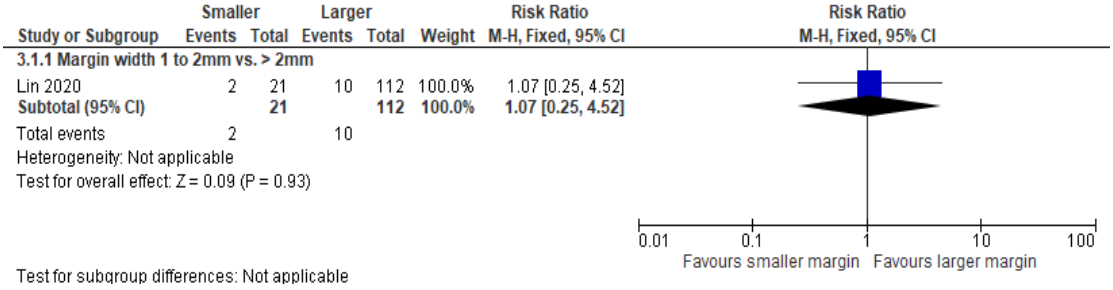


Figure 34 Local regional recurrence – Event data at 5 years follow-up



Appendix F – GRADE tables

Invasive breast cancer with or without DCIS

Table 39 Local recurrence – Hazard ratios at 10 years follow-up

Comparison / No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <1 mm vs ≥1 mm/ 2 (Keike 2008, Tang 2019)	Retrospective cohort study	1554	+/- 1.00	HR 1.71 (1.13, 2.58)	60 per 1000	42 more per 1000 (8 more to 95 more)	Serious[1]	Not serious	Not serious	Not serious	NA	Moderate
Radial margins 0.1 to 1 mm vs >2 mm/ 1 (Maishman 2017)	Prospective cohort study	938	+/- 1.00	HR 1.41 (0.93, 2.14)	53 per 1000	22 more per 1000 (4 fewer to 61 more)	Serious[1]	Not serious	NA[2]	Serious[3]	NA	Low
Radial margins 0.1 to 2 mm vs >2 mm/ 4 (Biglia 2014, Maishman 2017, Peterson	Prospective cohort study, retrospective cohort study	13266	+/- 1.00	HR 1.45 (1.04, 2.03)	30 per 1000	14 more per 1000 (1 more to 31 more)	Serious[1]	Not serious	Not serious	Not serious	NA	Moderate

Comparison / No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1999, Tyler 2018)												
Radial margins 0.1 to 2 mm vs >2 mm/ sensitivity analyses without Biglia 2014 (larger margin includes 2 mm) 3 (Maishman 2017, Peterson 1999, Tyler 2018)	Prospective cohort study, retrospective cohort study	11962	+/- 1.00	HR 1.63 (0.93, 2.87)	30 per 1000	19 more per 1000 (2 fewer to 57 more)	Not serious	Not serious	Serious[4]	Serious[3]	NA	Low
Radial margins 0.1 to 2 mm vs >2 mm/ sensitivity analyses without Peterson 1999 (unadjusted analysis)	Prospective cohort study, retrospective cohort study	12652	+/- 1.00	HR 1.31 (0.92, 1.86)	25 per 1000	8 more per 1000 (2 fewer to 21 more)	Not serious	Not serious	Not serious	Serious[3]	NA	Moderate

Comparison / No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
3 (Biglia 2014, Maishman 2017, Tyler 2018)												
Radial margins 1.1 to 2 mm vs >2 mm/				HR 1.81		43 more per 1000						
1 (Maishman 2017)	Prospective cohort study	797	+/- 1.00	(0.95, 3.45)	53 per 1000	(3 fewer to 130 more)	Serious[1]	Not serious	NA[2]	Serious[3]	NA	Low
1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												

Table 40 Local recurrence – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm/	Retrospective cohort study	139	+/- 1.00	RR 1.45 (0.06, 34.97)	0 per 1000	0 fewer per 1000 (0 more to 0 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1 (Goldstein 2003)												
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	153	+/- 1.00	RR 0.63 (0.04, 9.84)	17 per 1000	6 fewer per 1000 (16 fewer to 150 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	104	+/- 1.00	RR 0.43 (0.02, 10.43)	17 per 1000	10 fewer per 1000 (17 fewer to 160 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 0.1 to <2 mm vs ≥2 mm/ 4 (Kuru 2020 (A), Lupe 2011 (A), Smith 2014 (A), Smith 2003 (B))	Retrospective cohort study	8491	+/- 1.00	RR 2.53 (0.91, 7.03)	24 per 1000	36 more per 1000 (2 fewer to 144 more)	Very serious[1]	Not serious	Very serious[5]	Serious[3]	NA	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												
4. Sample size <500												

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
5. I2 > 66.6%												
(A) Radial margins 0.1 to < 2mm vs. ≥ 2mm												
(B) Radial margins 0.1 to 2 mm vs. > 2mm												

Table 41 Local recurrence – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <1 mm vs ≥1 mm/ 1 (Varghese 2008 [with radiotherapy] (A),Varghese 2008 [without radiotherapy] (B))	Retrospective cohort study	161	+/- 1.00	RR 2.24 (0.47, 10.73)	66 per 1000	81 more per 1000 (35 fewer to 640 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm/	Retrospective cohort study	139	+/- 1.00	RR 2.07 (0.62, 6.92)	67 per 1000	72 more per 1000 (25 fewer to 394 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1 (Goldstein 2003)												
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	153	+/- 1.00	RR 0.91 (0.41, 1.99)	153 per 1000	14 fewer per 1000 (89 fewer to 151 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	104	+/- 1.00	RR 0.44 (0.13, 1.52)	153 per 1000	86 fewer per 1000 (133 fewer to 80 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												
4. Sample size <500												
(A) Varghese 2008 reported number of events and totals												
(B) Varghese 2008 reported RR and 95% CI												

