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Review Article

Margin positivity and re-excision after breast-conserving surgery following neoadjuvant chemotherapy: A systematic review and meta-analysis☆

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ABSTRACT

Neoadjuvant chemotherapy (NACT) is increasingly used to facilitate breast-conserving surgery (BCS) in patients with early-stage and locally advanced breast cancer. However, tumour response to NACT is heterogeneous, and comparative studies have reported higher rates of margin involvement and re-excision compared with primary surgery. Despite its clinical significance, the incidence of positive margins and rates of re-excision remain incompletely defined. A systematic review and meta-analysis was conducted in accordance with PRISMA guidelines. PubMed, Embase, and Scopus were searched for studies reporting tumour-on-ink margin positivity following BCS after NACT. A random-effects meta-analysis was performed to estimate pooled rates of margin positivity and re-excision.

Seven retrospective cohort studies comprising 3962 patients were included, with six studies (3855 patients) eligible for quantitative synthesis. The pooled tumour-on-ink margin positivity rate following index BCS after NACT was 9.7% (95% CI 5.8–13.6%). The pooled re-excision rate was 14.0% (95% CI 0.0–30.6%), with substantial between-study heterogeneity. Re-excision rates varied widely, likely reflecting differences in institutional practice and thresholds for reoperation. Residual DCIS and invasive lobular carcinoma were the clinicopathological features most consistently associated with higher rates of margin positivity and re-excision. Tumour-on-ink margin positivity following BCS after NACT is comparable to that reported following primary surgery, while re-excision rates are higher and more variable. Improved risk stratification may assist surgical planning and patient counselling following NACT.

1. Introduction

Neoadjuvant chemotherapy (NACT) is an integral component of modern breast cancer management, enabling tumour downstaging and facilitating breast conservation. Landmark trials including KEYNOTE-522 and NeoSphere, have expanded the indications for NACT beyond locally-advanced disease to include biologically aggressive early-stage tumours, such that an increasing proportion of patients are now considered for breast-conserving surgery (BCS) following systemic therapy [1,2]. Randomised trials have demonstrated that BCS after NACT does not compromise local control or survival [3–5]. Nevertheless, achievement of negative surgical margins remains fundamental for local disease control following BCS [6].

Achieving clear margins after NACT presents distinct challenges. Among patients without a pathologic complete response (pCR), residual disease may be multifocal or discontinuous as a consequence of patchy tumour regression [7], and discordance between post-treatment imaging and final pathology is well-described [8]. Comparative studies have reported higher rates of margin involvement and re-excision following BCS after NACT compared with primary surgery [9]. However, reported rates of margin positivity vary widely, reflecting heterogeneity in patient selection, localisation techniques, surgical practice, pathological assessment, and margin definitions [10]. Such variation in surgical practice was highlighted by the UK NeST study, in which centres differed substantially in whether BCS aimed to excise the original tumour footprint or the post-treatment residual disease [11]. Much of the available evidence on margin outcomes is derived from small, single-institution series. Moreover, inconsistency in the definition of

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positive margins limits meaningful comparison and generalisability. Consequently, contemporary data using standardised tumour-on-ink definitions remain limited, and it is unclear whether margin positivity following BCS after NACT differs meaningfully from that observed in primary surgery.

In the context of the expanding use of BCS following NACT, a clearer understanding of expected margin outcomes is required to optimise surgical planning and appropriately counsel patients. Accordingly, we performed a systematic review and meta-analysis to estimate the pooled rate of positive margins – defined as invasive or in-situ carcinoma present at the inked margin – following BCS after NACT, to determine re-excision rates, and to synthesise evidence on clinicopathological factors associated with margin involvement, with the aim of informing surgical decision-making following NACT.

2. Methods

This systematic review was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) [CRD420261282712]. The PICO (Population, Intervention, Comparator, Outcome) framework was applied as follows: the population comprised female patients with invasive breast cancer; the intervention was BCS following NACT; no comparator was specified; and the outcomes were tumour-on-ink margin positivity and the requirement for further surgery (either margin re-excision or completion mastectomy).

