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World Journal of Surgical Oncology (2025) 23:162
https://doi.org/10.1186/s12957-025-03811-4

World Journal of Surgical Oncology

REVIEW

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Effect of re-excision on local recurrence in patients with involved or close margins after upfront breast-conserving surgery: a systematic review and meta-analysis

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Abstract

Background Involved margins after breast-conserving surgery are associated with increased risk of local recurrence. A systematic search and meta-analysis was conducted to investigate the still-unclear role of re-excision in reducing this risk.

Methods A systematic search of the English-language literature up to May 31, 2024, was performed using PubMed and Embase databases. Studies that met the following criteria were included in the meta-analysis: available full data, patients with breast cancer, involved or close margins after breast-conserving surgery, and comparison of local recurrence rates between patients who underwent re-excision and those who did not. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using the random effects model. Bias risk was assessed with Begg-Mazumdar and Egger tests.

Results Eight papers and 13 datasets were included in the analysis. Studies differed by sample selection: inclusion of patients with close margins and of both patients with invasive cancer and carcinoma in situ. Of the total 3728 patients, 1897 underwent re-excision and 1831 did not. The mean OR of local recurrence after re-excision was 1.034 (95% CI 0.656—1.629), with a *p*-value of 0.885. The mean OR of local recurrence after re-excision in patients with DCIS was 2.065 (95% CI 0.96 – 4.442), with a *p*-value of 0.063, and in patients with 10-years follow-up the mean OR was 1.47 (95% CI 0.75 – 2.86) with a *p*-value of 0.26.

Conclusion The local recurrence rate in this study did not differ between patients with involved or close margins after breast-conserving surgery who had or did not have additional surgery. The absence of local control effect remained in those with longer follow-up. A trend toward an increased risk of local recurrence was observed in patients with carcinoma in situ who underwent re-excision; however, this finding did not reach statistical significance. Thus, we recommend against routine re-excision and suggest it should be carried out only in selected cases, after thorough discussion of a multidisciplinary team.

Keywords Breast cancer, Re-excision, Recurrence, Systematic review, Meta-analysis

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Introduction

Local recurrence following breast cancer surgery is a consequence of a combination of clinical and pathological factors. These can be classified as non-modifiable, such as patient and tumor characteristics, and modifiable, such as adjuvant treatments and surgical resection margins [1, 2].

In the context of breast-conserving surgery, surgical resection margins are considered positive when the tumor reaches the inked margin for invasive carcinoma and close when the margin width is less than 2 mm for ductal carcinoma in situ (DCIS). [3, 4]. Positive or close surgical margins are associated with a twofold risk of local recurrence [5].

To reduce this risk, patients might undergo re-excision (excision of tissue in the previously operated tumor site) or, in some cases, a radiation tumor boost, or both [6, 7]. Alternatively, patients with positive margins may undergo completion mastectomy, particularly in cases where breast-conserving surgery is not feasible or when there is extensive residual disease. However, the effectiveness of re-excision in this setting has not been definitively established.

The aim of the present study was to investigate whether the risk of local recurrence after breast-conserving surgery with positive or close margins is lower in patients who undergo re-excision than in patients who do not.

Methods

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8], and the MOOSE Reporting Guidelines for Meta-analyses of Observational Studies [9].

Information sources and search strategy

A search of PubMed and EMBASE was performed until 31.05.2024 using the following Medical Topic Heading (MeSH) terms: *"breast neoplasm" [MeSH Terms] AND"recurrence"[MeSH Terms]* AND *"reoperation" [MeSH Terms].* In addition, the keywords *"re-excision"[All Fields], "local"[All fields] AND "recurrence"[All fields]* were used in the PubMed search, and equivalent terms in the EMBASE search (supplement 2). Review articles and editorials were manually screened as were the reference lists of all included articles.

Eligibility criteria and selection process

Inclusion and exclusion criteria were determined before onset of the investigation. Inclusion criteria were English language, full-text availability; comparative prospective or retrospective study design; patients of any age with breast carcinoma; breast-conserving surgery as the primary surgical procedure, positive or close margins; comparison of recurrence rates with and without re-excision. Exclusion criteria were conference abstracts, reviews, editorials and case reports; no cancerous or pre-cancerous margin involvement; and data unavailability. We included studies published between January 2000 and May 31, 2024. Exact numbers of recurrences and sample size were sought in each study and each subgroup; studies without these data were excluded. Two independent reviewers (NW and YN) screened the publications and selected the appropriate articles. Disagreements were resolved by discussion or by a third reviewer (ES).

Data collection process and data items

Two independent reviewers (NW and YN) extracted data from each included study. The Data was entered into a pre-prepared data-collection sheet. The two data sheets for each report were then reviewed and combined into a single table. Disagreements were resolved by discussion or by a third reviewer (ES).

The data collected included study population parameters – patient characteristics, inclusion of patients with invasive cancer, or carcinoma in-situ or both, inclusion (or not) of patients with margin involvement and small margin width, and similarity (or not) of group characteristics, and intervention parameters – type of primary and secondary surgeries, adjuvant treatments (for both re-excision and no re-excision groups). Primary outcome measures were the number and percentage of local recurrences in each group and the median or mean duration of follow-up. General study characteristics such as study design and limitations were recorded as well.