Table 42 Locoregional recurrence – Hazard ratios at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 2 mm vs >2 mm/ 1 (Chae 2022)	Retrospective cohort study	542	+/- 1.00	HR 4.65 (1.84, 11.75)	35 per 1000	128 more per 1000 (29 more to 377 more)	Serious[1]	Not serious	NA[2]	Not serious	NA	Moderate
Radial margins 0.1 to 1 mm vs >5 mm/ 1 (Behm 2013)	Retrospective cohort study	701*	+/- 1.00	HR 4.35 (1.67, 11.33)	Not Estimable	Not Estimable 3	Serious[1]	Not serious	NA[2]	Not serious	NA	Moderate
Radial margins 1.1 to 2 mm vs >5 mm/ 1 (Behm 2013)	Retrospective cohort study	701*	+/- 1.00	HR 1.55 (0.44, 5.46)	Not Estimable	Not Estimable 3	Serious[1]	Not serious	NA[2]	Serious[4]	NA	Low
1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias												
2. Only one study so no inconsistency												
3. Study did not report number of events												
4. 95% confidence intervals cross line of no effect												
* Study did not report sample size for the smaller margin												

Table 43 Locoregional recurrence – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <2 mm vs ≥2 mm/ 1 (Lupe 2011)	Retrospective cohort study	2056	+/- 1.00	RR 1.79 (0.62, 5.18)	11 per 1000	9 more per 1000 (4 fewer to 45 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												

Table 44 Locoregional recurrence – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 2 mm vs >2 mm/ 1 (Peterson 1999)	Prospective cohort study	529	+/- 1.00	RR 2.21 (1.27, 3.85)	81 per 1000	98 more per 1000 (22 more to 230 more)	Very serious[1]	Not serious	NA[2]	Not serious	NA	Low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												

Table 45 Pooled data combining local and locoregional recurrence – Hazard ratios at 10-year follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1 mm vs >2 mm/ 2 (Behm 2013, Masihman 2017)	Prospective cohort study, retrospective cohort study	1524*	+/- 1.00	HR 2.27 (0.76, 6.77)	26 per 1000 **	33 more per 1000 (6 fewer to 151 more)	Serious[1]	Not serious	Very serious[2]	Serious[3]	NA	Very low
Radial margins 0.1 to 2 mm vs >2 mm/ 5 (Biglia 2014, Chae 2022, Maishman 2017, Peterson 1999, Tyler 2018)	Prospective cohort study, retrospective cohort study	13808	+/- 1.00	HR 1.99 (1.14, 3.48)	30 per 1000	30 more per 1000 (4 more to 75 more)	Serious[1]	Not serious	Serious[4]	Not serious	NA	Low
Radial margins 1.1 to 2 mm vs >2 mm/ 2 (Behm 2013, Masihman 2017)	Prospective cohort study, retrospective cohort study	1383*	+/- 1.00	HR 1.75 (0.99, 3.11)	26 per 1000 **	20 more per 1000 (0 more to 55 more)	Serious[1]	Not serious	Not serious	Serious[3]	NA	Low

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias

2. I2 > 66.6%

3. 95% confidence intervals cross line of no effect

4. I2 between 33.3% and 66.6%%

* Behm 2013 did not report the sample size for the smaller margin

** Absolute risk was calculated with data from Maishman 2017 because Behm 2013 did not report number of events

Table 46 Pooled data combining local and locoregional recurrence – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	139	+/- 1.00	RR 1.45 (0.06, 34.97)	0 per 1000	0 fewer per 1000 (0 more to 0 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	very low
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	153	+/- 1.00	RR 0.63 (0.04, 9.84)	17 per 1000	6 fewer per 1000 (16 fewer to 150 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	very low
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	104	+/- 1.00	RR 0.43 (0.02, 10.43)	17 per 1000	10 fewer per 1000 (17 fewer to 160 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <2 mm vs ≥2 mm/ 4 (Kuru 2020 (A) Lupe 2011 (B) Lupe 2011 (C) Smith 2014 (A) Smitt 2003 (B))	Retrospective cohort study	10547	+/- 1.00	RR 2.30 (1.05, 5.02)	21 per 1000	28 more per 1000 (1 more to 86 more)	Very serious[1]	Not serious	serious[5]	Not serious	NA	very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												
4. Sample size <500												
5. I2 between 33.3% and 66.6%%												
(A) Radial margins 0.1 to < 2mm vs. ≥ 2mm												
(B) Radial margins 0.1 to 2 mm vs. > 2mm												
(C) Data reported separately for locoregional recurrence												

Table 47 Pooled data combining local and locoregional recurrence – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <1 mm vs ≥1 mm/ 1 (Varghese 2008 [with radiotherapy] (A),Varghese 2008 [without radiotherapy] (B))	Retrospective cohort study	161	+/- 1.00	RR 2.24 (0.47, 10.73)	66 per 1000	81 more per 1000 (35 fewer to 640 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	139	+/- 1.00	RR 2.07 (0.62, 6.92)	67 per 1000	72 more per 1000 (25 fewer to 394 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm/ 1 (Goldstein 2003)	Retrospective cohort study	153	+/- 1.00	RR 0.91 (0.41, 1.99)	153 per 1000	14 fewer per 1000 (89 fewer to 151 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm/	Retrospective cohort study	104	+/- 1.00	RR 0.44 (0.13, 1.52)	153 per 1000	86 fewer per 1000 (133 fewer to 80 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1 (Goldstein 2003)												
Radial margins 0.1 to 2 mm vs >2 mm/				RR 2.21		98 more per 1000						
1 (Peterson 1999)	Prospective cohort study	529	+/- 1.00	(1.27, 3.85)	81 per 1000	(22 more to 230 more)	Very serious[1]	Not serious	NA[2]	Not serious	NA	low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												
4. Sample size <500												

Table 48 Distant recurrence – Hazard ratios at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1 mm vs ≥5 mm/				HR 1.20		16 more per 1000						
1 (Bodilsen 2016)	Retrospective cohort study	1425	+/- 1.00	(0.44, 3.27)	81 per 1000	(45 fewer to 184 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross line of no effect