2.1. Search strategy

A systematic search of PubMed, Embase and Scopus was performed in October 2025. The search strategy combined terms relating to breast cancer, neoadjuvant chemotherapy, breast conserving surgery and surgical margins. Medical Subject Headings (MeSH) and Emtree terms were included where appropriate. The complete search strategy is provided in Supplementary Appendix 1. The search was restricted to studies published in English from 2010 onwards. Duplicates were removed using EndNote 21 prior to screening. Reference lists of included studies were manually reviewed to identify additional eligible publications.

2.2. Study selection

Studies were eligible if they included female patients with invasive breast cancer undergoing BCS following NACT and reported the number of patients with tumour-on-ink positive margins after index surgery, and/or re-excision rates attributable to margin involvement. Patients were included irrespective of pathological response to NACT, including those achieving a pCR. Exclusion criteria included studies utilising intra-operative pathological margin assessment (e.g. frozen section analysis), those without a defined margin positivity criterion, studies employing novel or experimental tumour localisation techniques (e.g. 3D-printed surgical guides), and studies including fewer than 50 eligible cases to minimise the influence of small descriptive case series. Conference abstracts were excluded.

Extracted data included study design, number of patients undergoing BCS following NACT, rates of pCR, rates of positive margins at index surgery, rates of subsequent surgical intervention (margin re-excision or completion mastectomy), and additional margin outcomes where reported, including positive and close margins and outcomes within the residual disease cohort. Clinicopathological variables, including clinical stage, residual tumour size, histological subtype, hormone receptor and HER2 status, presence of DCIS and multifocality were extracted where available.

2.3. Risk of bias assessment

Risk of bias was assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool. The certainty of evidence for each pooled outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Assessment of publication bias using funnel plots was planned if more than 10 studies were included in the meta-analysis. The search, screening, full-text review, data extraction and quality assessment were performed independently by 2 authors (N.K and T.H). Discrepancies were resolved through arbitration with the senior author (M.B).

2.4. Statistical analysis

The primary meta-analysis estimated the pooled rate of tumour-on-ink positive surgical margins among all patients undergoing BCS following NACT, including patients achieving pCR. Study-specific proportions and 95% confidence intervals were calculated and pooled using a random-effects inverse-variance model. A random-effects approach was selected to account for anticipated clinical and methodological heterogeneity between studies. Between-study variance (τ^2) was estimated using restricted maximum likelihood, and statistical heterogeneity was assessed using the I^2 statistic. Hartung-Knapp-Sidik-Jonkman adjustment was applied to analyses including more than two studies; conventional random-effects confidence intervals were used for analyses limited to two studies. Separate meta-analyses were performed to estimate pooled re-excision rates attributable to margin involvement and rates of positive and close margins (<1 mm). A subgroup analysis was performed among patients with residual invasive or in-situ disease following NACT, where these data were reported separately, to estimate tumour-on-ink margin positivity after exclusion of patients achieving pCR. All statistical analyses were performed using R (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value of < 0.05 was considered statistically significant.

3. Results

3.1. Study characteristics

The initial search identified 681 unique records, of which 98 articles underwent full-text review. Seven studies [9,14–19] met the inclusion criteria for systematic review, and six [9,14–18] were included in the quantitative synthesis (Fig. 1). All included studies were observational in design, the majority comprising retrospective single-institution cohort studies, alongside one large population-based cohort. Collectively, these studies included 3962 patients undergoing BCS following NACT, with 3855 patients contributing to the meta-analysis.