Heterogeneity, sensitivity, and publication bias

The heterogeneity of the studies was determined using the Cochran Q test and the I-squared statistic. The inconsistency index was considered present if the *Q*-test *p* value was less than 0.10. The higher the I-squared value, the greater the heterogeneity [9]. Sensitivity testing was conducted by removing individual studies from the overall result. Publication bias was analyzed using a funnel plot complemented by Begg-Mazumdar and Egger statistics [10]. The quality of the studies was assessed with the methodological index for non-randomized studies (MINORS) developed by Slim et al. [11] for purposes of meta-analysis.

Statistical analysis

Comprehensive meta-analysis software (version 4, Biostat Inc., Englewood, NJ, USA) was applied. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In individual studies/CIs were calculated using the random effects model to compare local recurrence

between patients who underwent reoperation and those who did not [12].

Protocol and registration

This systematic review and meta-analysis was prospectively registered in the PROSPERO international prospective register of systematic reviews (registration number: CRD42024567217). The full protocol is available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024567217.

Results

Systematic review of included studies

Of the 1074 studies generated by our literature search (Fig. 1), 1066 were excluded as follows: 101 were conducted in animals, were available only as abstracts, or were unavailable in English; 108 were editorials, letters, case reports, review articles, or guidelines; 266 were duplicates; and 591 did not meet other inclusion criteria. The remaining 8 papers and 13 datasets from six countries (USA, France, the Netherlands, the UK, South Korea, and Italy) were analyzed [13–20].

The eligible studies were published between 2000 and 2024, including three within the last 5 years. All were retrospective. Cohort size varied from 79 to 1078 (average, 468.4). The median follow-up time ranged from 4.2 to 10.4 years.

Appraisal of selected studies

There were some differences among the eligible studies in inclusion criteria in terms of margin involvement (radial, anterior, posterior), margin definition (close or involved), type of lesion at the involved margin (invasive cancer or carcinoma in situ), type of second surgery (breast-conserving, mastectomy), and duration of follow-up. None of the included studies evaluated patients who had received neoadjuvant systemic therapy; all datasets were based on patients who underwent upfront breast-conserving

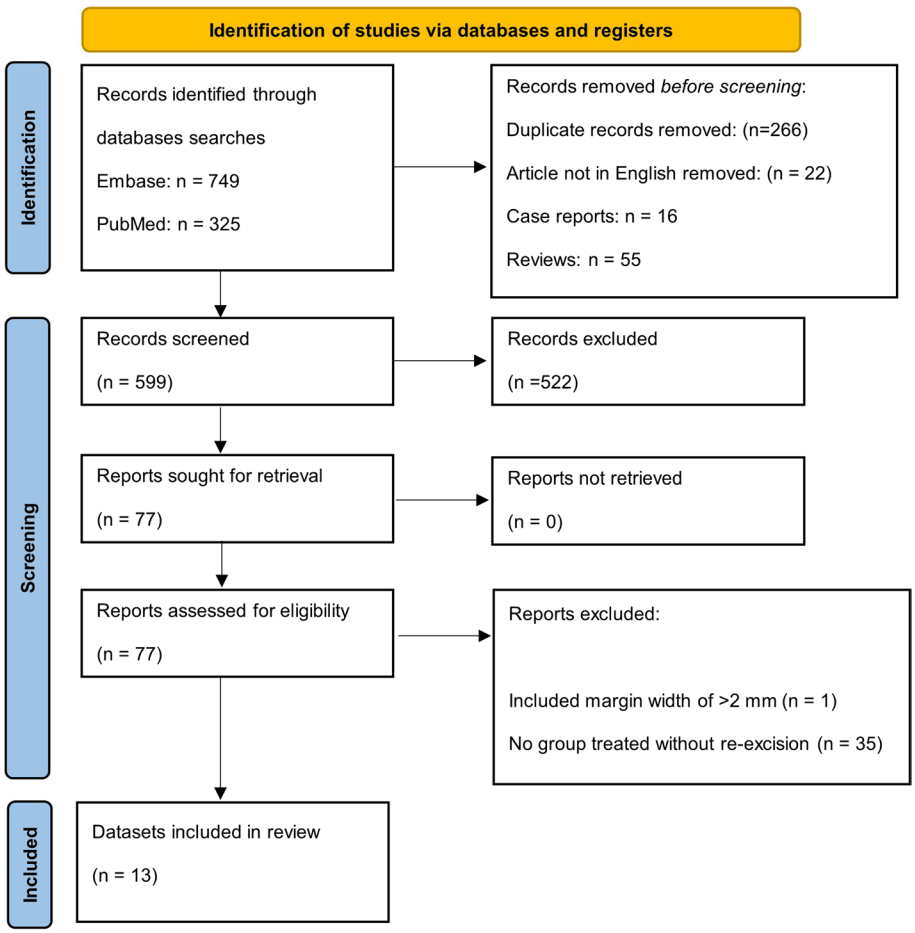


Fig. 1 PRISMA 2020 flow diagram illustrating the selection process of studies included in the systematic review and meta-analysis. The flowchart details records identified through database searches (PubMed and Embase), screening, eligibility assessment, and inclusion. After removing duplicates and ineligible studies, a total of 8 reports comprising 13 datasets were included in the final analysis

surgery. See Table 1 for an overview of the included studies and supplement 1 for more detailed summaries of the included studies.