Table 49 Distant recurrence – Hazard ratios at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1 vs >2 mm/ 2 (Behm 2013, Maishman 2017)	Prospective cohort study, retrospective cohort study	2889	+/- 1.00	HR 1.32 (0.97, 1.78)	103 per 1000	32 more per 1000 (3 fewer to 80 more)	Serious[1]	Not serious	Not serious	Serious[2]	NA	Low
Radial margins 0.1 to 2 vs >2 mm/ 2 (Behm 2013, Maishman 2017)	Prospective cohort study, retrospective cohort study	3238	+/- 1.00	HR 1.39 (1.14, 1.70)	105 per 1000	41 more per 1000 (14 more to 73 more)	Serious[1]	Not serious	Not serious	Not serious	NA	Moderate
Radial margins 1.1 to 2 vs >2 mm/	Prospective cohort study, retrospective cohort study	2857	+/- 1.00	HR 1.40 (1.03, 1.91)	103 per 1000	41 more per 1000 (3 more to 94 more)	Serious[1]	Not serious	Not serious	Not serious	NA	Moderate

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
2 (Behm 2013, Maishman 2017)												
1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias												
2. 95% confidence intervals cross line of no effect												

Table 50 Distant recurrence – Event data at 5years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	82	+/- 1.00	RR 1.80 (0.66, 4.91)	122 per 1000	98 more per 1000 (42 fewer to 477 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive carcinoma/	Retrospective cohort study	86	+/- 1.00	RR 1.98 (0.72, 5.41)	111 per 1000	108 more per 1000 (31 fewer to 490 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1 (Goldstein 2003)												
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	86	+/- 1.00	RR 1.10 (0.34, 3.52)	111 per 1000	11 more per 1000 (73 fewer to 280 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive or in situ carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	139	+/- 1.00	RR 1.24 (0.47, 3.28)	111 per 1000	27 more per 1000 (59 fewer to 253 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	153	+/- 1.00	RR 1.36 (0.55, 3.38)	102 per 1000	37 more per 1000 (46 fewer to 242 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	104	+/- 1.00	RR 1.09 (0.36, 3.35)	102 per 1000	9 more per 1000 (66 fewer to 239 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to <2 mm vs ≥2 mm - invasive or in situ carcinoma/ 1 (Lupe 2011)	Retrospective cohort study	2056	+/- 1.00	RR 1.36 (0.79, 2.34)	50 per 1000	18 more per 1000 (10 fewer to 67 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												
4. Sample size <500												

Table 51 Distant recurrence – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1.0 mm vs 1.1 to 2.0 mm - invasive carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	82	+/- 1.00	RR 1.18 (0.60, 2.32)	268 per 1000	49 more per 1000 (107 fewer to 355 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	86	+/- 1.00	RR 2.38 (1.00, 5.68)	133 per 1000	184 more per 1000 (0 more to 623 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	86	+/- 1.00	RR 2.01 (0.82, 4.95)	133 per 1000	135 more per 1000 (24 fewer to 527 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to 1.0 mm vs	Retrospective cohort study	139	+/- 1.00	RR 0.80 (0.43, 1.49)	267 per 1000	54 fewer per 1000	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1.1 to 2.0 mm - invasive or in situ carcinoma/ 1 (Goldstein 2003)						(152 fewer to 129 more)						
Radial margins 0.1 to 1.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	153	+/- 1.00	RR 1.57 (0.74, 3.33)	136 per 1000	77 more per 1000 (35 fewer to 316 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 1.1 to 2.0 mm vs 2.1 to 3.0 mm - invasive or in situ carcinoma/ 1 (Goldstein 2003)	Retrospective cohort study	104	+/- 1.00	RR 1.97 (0.88, 4.40)	136 per 1000	131 more per 1000 (17 fewer to 462 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded by one[4]	Very low
Radial margins 0.1 to 2 mm vs >2 mm - invasive	Prospective cohort study	529	+/- 1.00	RR 0.95 (0.54, 1.68)	151 per 1000	8 fewer per 1000 (70 fewer to 102 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
or in situ carcinoma/ 1 (Peterson 1999)												
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												
4. Sample size <500												

Table 52 Overall survival – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <2 mm vs ≥2 mm/ 1 (Lupe 2011)	Retrospective cohort study	2202	+/- 1.00	RR 1.02 (0.61, 1.71)	66 per 1000	1 more per 1000 (26 fewer to 47 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												

Table 53 Overall survival – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 2 mm vs >2 mm/ 1 Peterson 1999)	Prospective cohort study	614	+/- 1.00	RR 0.89 (0.50, 1.57)	141 per 1000	16 fewer per 1000 (70 fewer to 80 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												

Table 54 Breast cancer specific survival – Hazard ratios at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <2 mm vs ≥2 mm/ 1 (Tyler 2018)	Retrospective cohort study	10551	+/- 1.00	HR 1.25 (0.98, 1.59)	61 per 1000	15 more per 1000 (1 fewer to 36 more)	Serious[1]	Not serious	NA[2]	Serious[3]	NA	Low
1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												

Table 55 Breast cancer specific survival – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <2 mm vs ≥2 mm/ 1 (Lupe 2011)	Retrospective cohort study	2056	+/- 1.00	RR 1.28 (0.64, 2.53)	34 per 1000	9 more per 1000 (12 fewer to 52 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross line of no effect												

Table 56 Breast cancer specific survival – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 2 mm vs >2 mm/ 1 (Peterson 1999)	Prospective cohort study	529	+/- 1.00	RR 1.08 (0.57, 2.05)	110 per 1000	9 more per 1000 (47 fewer to 115 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	NA	Very low
Radial margins 0.1 to 2 mm vs 3 to 4 mm	Prospective cohort study	128	+/- 1.00	RR 2.74 (0.61, 12.37)	38 per 1000	67 more per 1000 (15 fewer to 437 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

(actuarial survival data)/ 1 (Guinot 2018)
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross line of no effect
4. Sample size <500

Table 57 Reoperation rates – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to <2 mm vs ≥2 mm/ 1 (Vos 2017)	Retrospective cohort study	296	0.80, 1.25	RR 9.05 (1.10, 74.22)	6 per 1000	45 more per 1000 (1 more to 411 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias												
2. Only one study so no inconsistency												
3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)												
4. sample size <500												