Margin definitions were generally aligned with the tumour-on-ink standard, with most studies either explicitly adopting this definition or reporting sufficient data to permit direct analysis. However, the study by Makineli et al. [17] defined positive margins as tumour on ink involving >2 mm of the inked margin, rather than any tumour on ink, and a sensitivity analysis excluding this study was therefore planned. The study by van Hemert et al. [19] was excluded from the meta-analysis due to its restriction to a cohort of invasive lobular carcinoma (ILC), limiting comparability with the mixed-histology cohorts of other included studies, but was retained in the systematic review. Study characteristics are summarised in Table 1.

3.2. Outcomes

3.2.1. Positive surgical margins

Meta-analysis of six studies demonstrated a pooled tumour-on-ink margin positivity rate of 9.7% (95% CI 5.8–13.6%) following index BCS after NACT (Fig. 2). Between-study heterogeneity was moderate ($I^2 = 58.7\%$). The study by van Hemert et al., which was excluded from

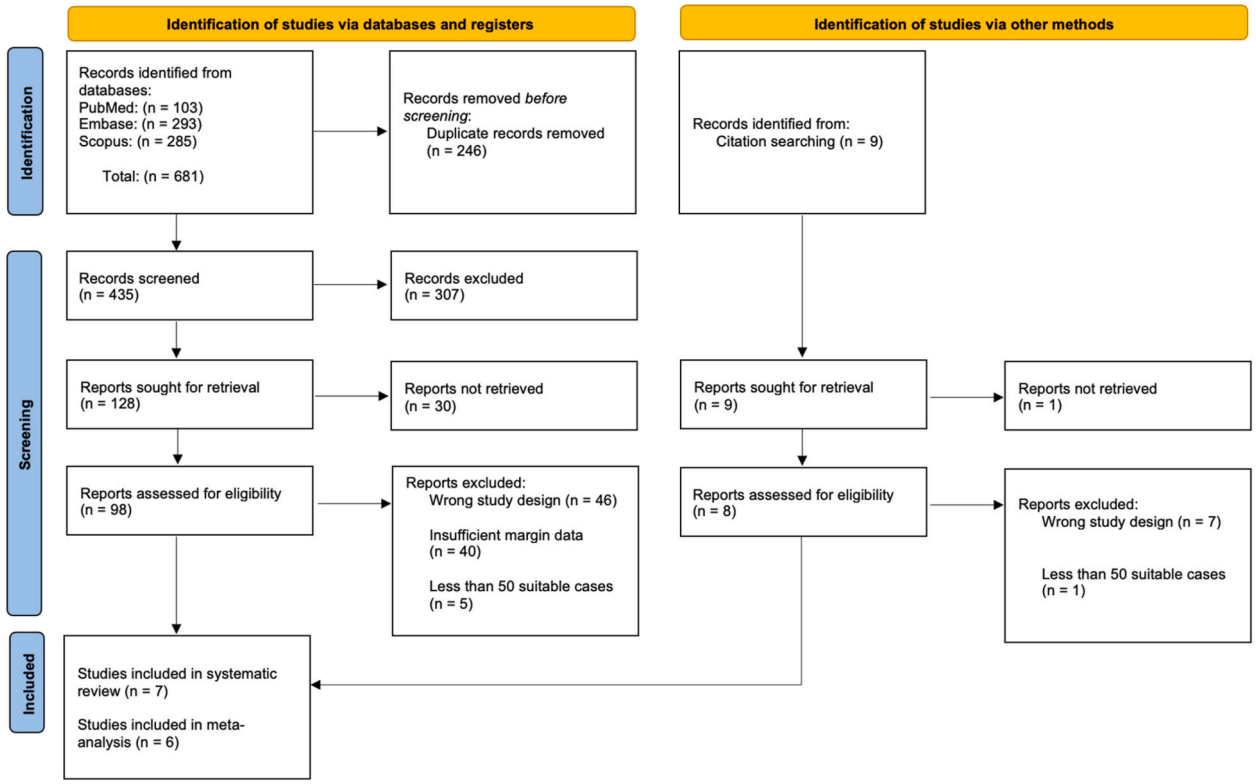


Fig. 1. PRISMA flow diagram of study selection.

the meta-analysis because it included only patients with ILC, reported a tumour-on-ink margin positivity rate of 51%, substantially higher than that observed in the mixed-histology cohorts [19]. Sensitivity analysis excluding the study by Makineli et al. yielded a pooled margin positivity rate of 10.4% (95% CI 4.4–16.3%), compared with 9.7% (95% CI 5.8–13.6%) in the primary analysis. Heterogeneity increased slightly (I^2 = 66.0%). The pooled estimate was therefore largely unchanged following exclusion of this study (Supplementary Fig. 1).