Patient characteristics were available in most studies, including factors known to increase recurrence risk, namely age, margin status, radiotherapy dose [21, 22], and systemic adjuvant treatments [21]. Generally, patients in the re-excision arm were younger and more likely to have positive margins. Notably, Only two studies presented adjuvant systemic therapy data, which showed no clinically relevant differences between patients in the re-excision arm and those in the control arm.

Re-excisions' definitive margins might have a critical effect on local recurrence but were not adequately reported. Three of the eight studies reported the status of the re-excision margins: 17–34.5% of patients had close or involved margins [13, 15, 20], and 6–9% had involved margins [13, 20]. Monteau et al. [15] noted that 6 of 61 patients with close or involved margins underwent mastectomy, and the rest received a radiation boost. In contrast, in the study of Vanni et al. [20], half of the 28 patients with positive margins received a radiation boost and half had standard radiation. It was not reported whether the definitive margin status affected local recurrence.

Meta-analysis

Overall, the eligible studies included 3728 patients: 1897 underwent reoperation and 1831 did not (Fig. 2a). The mean OR was 1.034 (95% CI 0.656–1.629), with Z-value (which tests the null hypothesis that the mean effect size is 1.000) 0.144 and *p*-value 0.885. With an alpha criterion of 0.050, the null hypothesis could not be rejected. The relevant funnel plot (Fig. 3) was symmetric, ruling out significant publication bias. The Q-value was 19.434 with 12 degrees of freedom and *p*-value 0.079. With an alpha criterion of 0.100, the null hypothesis could be rejected, indicating that the true effect size was the same in all these studies. The I-squared statistic was 38%, indicating that about 38% of the variance reflected true effects rather than sampling error. Tau-squared (the variance of true effect sizes) was 0.232 in log units, and tau (the standard deviation of true effect sizes), was 0.482 in log units. On the assumption that the true effects were normally distributed (in log units), the estimated prediction interval was 0.319 to 3.354. The true effect size in 95% of all comparable populations falls within this interval. The distribution of the true effect is shown in Fig. 4.

We performed subgroup analyses according to tumor histology. Most studies included mixed populations of patients with both ductal carcinoma in situ (DCIS) and invasive breast cancer. Some studies focused exclusively on patients with DCIS or presented separate datasets for this group. Consequently, we conducted a specific sub-meta-analysis of datasets including DCIS-only patients (Fig. 2b). The pooled odds ratio (OR) for local recurrence after re-excision in the DCIS-only datasets was 2.065 (95% CI 0.96 to 4.442; $p = 0.063$). Although this result was not statistically significant, the *p*-value approached the conventional threshold, indicating a possible trend toward increased risk. Only one dataset was found that included patients with invasive breast cancer exclusively; therefore, a separate sub-meta-analysis for invasive cancers was not conducted.

In addition, we conducted a subgroup analysis limited to studies with long-term follow-up (~ 10 years). This analysis showed no significant difference in local recurrence rates between patients who underwent re-excision and those who did not, with a pooled OR of 1.47 (95% CI 0.75 to 2.86; $p = 0.26$) (Fig. 2c).

Factors such as biologic subtype and tumor grade were not consistently reported and therefore could not be evaluated in the meta-analysis.

Sensitivity was measured by excluding individual studies and recalculating the overall meta-analysis outcome. This process was repeated for each of the studies. Deviations from the primary result were not significant. The median OR was 1.308 (range 0.377–9.273). The OR of publications within the lower range was 0.692 (95% CI 0.452- 1.058), and of publications within the upper range, 2.375 (95% CI 1.210–4.661). The range of true effects was 0.298 to 1.608. The sensitivity was limited because the odds ratios (ORs) of certain studies fell outside the prediction interval.

Scores for the quality of the studies, assessed with the MINORS method (Table 2), ranged between 0 and 2 with a median of 1.75. Comparison between studies with MINORS scores of 0 to 1.75 and studies with scores of 1.75 to 2 yielded ORs of 0.936 (95% CI 0.495–5.479) and 1.326 (95% CI 0.766–2.297), respectively, both in the range of true effects.

Discussion

The aim of this study was to determine if re-excision performed in patients with close or positive margins affect local control. We found that re-excision does not change the risk of local recurrence. Our meta-analysis of the studies identified by systematic literature search yielded a mean OR of 1.034 and a *p*-value of 0.885 (Fig. 2a). We found a trend toward an increased risk of local recurrence associated with re-excision in studies and subgroups that included only patients with DCIS (OR 2.065; $p = 0.062$), although this result did not reach statistical significance (Fig. 2b). Longer follow-up did not affect the local recurrence rate, regardless of the re-excision status. On analysis of the studies and subgroups with a longer

Table 1 Characteristics of the studies included in the systematic review and meta-analysis. The table summarizes study design, inclusion criteria, patient demographics, margin status, therapies (including type of re-excision and adjuvant treatments), and outcomes (local recurrence rates and follow-up duration)