Ductal carcinoma in situ only

Table 58 Local recurrence - Hazard ratio at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 1.9 mm vs. ≥2 mm/ 1 (Solin 2005)	Retrospective cohort study	757	+/- 1.00	HR 1.90 (1.08, 3.36)	40 per 1000	36 more per 1000 (3 more to 94 more)	Very serious [1]	Not serious	NA[2]	Not serious	NA	Low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency

Table 59 Local recurrence – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 0.1 to 0.9mm vs. ≥ 2mm/ 2 (Fregatti 2019, MacDonald 2005)	Prospective cohort study, retrospective cohort study	491	+/- 1.00	RR 1.12 (0.66, 1.88)	105 per 1000	12 more per 1000 (35 fewer to 92 more)	Very serious[1]	Not serious	Serious[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins 0.1 to 1.9mm vs. ≥ 2mm/	Retrospective cohort study	1705	+/- 1.00	RR 1.54 (0.95, 2.49)	40 per 1000	22 more per 1000 (2 fewer to 60 more)	Very serious[1]	Not serious	Not serious	Serious[3]	NA	Very low

2 (Dick 2011, Solin 2005)												
Radial margins 1.0 to 1.9mm vs. ≥ 2mm/ 2 (Fregatti 2019, MacDonald 2005)	Prospective cohort study, retrospective cohort study	426	+/- 1.00	RR 1.24 (0.62, 2.50)	105 per 1000	25 more per 1000 (40 fewer to 157 more)	Very serious[1]	Not serious	Not serious	Serious[3]	Downgraded an extra level[4]	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
3. I2 between 33.3% and 66.6%
4. 95% confidence intervals cross line of no effect
5. Sample size < 500

Table 60 Local recurrence – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins -0.1 to 1.9mm vs. ≥ 2mm/ 1 (Solin 2005)	Retrospective cohort study	757	+/- 1.00	RR 1.66 (1.02, 2.69)	80 per 1000	53 more per 1000 (2 to 135 more)	Very serious[1]	Not serious	NA[2]	Not serious	NA	Low
Radial margins 1 to 2mm vs. > 2mm/ 1 (Ekatah 2017)	Retrospective cohort study	456	+/- 1.00	RR 0.79 (0.36, 1.73)	94 per 1000	19 fewer per 1000 (60 fewer to 69 more)	Serious[3]	Not serious	NA[2]	Serious[4]	Downgraded an extra level[5]	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency

3. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias

4. 95% confidence intervals cross line of no effect

5. Sample size < 500

Table 61 Local recurrence invasive – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1 to 2mm vs. > 2mm (Local recurrence for invasive)*/				RR 0.50		47 fewer per 1000					Downgraded an extra level[4]	
1 (Ekatah 2017)	Retrospective cohort study	456	+/- 1.00	(0.11, 2.24)	94 per 1000	(83 fewer to 116 more)	Serious[1]	Not serious	NA[2]	Serious[3]		Very low

* 466 patients with DCIS were included in the study. There were 44 in breast tumour recurrences in the 466 patients of which 27 were DCIS and 17 were invasive cancer

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross line of no effect

4. Sample size < 500

Table 62 Local recurrence DCIS – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1 to 2mm vs. > 2mm (Local recurrence for DCIS)*/				RR 1.01		1 more per 1000					Downgraded an extra level[4]	
1 (Ekatah 2017)	Retrospective cohort study	456	+/- 1.00	(0.37, 2.79)	94 per 1000	(59 fewer to 168 more)	Serious[1]	Not serious	NA[2]	Serious[3]		Very low

* 466 patients with DCIS were included in the study. There were 44 in breast tumour recurrences in the 466 patients of which 27 were DCIS and 17 were invasive cancer

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross line of no effect
4. Sample size < 500

Table 63 Local recurrence (invasive breast cancer) – Event data at 0 to 14 years follow-up*

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1 mm vs. 2 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	855	+/- 1.00	RR 1.35 (0.37, 4.99)	9 per 1000	3 more per 1000 (6 fewer to 36 more)	Very serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 1 mm vs. 2 mm (surgery without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	2094	+/- 1.00	RR 0.81 (0.46, 1.43)	25 per 1000	5 fewer per 1000 (13 fewer to 11 more)	Very serious[1]	Not serious	NA[3]	Serious[4]	NA	Very low
Radial margins 1 mm vs. 2 mm (pooled total: surgery with or without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	2949	+/- 1.00	RR 0.88 (0.52, 1.48)	20 per 1000	2 fewer per 1000 (10 fewer to 10 more)	Very serious[1]	Not serious	Not serious	Serious[4]	NA	Very low
Radial margins 1 mm vs. ≥2 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	3723	+/- 1.00	RR 2.24 (0.84, 6.00)	5 per 1000	6 more per 1000 (1 fewer to 25 more)	Very serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 1 mm vs. ≥2 mm (surgery	Retrospective cohort study	7658	+/- 1.00	RR 1.20 (0.75, 1.92)	17 per 1000	3 more per 1000	Very serious[1]	Not serious	NA[3]	Serious[4]	NA	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
without radiotherapy) 1 (Mannu 2020)						(4 fewer to 16 more)						
Radial margins 1 mm vs. ≥2 mm (pooled total: surgery with or without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	11381	+/- 1.00	RR 1.32 (0.87, 2.02)	13 per 1000	4 more per 1000 (2 fewer to 13 more)	Very serious[1]	Not serious	Not serious	Serious[4]	NA	Very low
Radial margins 1 to 2 mm vs. 3 to 4 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	1539	+/- 1.00	RR 1.44 (0.48, 4.28)	7 per 1000	3 more per 1000 (4 fewer to 23 more)	Very serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 1 to 2 mm vs. 3 to 4 mm (surgery without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	3578	+/- 1.00	RR 1.19 (0.75, 1.89)	19 per 1000	4 more per 1000 (5 fewer to 17 more)	Very serious[1]	Not serious	NA[3]	Serious[4]	NA	Very low
Radial margins 1 to 2 mm vs. 3 to 4 mm (pooled total: surgery with or without radiotherapy)	Retrospective cohort study	5117	+/- 1.00	RR 1.23 (0.80, 1.88)	15 per 1000	3 more per 1000 (3 fewer to 13 more)	Very serious[1]	Not serious	Not serious	Serious[4]	NA	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
1 (Mannu 2020)												
Radial margins 2 mm vs. 3 to 4 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	1128	+/- 1.00	RR 1.23 (0.33, 4.56)	7 per 1000	2 more per 1000 (5 fewer to 25 more)	Very serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 2 mm vs. 3 to 4 mm (surgery without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	2556	+/- 1.00	RR 1.29 (0.77, 2.18)	19 per 1000	6 more per 1000 (4 fewer to 22 more)	Very serious[1]	Not serious	NA[3]	Serious[4]	NA	Very low
Radial margins 2 mm vs. 3 to 4 mm (pooled total: surgery with or without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	3684	+/- 1.00	RR 1.28 (0.79, 2.09)	15 per 1000	4 more per 1000 (3 fewer to 16 more)	Very serious[1]	Not serious	Not serious	Serious[4]	NA	Very low
Radial margins 1 to 2 mm vs. ≥3 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	3723	+/- 1.00	RR 2.16 (0.94, 4.96)	5 per 1000	6 more per 1000 (0 more to 20 more)	Very serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 1 to 2 mm vs. ≥3 mm	Retrospective cohort study	7658	+/- 1.00	RR 1.49 (1.04, 2.12)	15 per 1000	17 more per 1000	Very serious[1]	Not serious	NA[3]	Not serious	NA	Low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
(surgery without radiotherapy) 1 (Mannu 2020)						(1 more to 17 more)						
Radial margins 1 to 2 mm vs. ≥3 mm (pooled total: surgery with or without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	11381	+/- 1.00	RR 1.57 (1.13, 2.17)	12 per 1000	7 more per 1000 (2 more to 14 more)	Very serious[1]	Not serious	Not serious	Not serious	NA	Low