3.2.2. Rates of re-excision

Five studies reported re-excision rates attributable to margin involvement and were included in a separate meta-analysis [9,14–16,18]. The pooled re-excision rate was 14.0% (95% CI 0.0–30.6%) (Fig. 3), with substantial between-study heterogeneity (I^2 = 97%). Three included studies reported the type of operation performed, and of 131 re-excisions, 69 (52.7%) were completion mastectomies.

3.2.3. Positive and close margins

Two studies reported the combined rate of positive and close margins, defined as tumour within 1 mm of the inked margin [9,14]. The pooled rate was 27.6% (95% CI 9.5–45.7%) (Fig. 4), with substantial between-study heterogeneity (I^2 = 89%).

3.2.4. Residual disease cohort

A subgroup analysis was performed including only patients with residual disease following NACT. Two studies reported outcomes separately according to pathological response; of 467 patients, 131 (28.1%) achieved breast pCR and 336 had residual invasive or in-situ disease [14,16]. The pooled tumour-on-ink margin positivity rate was 11.6% (95% CI 8.2-15.0%), modestly higher than that observed in the overall cohort, with no observed between-study heterogeneity (I^2 = 0%) (Fig. 5).

3.3. Risk of bias/certainty of evidence (GRADE)

ROBINS-I was used to assess risk of bias across all included studies. Six studies were judged to be at moderate risk of bias, while one was considered to be at serious risk of bias. The most important contributors to bias were confounding and selection bias, primarily reflecting the retrospective design of included cohorts (Supplementary Table 1). The certainty of evidence for all pooled outcomes was assessed using the GRADE framework. The certainty of evidence was rated as low for tumour-on-ink margin positivity, re-excision rates, and tumour-on-ink margins within the residual disease cohort, and very low for the pooled estimate of positive and close margins (<1 mm). The lower certainty for the latter reflected substantial heterogeneity and serious imprecision. No upgrading factors were identified (Supplementary Table 2).

3.4. Clinicopathological predictors of margin positivity

Due to heterogeneity in reporting, formal statistical analysis of clinicopathological predictors was not feasible. However, narrative synthesis identified several factors associated with an increased risk of positive margins or reoperation following index BCS. The presence of a DCIS component alongside residual invasive carcinoma was the most consistently supported predictor. Ploumen et al. reported significantly higher rates of positive margins in tumours with associated DCIS compared to invasive carcinoma alone (12.8% vs 4.9%, $p < 0.001$), with DCIS independently associated with margin positivity on multivariable analysis (OR 2.61, 95% CI 1.98 - 3.44). Consistent with this, Choi et al. demonstrated markedly higher re-excision rates in the presence of residual DCIS after NACT (48.2% for DCIS alone and 42.9% for invasive carcinoma with DCIS, compared with 17.3% for invasive disease alone).

Histological subtype, particularly ILC, was associated with higher rates of margin involvement. In an ILC-restricted cohort, van Hemert et al. observed tumour-positive margins in 51% of patients, with re-excision required in approximately one-third of patients. Devane et al. also identified lobular histology as a strong predictor of re-excision in a mixed histology cohort (OR 17.0). With regards to tumour burden, higher clinical T stage (cT $\geq$ 3) was independently associated with

Table 1
Summary of characteristics of included studies.