Reference	Design	Inclusion criteria		Study groups key characteristics			Therapy[b]			Outcome		
					R	C		R	C		R	C
Tartter et al. (2000) USA [13]	Retrospective Funding: none No conflict of interests	Therapy Initial margin margin width (mm) Lesion at the margin	BCS RT 1 IBC, DCIS	Sample size N **Age, yr (mean)*** Margin status (%) Positive Close Unknown	91 **54** 18 2 80	134 **58** 16 14 69	Re-excision: BCS			IBTR rate[c] N_{event}/N_{total} % Follow-up Length (Months)	9/91 10 75	16/134 12 75
Chism et al., (2006) USA [14]	Retrospective Funding: none No conflict of interests	Stage Therapy Initial margin margin width (mm) Margin direction Lesion at the margin	I,II BCS, RT 2 Radial IBC, DCIS	Sample size n ***Age, yr (%)**** 70 **<** ***40 >*** ***Margin status (%)**** Positive Close	846 **16** **8** **62** **38**	199 **28** **5** **27** **73**	Re-excision: BCS RT: Boost (%) Adjuvant therapy (%) None Yes	100 37 63	100 35 65	IBTR rate N_{event}/N_{total} % Follow-up Length (Months)	51/846 6 120	10/199 5 120
Monteau et al. (2009) France [15]	Retrospective Funding: none No conflict of interests	Stage Therapy Initial margin margin width (mm) Focal/diffuse Length (mm) Lesion at the margin	0 BCS, RT 2 focal < 15 DCIS	Sample size n Age (%) 60 < 40 ≥ ***Margin status (%)**** Positive Close	61 20 5 ***74*** 26	147 29 3 ***50*** 50	Re-excision: BCS **RT Boost (%)*** **dose**	**58** **60**	**92** **67**	IBTR rate N_{event}/N_{total} % Follow-up Length (Months)	6/61 10 118	11/147 7 79
Jaffré et al.(2013) France [16]	Retrospective Funding: none No conflict of interests	Therapy Initial margin margin width (mm) Lesion at the margin	BCS RT, Boost 3 IBC, DCIS	Sample size n	206	248	Re-excision: BCS RT Boost % Additional dose (Gy)	100 16	100 16	***IBTR rate**** N_{event}/N_{total} **%** Follow-up Length (Months)	***11/206*** 5 60	***29/248*** 12 60
Vos et al. (2017) The Netherlands [17]	Retrospective Funding: none No conflict of interests	Therapy Initial margin Margin width (mm) **Focal/diffuse** **Length (mm)** Lesion at the margin	BCS 0 **Focal** **≤ 4** IBC, DCIS	Sample size n ***Age (%)**** 60 **<** ***40 ≥***	586 **25** **8**	492 **43** **4**	**Re-excision (%)** **BCS** **Mastectomy** RT Boost (%)[a] ***Adjuvant therapy (%)**** None Yes	**46** **54** 100 **29** **71**	**0** **0** 100 **37** **63**	IBTR rate N_{event}/N_{total} % Follow-up Length (Months)	6/586 1 60	13/492 3 60
Boundouki et al. (2019) UK [18] ***Dataset 1***	Retrospective Funding: none No conflict of interests	Therapy **Initial margin** Initial margin **Margin width (mm)** **Lesion at the margin**	BCS **Anterior** **2** **IBC, DCIS**	Sample size n Age, yr (mean) Margin status (%) Positive Close	57 58 54 46	220 60 24 76	BCS RT Boost: not reported BCS			IBTR rate 1.N_{event}/N_{total} 2.% Follow-up 3. Length (Months)	4/57 7 125	12/220 5 120
Dataset 2		**Margin width (mm)** **Lesion at the margin**	**2** **DCIS**	Sample size n	14	35	BCS			1. N_{event}/N_{total} 2. % 3. Length (Months)	3/14 21 125	1/35 3 120

Table 1 (continued)

Reference	Design	Inclusion criteria		Study groups key characteristics	R	C	Therapy[b]	R	C	Outcome	R	C
Dataset 3		**Margin width (mm)** **Lesion at the margin**	**2** **IBC**	n	43	185	BCS			1. N_{event}/N_{total} 2. % 3. Length (Months)	1/43 2 125	11/185 6 120
Dataset 4		**Margin width (mm)** Lesion at the margin	***1*** IBC, DCIS	n	46	136	BCS			1. N_{event}/N_{total} 2. % **3. Length (Months)**	1/46 2 ***60***	1/136 1 ***60***
Dataset 5		**Margin width (mm)** Lesion at the margin	***1*** IBC, DCIS	n	46	136	BCS			1. N_{event}/N_{total} 2. % **3. Length (Months)**	3/46 7 ***120***	3/136 2 ***120***
Lee et al. (2022) Korea [19]	Retrospective Funding: none No conflict of interests	Therapy Initial margin Margin width (mm) Length (mm) Margin direction Lesion at the margin	BCS, RT 0 ≤ 35 Radial DCIS	Sample size n Age, yr (mean)	24 48	344 51	Re-excision: BCS **RT Boost** **Dose (Gy)**	**10**	**15**	IBTR rate N_events/N_total % Follow-up Length (Months	1/24 4 51	4/344 1 50
Vanni et al. (2024) Italy [20]	Retrospective Funding: none No conflict of interests	Stage Initial surgery Initial margin margin width (mm) Lesion at margin	0 BCS 2 DCIS									
Dataset 1				Sample size n **Age (%)*** **60 <** **40 ≥** **Margin status (%)*** **Positive** **Close**	32 **28** **13** **100** **0**	47 **26** **9** **11** **89**	Re-excision BCS Mastectomy RT Boost **% (of BCS or controls)***	47 53 **0**	0 0 **57**	IBTR rate 1.N_{event}/N_{total} 2.% Follow-up 3. Length (Months)	4/32 13 66	3/47 6 66
Dataset 2				Sample size n **Age (%)*** **60 <** **40 ≥** **Margin status (%)*** **Positive** **Close**	15 **40** **0** **100** **0**	47 **26** **9** **11** **89**	Re-excision BCS Mastectomy RT Boost %	100 0 0	0 0 57	1. N_{event}/N_{total} 2. % 3. Length (Months)	0/15 0 66	3/47 6 66