* Study reported the number of people with follow-up times in 5 year intervals from 0-4 years to 14 years. Results were not stratified by follow-up time and mean follow-up time is not reported

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias

2. >33.3% of the weight in a meta-analysis came from partially applicable studies (64% of people with radiotherapy had a follow-up time of 0 to 4 years and our protocol specified at least 5 years)

3. Only one study so no inconsistency

4. 95% confidence intervals cross line of no effect

Table 64 Local recurrence (invasive breast cancer) – Rate ratios at 0 to 14 years follow-up*

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1 mm vs. ≥5 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	2595	+/- 1.00	Rate Ratios 2.49 (0.64, 9.69)	4 per 1000	6 more per 1000 (1 fewer to 35 more)	Serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 1 mm vs. ≥5 mm (surgery without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	5082	+/- 1.00	Rate Ratios 1.34 (0.69, 2.60)	14 per 1000	5 more per 1000 (4 fewer to 22 more)	Serious[1]	Not serious	NA[3]	Serious[4]	NA	Low
Radial margins 1 mm vs. ≥5 mm (pooled total: surgery with or without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	7677	+/- 1.00	Rate Ratios 1.51 (0.83, 2.74)	10 per 1000	5 more per 1000 (2 fewer to 17 more)	Serious[1]	Not serious	Not serious	Serious[4]	NA	Low
Radial margins 2 mm vs. ≥5 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	2628	+/- 1.00	Rate Ratios 2.08 (0.48, 9.01)	4 per 1000	4 more per 1000 (2 fewer to 32 more)	Serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 2 mm vs. ≥5 mm (surgery without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	5172	+/- 1.00	Rate Ratios 2.03 (1.16, 3.55)	14 per 1000	14 more per 1000 (2 fewer to 36 more)	Serious[1]	Not serious	NA[3]	Not serious	NA	Moderate
Radial margins 2 mm vs. ≥5 mm (pooled total: surgery with or without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	7800	+/- 1.00	Rate Ratios 2.04 (1.21, 3.43)	10 per 1000	10 more per 1000 (2 fewer to 24 more)	Serious[1]	Not serious	Not serious	Not serious	NA	Moderate
Radial margins 3 to 4 mm vs. ≥5 mm (surgery with radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	2868	+/- 1.00	Rate Ratios 1.58 (0.39, 6.40)	4 per 1000	2 more per 1000 (2 fewer to 22 more)	Serious[1]	Serious[2]	NA[3]	Serious[4]	NA	Very low
Radial margins 3 to 4 mm vs. ≥5 mm (surgery without radiotherapy) 1 (Mannu 2020)	Retrospective cohort study	5564	+/- 1.00	Rate Ratios 1.27 (0.70, 2.30)	14 per 1000	4 more per 1000 (4 fewer to 18 more)	Serious[1]	Not serious	NA[3]	Serious[4]	NA	Low
Radial margins 3 to 4 mm vs. ≥5 mm (pooled total: surgery	Retrospective cohort study	8432	+/- 1.00	Rate Ratios 1.31	10 per 1000	3 more per 1000	Serious[1]	Not serious	Not serious	Serious[4]	NA	Low

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
with or without radiotherapy) 1 (Mannu 2020)				(0.76, 2.27)		(2 fewer to 13 more)						

* Study reported the number of people with follow-up times in 5 year intervals from 0-4 years to 14 years. Results were not stratified by follow-up time and mean follow-up time is not reported

1. >33.3% of the weight in a meta-analysis came from studies at moderate risk of bias

2. >33.3% of the weight in a meta-analysis came from partially applicable studies (64% of people with radiotherapy had a follow-up time of 0 to 4 years and our protocol specified at least 5 years)