Study	Authors	Publication year	Journal	Country	Study design	No. of BCS post NACT	Total tumour-on-ink margins	Margin positivity rate (%)	Re-excision Threshold	Re-excision rate (%)	pCR definition	Breast pCR rate (%)
Margins in breast-conserving surgery after neoadjuvant therapy	Choi et al.	2018	ASO	U.S	R	<382	32	8.4	<2 mm from ink	26.4	ypT0	27.5
The impact of neoadjuvant chemotherapy on margin re-excision in breast-conserving surgery	Devane et al.	2020	WJS	Ireland	R	69	16	23.3	<1 mm from ink	31.9	ypT0/is	21.7
Guiding breast conserving surgery in patients after neoadjuvant systemic therapy for breast cancer: A comparison of radioactive seed localisation with the ROLL technique	Donker et al.	2013	ASO	Netherlands	R	154	20	13	Tumour on ink	7.8	ypT0/is	33.8
The role of radioactive iodine-125 seed localisation in breast conserving therapy following neoadjuvant chemotherapy	Gobardhan et al.	2013	Annals of Oncology	Netherlands	R	85	7	8.2	Tumour on ink >4 mm	3.5	ypT0	30.6
Clinicopathological factors affecting positive margins after breast conserving surgery: A comparative study of low and high-volume hospitals	Makineli et al.	2025	Breast Care	Netherlands	R	109	11	10.1	-	-	-	-
Surgical outcomes and prognosis of HER2+ invasive breast cancer patients with a DCIS component treated with breast-conserving surgery after neoadjuvant systemic therapy	Ploumen et al.	2024	EJSO	Netherlands	R	3056	247	8.1	Tumour on ink >4 mm	3.1	ypT0/is	58.8
Breast surgery after neoadjuvant chemotherapy in patients with lobular carcinoma: surgical and oncologic outcome	van Hemert et al.	2024	Breast Cancer Research & Treatment	Netherlands	R	107	55	51	Tumour on ink >4 mm	33	-	-

DCIS = ductal carcinoma in-situ, ROLL = radioguided occult lesion localisation, R = retrospective, BCS = breast-conserving surgery, NACT = neoadjuvant chemotherapy, pCR = pathologic complete response, ASO = Annals of Surgical Oncology, WJS = World Journal of Surgery, EJSO = European Journal of Surgical Oncology, US = United States.

margin positivity in one study [19], while patients requiring re-excision had significantly larger tumours at presentation in another [9]. Evidence for multifocal disease as a predictor was limited, with no significant association identified in the available data and inconsistent reporting across studies. With respect to tumour biology, evaluation across included studies was limited. Devane et al. reported significantly higher re-excision rates in oestrogen receptor–positive/HER2-negative tumours and lower rates in HER2-positive disease, suggesting that less chemosensitive subtypes may be associated with an increased risk of inadequate excision following NACT. Similarly, Ploumen et al. observed higher crude rates of margin positivity in oestrogen receptor–positive tumours. However, receptor subtype was not independently associated