Abbreviations: *BCS* breast-conserving surgery, *RT* radiotherapy, *IBTR* in-breast tumor recurrence, *IBC* invasive breast cancer, *DCIS* ductal carcinoma in situ, *R* re-excision group, *C* control group

[*] Statistically significant difference ($p < 0.05$)

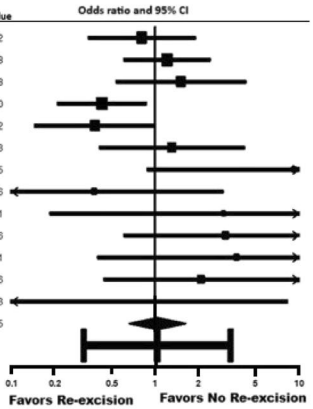
[a] Percentage of patients receiving RT boost out of all patients treated with BCS in the re-excision group

[b] Therapy after initial surgery, including re-excision type, radiotherapy boost (percentage and/or dosage), and adjuvant systemic therapy (endocrine therapy, chemotherapy, immunotherapy)

[c] Local recurrence rate presented as number of events (N_{event}) over total number of patients (N_{total})

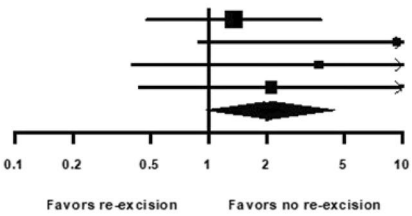
a

Study name	Sub-group	Country	Year	Odds Ratio	Lower limit	Upper limit	Z-value	p-value
Tartter PI	Included DCIS, IDC or ILC with involved or close resection margin, local recurrence	USA	2000	0.809	0.341	1.920	-0.480	0.632
Chism DB	Positive or close margins, invasive cancer or DCIS, both groups treated with radiotherapy, local recurrence	USA	2006	1.212	0.604	2.432	0.542	0.588
Monteau A	Anterior margin, reoperation vs. radiotherapy with increased dosage only, local recurrence	France	2009	1.514	0.531	4.313	0.776	0.438
Jaffre I	Patients with IDC and BCS, followed for 6.2 years, local recurrence	France	2013	0.426	0.207	0.875	-2.322	0.020
Vos EL	Focally positive margin only (did not include extensive positive margin), local recurrence	The Netherlands	2017	0.381	0.144	1.010	-1.939	0.052
Boundouki G 1	Anterior margin only, margin width or 2 mm or less (10yr dataset), local recurrence	UK	2019	1.308	0.406	4.220	0.450	0.653
Boundouki G 2	Subgroup analysis, carcinoma in situ, local recurrence	UK	2019	9.273	0.873	98.510	1.847	0.065
Boundouki G 3	Subgroup analysis, invasive carcinoma, local recurrence	UK	2019	0.377	0.047	2.999	-0.923	0.356
Boundouki G 4	Anterior margin only: margin width of 1 mm or less (5yr dataset), local recurrence	UK	2019	3.000	0.184	48.954	0.771	0.441
Boundouki G 5	Anterior margin only: margin width of 1 mm or less (10yr dataset), local recurrence	UK	2019	3.093	0.602	15.894	1.352	0.176
Lee JH	DCIS found in resection margin, both groups treated with radiotherapy, local recurrence	South Korea	2022	3.696	0.397	34.425	1.148	0.251
Vanni G1	DCIS and close resection margin, included patients whose reoperation was mastectomy or BCS, local recurrence	Italy	2024	2.095	0.436	10.073	0.923	0.356
Vanni G2	Patients with DCIS and close resection margin, included patients whose reoperation was BCS, local recurrence	Italy	2024	0.410	0.020	8.396	-0.579	0.563
Pooled				1.034	0.656	1.629	0.144	0.885
Prediction Interval				1.034	0.319	3.354		



b

Study name	Country	Year	Margin status	Follow-up length (months)	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Monteau A	France	2009	<2 mm	80-120	1.349	0.475	3.827	0.562	0.574
Boundouki G.	UK	2019	<2 mm	120	9.273	0.873	98.510	1.847	0.065
Lee JH.	Korea	2022	Positive	50	3.696	0.397	34.425	1.148	0.251
Vanni G	Italy	2024	<2 mm	66	2.095	0.436	10.073	0.923	0.356
Pooled					2.065	0.960	4.442	1.856	0.063
Prediction Interval									



c

Study name	Country	Year	Lesion at the margin	Max margin width (mm)	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Chism	USA	2006	Invasive and non-invasive	2	1.21	0.60	2.43	0.54	0.59
Boundouki 1	UK	2019	Invasive and non-invasive	2	1.31	0.41	4.22	0.45	0.65
Boundouki 2	UK	2019	Non-invasive	2	9.27	0.87	98.51	1.85	0.06
Boundouki 3	UK	2019	Invasive	2	0.38	0.05	3.00	-0.92	0.36
Boundouki 5	UK	2019	Invasive and non-invasive	1	3.09	0.60	15.89	1.35	0.18
Pooled					1.47	0.75	2.86	1.12	0.26
Prediction Interval					1.47	0.30	7.08		