3. Only one study so no inconsistency

4. 95% confidence intervals cross line of no effect

Table 65 Local regional recurrence – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins ≤ 2mm vs. > 2mm (with radiotherapy)/ 2 (Livingston-Rosanoff 2021, Zee 2015)	Prospective cohort study, retrospective cohort study	1054	+/- 1.00	RR 1.55 (1.03, 2.33)	71 per 1000	39 more per 1000 (2 more to 94 more)	Very serious[1]	Not serious	Not serious	Not serious	NA	Low
Radial margins ≤ 2mm vs. > 2mm (without radiotherapy)/ 2 (Livingston-Rosanoff 2021, Zee 2015)	Prospective cohort study, retrospective cohort study	610	+/- 1.00	RR 1.50 (1.07, 2.10)	170 per 1000	85 more per 1000 (13 more to 187 more)	Very serious[1]	Not serious	Not serious	Not serious	NA	Low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias

Table 66 Re-operation rates – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins < 2mm vs. ≥ 2mm/ 1 (Vos 2017)	Retrospective cohort study	77	0.80, 1.25	RR 1.58 (0.43, 5.87)	88 per 1000	51 more per 1000 (51 fewer to 429 more)	Very serious[1]	Not serious	NA[2]	Very serious[3]	Downgraded an extra level[4]	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Sample size < 500

Table 67 Re-operation rates – Event data at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins < 2mm vs. ≥ 2mm/ 1 (Shaikh 2016)	Retrospective cohort study	487	0.80, 1.25	RR 0.49 (0.35, 0.69)	585 per 1000	298 fewer per 1000 (381 fewer to 181 fewer)	Very serious[1]	Not serious	NA[2]	Not serious	Downgraded an extra level[3]	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. Sample size < 500

Neoadjuvant therapy

Table 68 Local recurrence - Hazard ratios at 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins ≤ 2mm vs. > 2mm/ 1 (Rozier 2001)	Retrospective cohort study	218	+/- 1.00	HR 2.48 (1.26, 4.88)	168 per 1000	248 more per 1000 (44 more to 651 more)	Serious[1]	Not serious	NA[2]	Not serious	Downgraded an extra level[3]	Low

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. Only one study so no inconsistency
3. Sample size < 500

Table 69 Local recurrence – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1 to 2mm vs. > 2mm/ 1 (Choi 2018)	Retrospective cohort study	277	+/- 1.00	RR 0.46 (0.13, 1.61)	63 per 1000	34 fewer per 1000 (55 fewer to 39 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross line of no effect
4. sample size <500

Table 70 Distant recurrence – Event data at 5 and 10 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins ≤ 2mm vs. > 2mm/ 1 (Rouzier 2001)	Retrospective cohort study	218	+/- 1.00	RR 1.10 (0.67, 1.80)	283 per 1000	28 more per 1000 (94 fewer to 227 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low
Radial margins ≤ 2mm vs. > 2mm/ 1 (Rouzier 2001)	Retrospective cohort study	218	+/- 1.00	RR 1.13 (0.78, 1.65)	393 per 1000	51 more per 1000 (88 fewer to 254 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

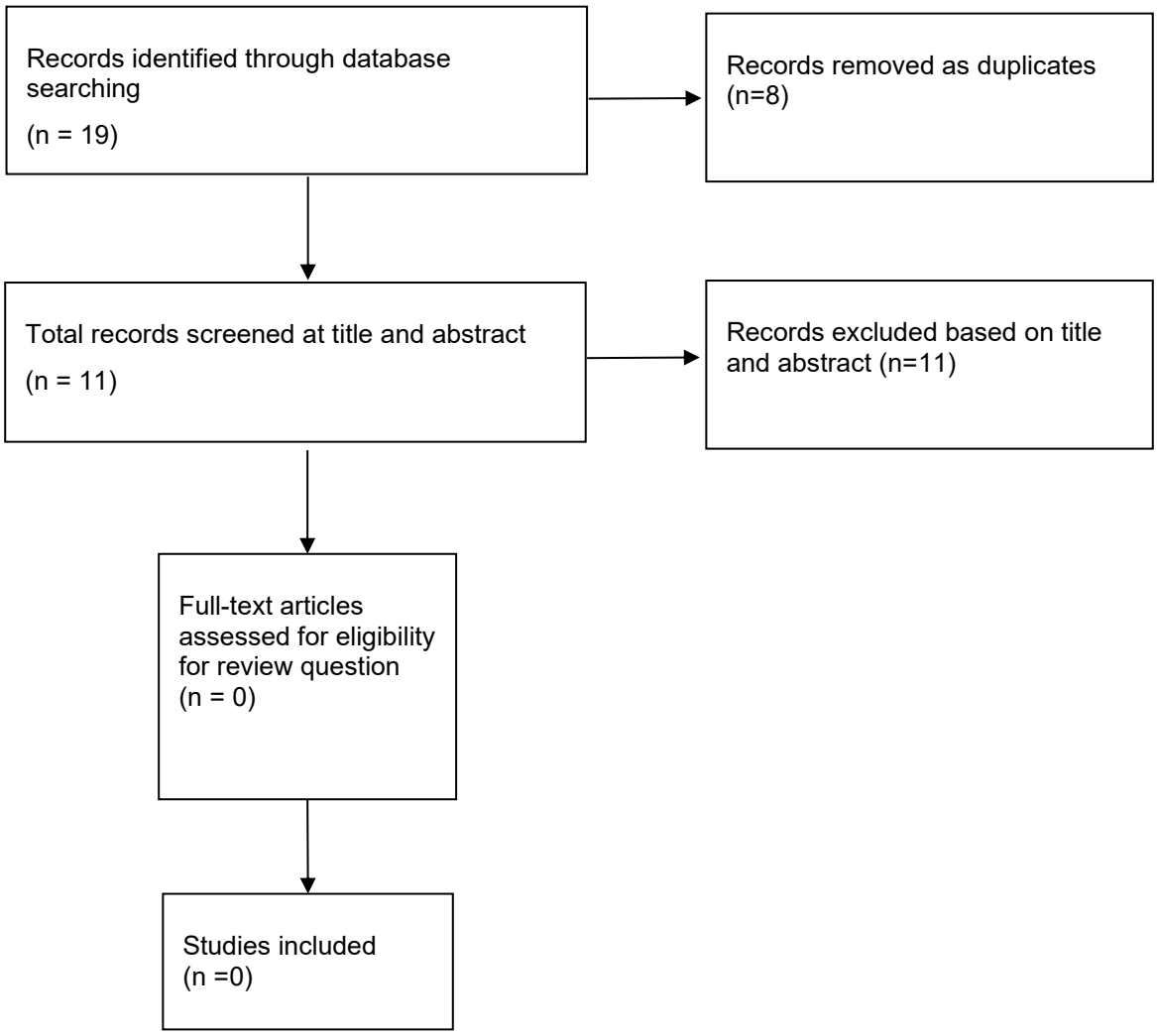
1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross line of no effect
4. Sample size < 500