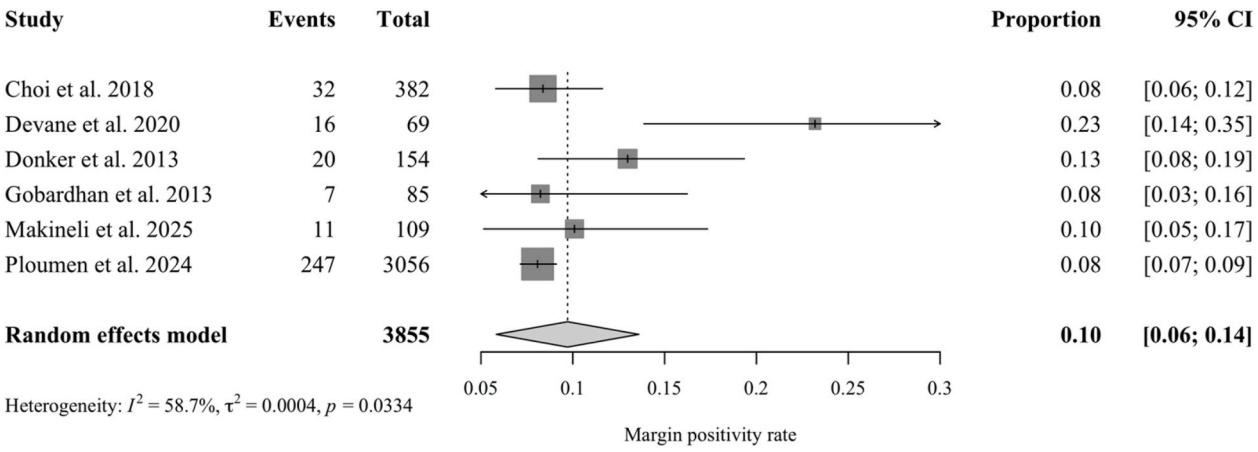


Fig. 2. Forest plot of tumour-on-ink margin positivity rates following BCS after NACT.

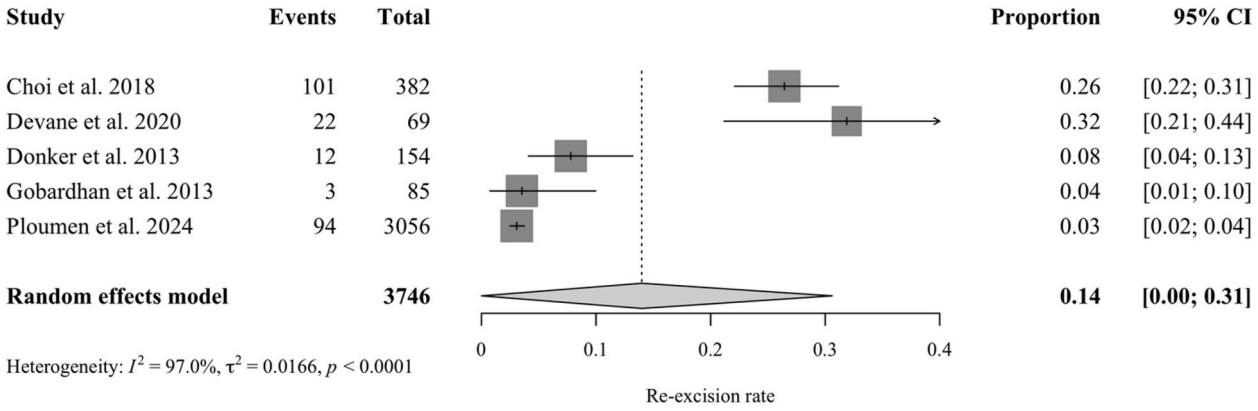


Fig. 3. Forest plot of re-excision rates attributable to margin involvement following BCS after NACT.

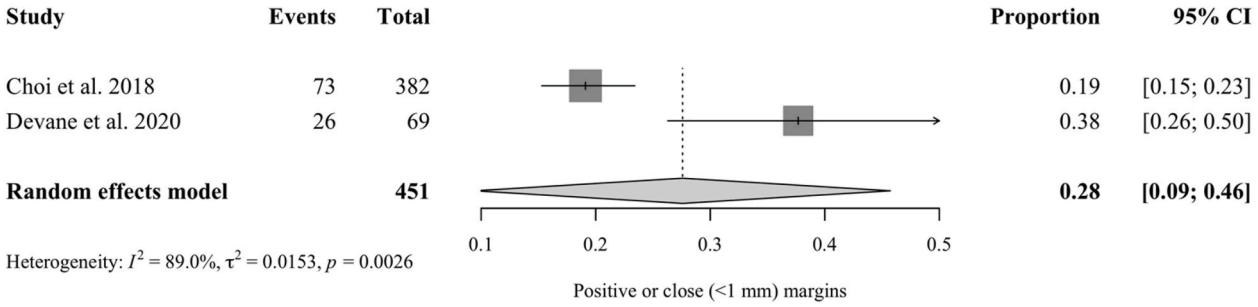


Fig. 4. Forest plot of combined positive and close (<1 mm) margin rates following BCS after NACT.