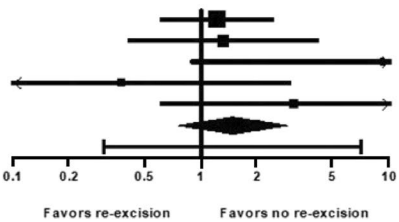


Fig. 2 **a** Forest plot of all datasets included in the meta-analysis, showing odds ratios (OR) and 95% confidence intervals (CI) for local recurrence after re-excision versus no re-excision. Each horizontal line represents the 95% CI for the individual study, and the box indicates the weight of each study in the meta-analysis. The diamond represents the pooled odds ratio and its 95% CI. A random-effects model was applied to account for potential heterogeneity between studies. DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; BCS = breast-conserving surgery. **b** Forest plot of the subgroup meta-analysis for studies and datasets that included only patients with ductal carcinoma in situ (DCIS). Each horizontal line represents the 95% confidence interval (CI) for an individual study, and the box indicates the weight of the study in the meta-analysis. The diamond represents the pooled odds ratio (OR) and its 95% CI. A random-effects model was applied to account for potential heterogeneity between studies. **c** Forest plot of the subgroup meta-analysis for studies and datasets including patients with ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC), with approximately 10 years of follow-up. Each horizontal line represents the 95% confidence interval (CI) for an individual study, and the box size reflects the weight of the study in the meta-analysis. The diamond represents the pooled odds ratio (OR) and its 95% CI. A random-effects model was applied to account for potential heterogeneity between studies

follow-up, the mean OR was 1.47 and the *p*-value, 0.26 (Fig. 2c).

To our knowledge, this is the first meta-analysis to investigate the impact of re-excision on local recurrence in patients with close or positive surgical margins after breast-conserving surgery. There are several possible reasons why patients who underwent re-excision had the same recurrence rate as those who did not. First, the estimated residual cancer burden in the no-re-excision group was low enough that the appropriate radiation

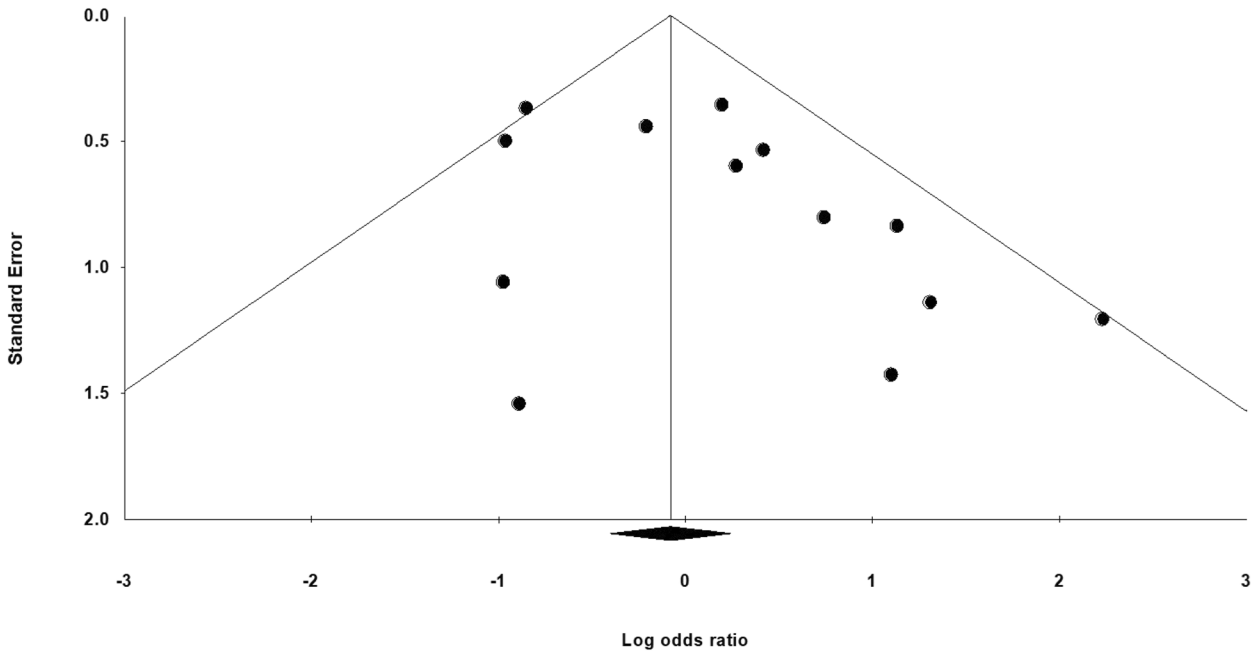


Fig. 3 Funnel plot assessing publication bias for the studies included in the meta-analysis. The vertical line represents the pooled effect size (log odds ratio), and the diagonal lines indicate the pseudo 95% confidence limits. Each dot represents an individual study. The symmetrical distribution of studies within the funnel suggests a low likelihood of significant publication bias

delivered successfully ablated microscopic cancer foci. Second, patients properly selected for nonoperative management have no high-risk features and favorable disease biology; thus, the administration of appropriate systemic therapy alone can lead to good overall and local outcomes. Third, re-excisions vary in terms of performance and quality. There is no standard for re-excision, no well-defined universally accepted technique, and no well-tested means of validating the excision of all residual cancer. Furthermore, the location and extent of resection range from excision of a small sample of the suspected margin to large-volume excisions of the entire cavity. Poor re-excision techniques may leave behind significant residual disease volume and thus have a negligible effect on recurrence. Our study demonstrated a trend toward a two-fold increase in local recurrence after re-excision in patients with DCIS (this finding did not reach statistical significance), aligning with the observations of Langhans et al. [21], who reported more than a twofold increase in positive re-excision margins in patients with DCIS.