Table 71 Local regional recurrence – Event data at 5 years follow-up

Comparison/ No. of studies	Study design	Sample size	MIDs	Effect size (95% CI)	Absolute risk: control	Absolute risk difference (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other reasons	Quality
Radial margins 1 to 2mm vs. > 2mm/ 1 (Lin 2020)	Retrospective cohort study	133	+/- 1.00	RR 1.07 (0.25, 4.52)	89 per 1000	6 more per 1000 (67 fewer to 315 more)	Very serious[1]	Not serious	NA[2]	Serious[3]	Downgraded an extra level[4]	Very low

1. >33.3% of the weight in a meta-analysis came from studies at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross line of no effect
4. Sample size < 500

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified for this review.

Appendix I – Health economic model

No economic modelling was undertaken for this review.

Appendix J – Excluded studies

The systematic review by Bundred et al. 2022 included studies that did not meet the inclusion criteria in our protocol. A list of these studies with the reason for exclusion can be seen in the evidence table for Bundred, 2022.

Study	Reason for exclusion
Barbour, Samantha, Moore, Julie, Dunn, Nathan et al. (2017) Patterns of care for ductal carcinoma in situ of the breast: Queensland's experience over a decade. Breast (Edinburgh, Scotland) 35: 169-176	- Study does not contain a relevant intervention *The margin width >10 mm is the reference variable in the analysis. A margin width of 10 mm was considered to be too wide to compare against <2 mm.*
Bhatti, Abu Bakar, Khan, Amina, Muzaffar, Narjis et al. (2014) Safe negative margin width in breast conservative therapy: results from a population with a high percentage of negative prognostic factors. World journal of surgery 38(11): 2863-70	- More than 25% of participants had neoadjuvant therapy
Bodilsen, Anne, Bjerre, Karsten, Offersen, Birgitte V et al. (2016) Importance of margin width in breast-conserving treatment of early breast cancer. Journal of surgical oncology 113(6): 609-15	- Data not reported in an extractable format *Data was not reported separately for regional recurrence and for distant recurrence: The primary outcome was ipsilateral breast tumour recurrence as a first event, including with simultaneous regional or distant recurrence.*
Chen, Allen M., Meric-Bernstam, Funda, Hunt, Kelly K. et al. (2004) Breast Conservation After Neoadjuvant Chemotherapy: The M.D. Anderson Cancer Center Experience. Journal of Clinical Oncology 22(12): 2303-2312	- Study does not contain a relevant intervention *Study combines data related to positive and close margins*
Cho, Won Kyung, Choi, Doo Ho, Kim, Haeyoung et al. (2019) Adjuvant radiation therapy in small ductal carcinoma in situ. Breast (Edinburgh, Scotland) 43: 55-58	- Study does not contain a relevant intervention *It is unclear if resection margin <2 mm included tumour at ink*

Study	Reason for exclusion
Clement, Zackariah, McLeay, William, Hoffmann, Clive et al. (2019) Re-excision rate after sector resection for breast cancer: A 5-year retrospective cohort study. Breast disease 38(1): 7-13	- Study does not contain a relevant intervention *Re-operation rates are only reported in participants with positive margins*
Clement, Zackariah, McLeay, William, Hoffmann, Clive et al. (2018) Role of radiotherapy in women over the age of 65 after breast conserving surgery for breast cancer: A 5-year retrospective study. Breast disease 37(4): 197-205	- Study does not contain a relevant intervention *Lowest margin was likely to include 0 mm: <2 mm*
Kelly, Bridget N, Kantor, Olga, Tang, Rong et al. (2021) Similar rates of residual disease in patients with DCIS within 2 mm of lumpectomy margin regardless of the presence of invasive carcinoma. Breast cancer research and treatment 186(3): 807-814	- Follow-up less than 5 years *Follow-up was 2 years*
Lepomaki, Maiju, Karhunen-Enckell, Ulla, Tuominen, Jalmari et al. (2022) Tumor margins that lead to reoperation in breast cancer: A retrospective register study of 4,489 patients. Journal of surgical oncology 125(4): 577-588	- Follow-up less than 5 years
Li, Chunyan, Yang, Yilan, Wang, Jiangfeng et al. (2021) Characteristics, prognosis, risk factors, and management of recently diagnosed ductal carcinoma in situ with microinvasion. Cancer medicine 10(20): 7203-7212	- Data not reported in an extractable format *89% had mastectomy; data was not reported separately for breast conserving surgery*
Mohammad, A. (2017) The effect of age and safety margin on local recurrence and survival after breast conservative surgery for early breast cancer. Archives of the Balkan Medical Union 52(2): 176-180	- Study does not contain a relevant intervention *Margins are not defined in millimetres*
Monaghan, Alex, Chapinal, Nuria, Hughes, Lauren et al. (2019) Impact of SSO-ASTRO margin guidelines on reoperation rates following breast-conserving surgery. American journal of surgery 217(5): 862-867	- Follow-up time was not reported
Ozkaya Akagunduz, Ozlem, Ergen, Arzu, Erpolat, Petek et al. (2018) Local recurrence outcomes after breast conserving surgery and adjuvant radiotherapy in ductal carcinoma in situ of the breast and a comparison with ECOG	- Study does not contain a relevant intervention *Surgical margins reported as <5 mm and ≥5 mm*