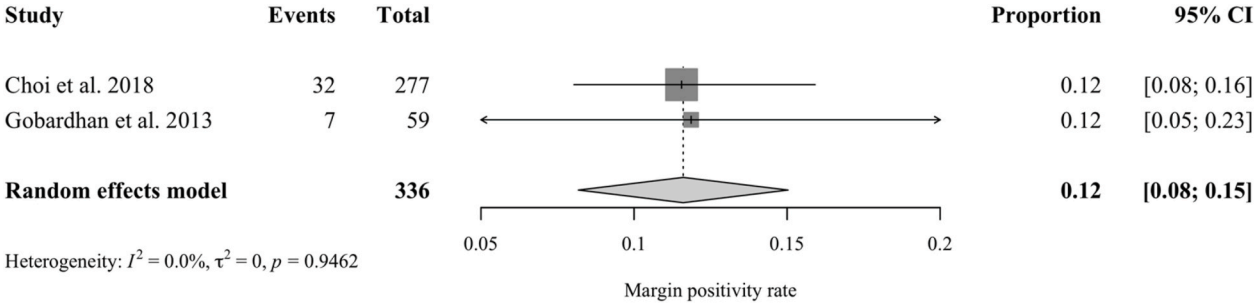


Fig. 5. Forest plot of tumour-on-ink margin positivity rates among patients with residual invasive or in-situ disease following NACT.

with margin status on multivariable analysis, with the presence of DCIS emerging as the dominant predictive factor.

4. Discussion

In this systematic review and meta-analysis, tumour-on-ink margins following BCS after NACT were observed in approximately one in ten patients, including those patients who achieved a pCR. Re-excision rates were higher and more variable, reflecting differences in surgical practice rather than margin positivity alone. As the use of NACT expands in early-stage breast cancer, these findings have important implications for surgical planning and patient counselling.

The pooled tumour-on-ink margin rate of 9.7% following BCS after NACT is broadly comparable to rates reported in primary BCS populations, which were estimated at 9.4% in a large 2022 meta-analysis [20]. This suggests that, in appropriately selected patients, BCS after NACT does not appear to confer a substantially increased risk of incomplete excision compared with upfront surgery, despite recognised challenges associated with residual disease heterogeneity and imaging-pathology discordance [8]. Earlier comparative studies reported higher rates of margin involvement and re-excision in the post-neoadjuvant setting – often in the 15-20% range; however, much of this literature spans earlier treatment eras and may pre-date contemporary systemic therapy, localisation techniques and margin guidelines, which may account for the observed discrepancy [21]. In addition, there remains variation regarding excision specimens in patients undergoing BCS who have achieved a favourable radiological response, with some surgeons continuing to excise the original footprint of the tumour seen at diagnosis, whilst others perform a more minimal excision of the marked area [11].

In contrast, re-excision rates demonstrated marked variability across studies, even where tumour-on-ink margin rates were similar. This divergence highlights the influence of institutional margin policies and thresholds for reoperation. In some cohorts, re-excision was frequently undertaken for close but negative margins, whereas in others, focally involved margins were managed with adjuvant radiotherapy alone. In contrast to most international guidance, Dutch national practice has historically allowed omission of re-excision for focally positive tumour-on-ink margins when adjuvant whole-breast radiotherapy with tumour-bed boost is delivered, due to the observation that this has no adverse impact on disease-free or overall survival, albeit with a small absolute difference in ipsilateral breast tumour recurrence compared with re-excision [22].

Although the SSO–ASTRO consensus guideline defines a negative margin as “no tumour on ink", the pooled positive/close margin rate of 27.6% suggests that substantially more patients may be considered for re-excision in centres following the UK Association of Breast Surgery (ABS) guidance, which recommends consideration of re-excision for margins <1 mm from ink. This distinction has important implications when discussing the potential need for further surgery with patients.