Nonsurgical management of patients with close or positive margins frequently entails whole-breast radiation with

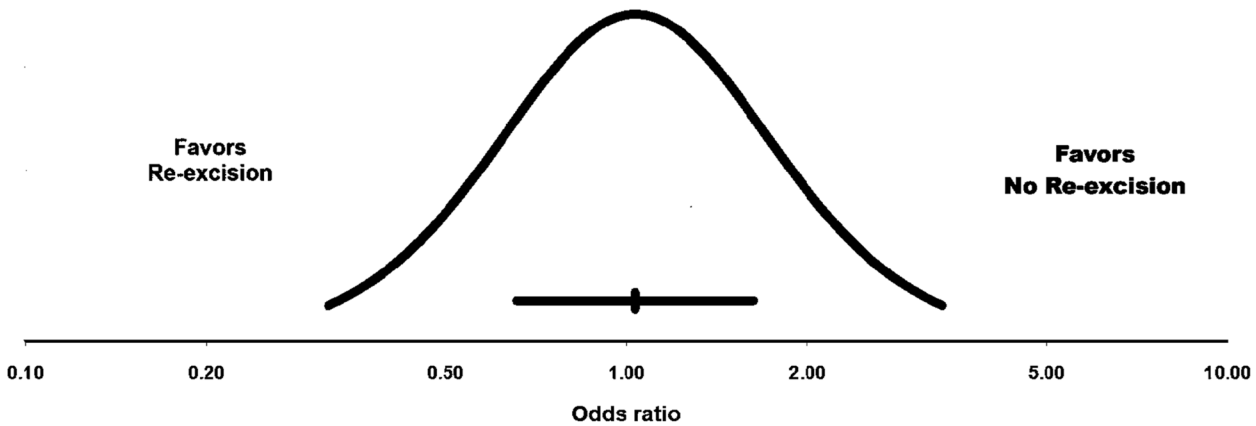


Fig. 4 Distribution curve of the true effect size, assuming a normal distribution of effects (on a log scale). The plot illustrates the pooled odds ratio (OR), its 95% confidence interval (CI), and the prediction interval, which ranges from 0.319 to 3.354. This interval represents the range in which the true effect size is expected to fall in 95% of comparable populations. The central point reflects the pooled OR, while the thick horizontal line indicates the 95% CI. The extended horizontal line represents the prediction interval, accounting for between-study heterogeneity

Table 2 Quality assessment of included non-randomized studies using predefined methodological criteria. Studies are presented by the first author's surname. Each study was assessed across key methodological domains, including study aim, inclusion of consecutive patients, prospective data collection, appropriateness of endpoints, unbiased assessment, follow-up duration, loss to follow-up, prospective calculation of study size, adequacy of control groups, contemporaneity of study and control groups, baseline equivalence, and statistical analyses

Criterion/Studies*	Tartter	Chism	Monteau	Jaffre	Vos	Boundouki	Lee	Vanni
Clearly stated aim: The question addressed should be precise and relevant in the light of available literature	2	2	1	2	2	2	2	2
Inclusion of consecutive patients: All patients potentially fit for inclusion (satisfying the criteria for inclusion) were included in the study during the study period (no exclusion or details about the reasons for exclusion)	1	2	1	2	2	1	2	2
Prospective collection of data: Data were collected according to a protocol established before the beginning of the study	0	2	0	2	1	0	2	2
Endpoints appropriate to the aim of the study: An unambiguous explanation of the criteria used to evaluate the main outcome are reported. The criteria should be in accordance with the question addressed by the study. The endpoints should be assessed on an intention-to-treat basis	2	2	2	1	2	2	0	0
Unbiased assessment of the study endpoint: Blind evaluations of the objective endpoints and double-blind evaluation of the subjective endpoints were performed. Otherwise, the reasons for not blinding should be stated	1	2	2	1	2	2	0	2
Follow-up period appropriate to the aim of the study: The follow-up should be sufficiently long to allow for assessment of the main endpoint and possible adverse events	2	2	2	1	2	2	2	2
Loss to follow-up less than 5%: All patients are included in the follow up. Otherwise, the proportion lost to follow-up does not exceed the proportion experiencing the major endpoint	1	2	2	2	2	2	2	2
Prospective calculation of study size: Information should be provided on the size of the detectable difference of interest with calculation of the 95% confidence interval, according to the expected incidence of the outcome event. Information should be provided about the level for statistical significance and estimates of power when comparing outcomes	1	2	2	2	2	2	0	2
Adequate control group: The control group should be defined by a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data	1	2	2	2	1	2	1	2
Contemporary groups: The control and studied groups should be managed during the same time period (no historical comparison)	1	2	2	1	1	2	2	1
Baseline equivalence of groups: The groups should be similar in terms of the criteria other than the studied endpoints, with absence of confounding factors that could bias the interpretation of the results	1	2	2	1	2	2	0	2
Adequate statistical analyses: The statistics should be in accordance with the type of study, with calculation of confidence intervals or relative risk	1	2	2	2	2	2	2	2
Total	14	24	20	19	21	21	15	21
Average	1.17	2.00	1.67	1.58	1.75	1.75	1.25	1.75