Study	Reason for exclusion
E5194 study. Breast (Edinburgh, Scotland) 42: 10-14	
Pilewskie, Melissa and Morrow, Monica (2018) Margins in breast cancer: How much is enough?. Cancer 124(7): 1335-1341	- Review article but not a systematic review
Rouzier, Roman, Extra, Jean-Marc, Carton, Mathieu et al. (2001) Primary Chemotherapy for Operable Breast Cancer: Incidence and Prognostic Significance of Ipsilateral Breast Tumor Recurrence After Breast-Conserving Surgery. Journal of Clinical Oncology 19(18): 3828-3835	- Study does not contain a relevant intervention *Study combines data related to positive and close margins*
Shah, Chirag, Hobbs, Brian P, Vicini, Frank et al. (2020) The Diminishing Impact of Margin Definitions and Width on Local Recurrence Rates following Breast-Conserving Therapy for Early-Stage Invasive Cancer: A Meta-Analysis. Annals of surgical oncology 27(12): 4628-4636	- Systematic review used as source of primary studies
Tartter, Paul Ian, Kaplan, Jess, Bleiweiss, Ira et al. (2000) Lumpectomy margins, reexcision, and local recurrence of breast cancer. The American Journal of Surgery 179(2): 81-85	- Sample size less than 100 participants *There were 65 participants with clear margins (no residual tumour was found in the a re-excision specimen). There were 21 participants with close margins (tumour within 1 mm of the inked margin).*
Tomasicchio, Giovanni, Picciariello, Arcangelo, Stucci, Luigia S et al. (2022) Outcome and risk factors for local recurrence after breast conserving surgery in patients affected by ductal carcinoma in situ. Minerva surgery 77(6): 536-541	- Study does not contain a relevant intervention *Margins are reported as positive (≤2 mm) and negative (>2 mm). No data reported separately for >0 mm.*
Vanni, Gianluca, Materazzo, Marco, Pellicciaro, Marco et al. (2020) Does Age Matter? Estimating Risks of Locoregional Recurrence After Breast-conservative Surgery. In vivo (Athens, Greece) 34(3): 1125-1132	- Study does not contain a relevant intervention *Surgical margins reported as medians*
Voogd, A C, Nielsen, M, Peterse, J L et al. (2001) Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. Journal of clinical oncology :	- Study does not contain a relevant intervention *Tumour at ink was compared to tumour not at ink*

Study	Reason for exclusion
official journal of the American Society of Clinical Oncology 19(6): 1688-97	
Yoon, Tae In, Lee, Jong Won, Lee, Sae Byul et al. (2018) No Association of Positive Superficial and/or Deep Margins with Local Recurrence in Invasive Breast Cancer Treated with Breast-Conserving Surgery. Cancer research and treatment 50(1): 275-282	- Study does not contain a relevant intervention *Tumour at ink was compared to tumour not at ink*
Yoshida-Ichikawa, Yuko, Horimoto, Yoshiya, Shikama, Naoto et al. (2021) Ipsilateral breast tumor control following hypofractionated and conventional fractionated whole-breast irradiation for early breast cancer: a long-term follow-up. Breast cancer (Tokyo, Japan) 28(1): 92-98	- Study does not contain a relevant intervention *Only reports margins <5 mm and ≥5 mm*

Appendix K – Methods

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2023 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence table and relevant data was included).

Incorporating published evidence syntheses

If published evidence syntheses were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting information from primary studies. Syntheses considered for inclusion in this way were quality assessed to assess their suitability using the appropriate checklist, as outlined in Table 72. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in Table 72, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Table 72: Checklists for published evidence syntheses

Type of synthesis	Checklist for quality appraisal
Systematic review of quantitative evidence	ROBIS

Each published evidence synthesis was classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.

- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.

- Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.

- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).

- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in Table 73. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 73 Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.

Quality	Applicability	Use of published evidence synthesis
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager V5.3. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Random effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

. Non-randomised controlled trials and cohort studies were quality assessed using the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool. Evidence for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

- Critical risk of bias (ROBINS-E only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.

- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision threshold that were used in the guideline are given in Table 74 and also reported in the relevant evidence reviews.

Table 74 Identified Clinical decision thresholds

Outcome	Clinical decision threshold	Source
Breast Q	4 points	Evidence review A: surgery to the breast (NG101 2018 update)
FACT-G total	3-7 points	Evidence review A: surgery to the breast (NG101 2018 update)
FACT-B total	7-8 points	Evidence review A: surgery to the breast (NG101 2018 update)
TOI (trial outcome index) of FACT-B	5-6 points	Evidence review A: surgery to the breast (NG101 2018 update)

Outcome	Clinical decision threshold	Source
BCS of FACT-B	2-3 points	Evidence review A: surgery to the breast (NG101 2018 update)
SF-36	one-half of an SD	Reeve BB, Potosky AL, Smith AW, Han PK, Hays RD, Davis WW, Arora NK, Haffer SC, Clauser SB. Impact of cancer on health-related quality of life of older Americans. JNCI: Journal of the National Cancer Institute. 2009 Jun 16;101(12):860-8.
EQ-5D	0.08 for UK-based scores and 0.07 for VAS scores	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007 Dec 21;5:70.
EORTC-QLQ-C30	-8 to 12 for global quality of life	Musoro JZ, Coens C, Fiteni F, Katarzyna P, Cardoso F, Russell NS, King MT, Cocks K, Sprangers MA, Groenvold M, Velikova G, Flechtner HH, Bottomley A; EORTC Breast and Quality of Life Groups. Minimally Important Differences for Interpreting EORTC QLQ-C30 Scores in Patients With Advanced Breast Cancer. JNCI Cancer Spectr. 2019 Jun 4;3(3):pkz037.

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 standard deviations was used. For SMDs that were back converted to one of the original scales to aid interpretation, rating of imprecision was carried out before back calculation. For relative risks and hazard ratios, where no other clinical decision threshold was available, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used. Odds ratios were converted to risk ratios before presentation to the committee to aid interpretation.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials, non-randomised controlled trials and cohort studies (which were quality assessed using the Cochrane risk of bias tool or ROBINS-I) were initially rated as high quality while data from other study types were initially rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 75. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 75: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.