The subgroup analysis of patients with residual disease following NACT is especially pertinent, as these are the patients in whom the risk of positive margins is most relevant when planning BCS. However, only two studies reported outcomes separately for this cohort, highlighting a notable gap in the current literature. Within this limited evidence base, the pooled tumour-on-ink margin positivity rate was 11.6%, only modestly higher than that observed in the overall cohort. This may partly reflect careful selection of patients with residual disease for BCS, although neither study specifically explored the factors underlying the observed margin rate. Although this estimate should be interpreted cautiously, it is likely to be more relevant when counselling patients with residual disease who are considering BCS after NACT.

Although formal statistical analysis of clinicopathological predictors was not feasible, several patterns emerged across studies that merit consideration. In particular, the presence of residual DCIS alongside invasive carcinoma was the most consistent predictor of both margin positivity and re-excision. Such findings likely reflect the discontinuous growth pattern of DCIS and its relative resistance to neoadjuvant therapy, allowing persistence beyond the boundaries of residual invasive disease. This is supported by findings from the I-SPY2 adaptive neoadjuvant breast cancer trial, which demonstrated residual DCIS in approximately 21% of patients achieving pCR of invasive disease [23]. These authors also noted that among the patients who achieved pCR, those with DCIS trended toward worse event-free survival and distant recurrence-free survival, although statistical significance was not achieved.

Lobular histology also appeared to be associated with higher rates of margin involvement. This association may partially reflect limitations in preoperative radiological assessment, as the infiltrative growth pattern of ILC, characterised by discohesive tumour cell spread with minimal stromal reaction, often results in subtle or diffuse residual disease that is difficult to detect and delineate on conventional imaging [24]. Consequently, tumour extent may be underestimated, increasing the risk of margin positivity at surgery. In addition, lobular cancers are rarely chemosensitive and therefore prone to higher rates of extensive residual disease after NACT. Together with the findings regarding residual DCIS, these observations suggest that the distribution of residual disease—rather than its volume alone—may be an important determinant of margin status following BCS after NACT.

Evidence for other clinicopathological predictors was less consistent. Associations between tumour burden, receptor subtype and margin status varied across included studies, likely reflecting the limited statistical power of individual observational cohorts together with heterogeneity in patient selection, pathological response and methods of predictor assessment. Consequently, firm conclusions regarding these factors cannot be drawn. Future studies using standardised reporting of clinicopathological variables will be important to better define predictors of margin positivity in the post-neoadjuvant setting.

Collectively, our findings indicate that tumour-on-ink margins after BCS following NACT are relatively uncommon, while re-excision rates are more strongly driven by institutional practice than by margin positivity alone. Consideration of residual disease characteristics, particularly the presence of DCIS and lobular histology, may assist in preoperative counselling, selection of surgical approach and consideration of wider excision or oncoplastic techniques in higher-risk subgroups.

This study has several limitations. All included studies were observational and predominantly retrospective, introducing susceptibility to confounding and selection bias. There was heterogeneity in study design, patient populations, surgical practices and margin definitions. Re-excision rates were particularly influenced by institutional practice patterns and local guidelines, limiting comparability. In addition, inconsistent reporting of clinicopathological variables precluded formal statistical analysis of predictors, and the relatively small number of included studies limited formal assessment of publication bias.

To our knowledge, this is the first study to systematically synthesise contemporary margin positivity rates and associated clinicopathological predictors in patients undergoing BCS in the post-neoadjuvant setting. Tumour-on-ink margins occur in approximately one in ten patients, while re-excision rates vary and reflect local institutional practice patterns. Residual disease characteristics, particularly DCIS and lobular histology, appear to influence margin outcomes, underscoring the need for standardised reporting and further prospective study in this setting.

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Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2026.112128.

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