Scoring: 0 = not reported; 1 = reported but inadequate; 2 = reported and adequate

The global ideal score is 16 for non-comparative studies and 24 for comparative studies

*Studies are presented by the first author's surname

an increased dose or with a tumor-bed boost to mitigate the elevated risk for local recurrence [22]. Re-excision can prompt patient anxiety and stress, worsen cosmesis, delay adjuvant therapies, and increase healthcare costs [23]. The addition of a radiation boost also worsens the cosmetic outcome [24] but it does not increase anxiety or costs or delay systemic treatment. Thus, it could be more convenient for patients, cost-effective for the healthcare system, and oncologically safe.

We recommend against a routine re-excision in patients with positive or close margins – we suggest that a more selective approach be used instead. Patients with residual cancer in their re-excision specimens have a nearly threefold increase in local recurrences [25], but if done properly, re-excisions may be most beneficial in this group of patients. Residual cancer in re-excision specimens has been associated with several predictive factors: large tumor size, nodal involvement, great extent of margin involvement, and multiple involved margins [25–32]. Similarly, rates of residual disease after breast conserving surgery have been found to be higher in the presence of specific enhancement

patterns on postoperative magnetic resonance imaging [33]. Thus, patients harboring these factors or with suspicious imaging findings are more likely to benefit from re-excision. DCIS outside the invasive tumor in the first specimen is also known as a risk factor for residual tumor [25]· in the re-excision specimens, However, unlike the other predictive factors, we recommend against routine re-excision in these patients because our analysis suggests no local control benefit. A decision to re-excise, especially in cases of DCIS, should follow a thorough discussion by a multidisciplinary team.

In cases where re-excision is deemed necessary, we propose several strategies to optimize surgical outcomes. First, careful marking of the surgical specimen during the initial breast-conserving surgery is essential to accurately identify the location of involved or close margins. Additionally, marking areas of concern within the breast during the primary surgery can facilitate more precise targeting for any subsequent procedures. Prior to re-excision, re-imaging the breast is recommended to both assist in planning image-guided surgery and to help determine whether a repeat breast-conserving surgery is feasible or if mastectomy should be considered. Finally, a multidisciplinary review of the pathological findings in collaboration with the pathologist can help pinpoint the specific margin and area of concern, ensuring a more focused and effective re-excision.

Our study has several limitations. First, all studies included in this meta-analysis were retrospective; most had a small number of participants and were conducted at one or two centers, limiting the generalizability of the findings. Second, the cohorts varied in age and in the nature and extent of margin involvement. Differences between the re-excision and control arms suggest potential selection bias, as patients at higher risk for recurrence were more likely to undergo re-excision. Third, some studies included both patients with invasive carcinoma and those with ductal carcinoma in situ (DCIS), while others focused on one or the other. Additionally, a few studies included only patients with tumor-on-ink margins, whereas others included patients with small margin widths, which may have contributed to variation in local recurrence risk. Fourth, the status of definitive re-excision margins was inconsistently reported; close or involved margins after re-excision may have affected local recurrence rates, but these data were not consistently available. Fifth, incomplete and inconsistent reporting of biologic subtype, tumor grade, and tumor density limited our ability to assess their potential impact on local recurrence. Similarly, incomplete reporting of radiation dosage details prevented us from evaluating the influence of radiation therapy on outcomes. Sixth, our meta-analysis was limited by heterogeneity in how surgical margin status was defined across the included studies. Finally, all included studies evaluated patients who underwent upfront surgery, excluding those treated with neoadjuvant systemic therapy. This limits the applicability of our findings to patients treated with primary surgery. Further prospective, randomized controlled trials are needed to address these limitations and provide more definitive evidence.

Conclusion

This meta-analysis demonstrates that re-excision due to involved or close resection margins does not reduce the local recurrence rate in the short- and long-term and may indeed increase this risk in patients with DCIS. We recommend against routine re-excisions in patients with positive margins. Re-excisions should be limited to patients with clinical or pathological predictors of residual disease or with radiological findings suggestive of residual cancer, and a decision to perform re-excision or not should take place in a multidisciplinary team discussion. Our results also emphasize the importance of thorough radiological assessment and careful surgical planning before surgery to achieve clear margins at the first and only attempt.

Abbreviations

DCIS	Ductal carcinoma in situ
MINORS	Methodological index for non-randomized studies

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03811-4.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Acknowledgements

Not applicable.

Authors' contributions

N.W. and E.S. conceived of the presented idea, designed the search strategy, and formulated the inclusion and exclusion criteria. N.W. systematically searched the literature, and together with Y.N., screened the databases'search results and reviewed the reports that were found eligible for the review. Y.N. conducted the meta-analysis. N.W. and Y.N. wrote the manuscript draft, which was then revised by E.S., Y.N., and N.W. to the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The full search stragedy, results, and data collection reports are available on reasnble request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 14 February 2025 Accepted: 13 April 2025
Published online: 25 April 2025

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