Editorial Commentary

Critical appraisal of the 2 mm threshold in ductal carcinoma in situ: methodological concerns in meta-analysis of margin width and local recurrence risk

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Ezzat *et al.* have recently reported the results of systematic review and meta-analysis on the impact of resection margin width on local recurrence in ductal carcinoma in situ (DCIS) (1). While the study provides valuable insights, particularly in supporting a 2 mm margin threshold, we wish to highlight several methodological shortcomings and unacknowledged limitations that could impact the reliability and applicability of the findings.

Methodological concerns

The authors pooled data from 31 studies encompassing 40,265 patients, but a significant proportion of these were retrospective, introducing selection bias and inconsistency in treatment protocols (2,3). The lack of standardized surgical, radiotherapeutic, and pathological assessment criteria across studies limits the validity of the meta-analysis. Additionally, variations in radiotherapy dose, techniques, and fractionation regimens were not adequately accounted for in the statistical adjustments, potentially confounding the impact of margin width (4,5).

While the authors attempt to categorize margin widths into distinct subgroups, there remains ambiguity regarding how margins were defined across studies. Some included studies did not specify whether margin width was measured on invasive or *in situ* components, nor was there a standardized pathological assessment method for margin clearance (6,7). This variability weakens the conclusions drawn regarding the optimal margin threshold.

Recent studies, including one by Vanni *et al.*, highlight the potential for surgical de-escalation in cases where re-excision is considered in patients with margins less than 2 mm and a diagnosis of DCIS. Their work suggests that careful selection of patients may allow for less aggressive surgical approaches, avoiding unnecessary re-excision while still managing recurrence risk effectively (8).

Disease heterogeneity and risk stratification

DCIS is a heterogeneous disease, and recurrence risk is influenced by molecular subtypes, tumor biology, and receptor status (9,10). The study does not stratify local recurrence risk based on factors such as human epidermal growth factor receptor 2 (HER2) status, Ki-67 proliferation index, or intrinsic subtype classification (11,12). Given that aggressive subtypes may recur despite wide margins, the authors' emphasis on margin width alone oversimplifies the recurrence risk assessment (12,13).

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While the authors acknowledge that 27.3% of patients received endocrine therapy, they do not explore its potential impact on recurrence rates. Given that adjuvant endocrine therapy significantly reduces local recurrence in hormone receptor-positive DCIS (14,15), failing to stratify patients by systemic therapy use introduces an important confounder that could misattribute risk reduction to margin width rather than adjuvant therapy.

Radiotherapy considerations

The claim that boost radiotherapy mitigates recurrence risk in patients with close (<2 mm) margins lacks sufficient subgroup analysis to substantiate this conclusion (1,16). The meta-analysis does not adequately separate studies that used modern intensity-modulated radiotherapy versus older techniques, and the dose-response relationship for boost radiation is not clearly defined. Moreover, the potential negative impact of boost on cosmetic outcomes and fibrosis was not addressed (17,18).

Selection bias

Most of the included studies derive from institutional databases, which inherently exclude patients who undergo mastectomy due to multifocal or extensive disease. This biases the population toward patients with smaller-volume disease and may not reflect real-world outcomes, particularly in patients with large, high-grade DCIS who are more likely to undergo mastectomy or wider excisions (19,20).

Statistical limitations

While the authors employ meta-analytic techniques, several statistical concerns warrant mention. First, the random-effects model assumes heterogeneity but does not adequately explore sources of bias beyond subgroup analyses (21,22). Additionally, the authors imputed missing confidence intervals, which can introduce estimation bias if the imputation method is not robust (23). The high heterogeneity observed in some comparisons suggests that pooling these studies may not yield reliable effect estimates. Furthermore, the reliance on odds ratios and relative risks without absolute risk reductions in all comparisons limits the clinical interpretability of the findings (24,25). A sensitivity analysis assessing the impact of study quality on effect size was also not reported, raising concerns about potential publication bias skewing the results.

Alignment with international guidelines

The findings of this study are consistent with international guidelines, particularly those from the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO), which recommend a minimum 2 mm clear margin for DCIS treated with breast-conserving surgery and whole-breast radiotherapy (26). Notably, American guidelines also support individualized decision-making, permitting narrower margins in selected cases based on patient and tumor characteristics (27). Similarly, European guidelines, including those from the European Society for Medical Oncology (ESMO), advocate for a 2 mm margin but allow for smaller margins when combined with boost radiotherapy (28,29). The recent update by the UK's Association of Breast Surgery (ABS) to endorse a 2 mm margin threshold aligns with these global trends, although it falls short in addressing alternative strategies such as the integration of systemic therapy or tailoring margins based on recurrence risk stratification (30,31). These variations underscore the need for further research and international consensus to support evidence-based, individualized treatment planning for patients with DCIS.

Emerging evidence and alternative approaches

Recent studies have shown that low-dose tamoxifen (5 mg daily for 2 years) significantly reduces the risk of breast cancer recurrence by 50% in both breasts with minimal adverse effects, making it a promising option for patients with estrogen receptor-positive DCIS and narrower surgical margins, and this approach could be considered in select cases (32,33). Furthermore, the definition of local recurrence in the study lacks clarity, which is crucial for interpreting the findings. Without a standardized definition, the reported rates of local recurrence may vary significantly across studies, potentially leading to inconsistencies in the conclusions drawn (34,35). Additionally, the authors did not analyze overall survival, a critical outcome in evaluating the efficacy of treatment strategies for DCIS. Overall survival is an essential metric that encompasses not only local recurrence but also the broader implications of treatment decisions on patient longevity and quality of life (35,36). The omission of this analysis limits the comprehensive understanding of the impact of resection margin width and associated therapies on patient outcomes. Recent emerging evidence comparing breast-conserving surgery plus radiation with mastectomy for DCIS suggests that patients

undergoing breast-conserving therapy experience superior overall survival compared to those receiving mastectomy, despite a higher risk of ipsilateral breast tumor recurrence (IBTR) (37,38). Research, including our own, shows that many patients with pure DCIS harbor circulating tumor cells (CTCs), and according to our hypothesis, these cells are inclined to return to the original tumor site that could harbor a supportive microenvironment when these CTCs are activated (39,40). Wider margins and boost radiation are likely to cause greater disruption of the surrounding tumor microenvironment thus leading to a lower incidence of local recurrence. We have postulated that in the absence of the supportive microenvironment, such activated CTCs may pursue a niche at another site, including distant organs (41,42). There has been a paradigm shift towards treating local recurrence after initial breast conserving therapy for DCIS with repeat breast conserving surgery, and therefore it is important to establish whether local recurrence influences overall survival (43-45).

Conclusions

While the study provides a compelling case for a 2 mm margin threshold, its methodological limitations necessitate caution in clinical application. Future research should incorporate prospective cohort studies with standardized definitions, detailed histopathological stratification, and comprehensive analysis of systemic therapy impact (46,47). Additionally, randomized trials evaluating the necessity of re-excision versus adjuvant radiation intensification in close-margin cases would provide more robust evidence for practice-changing recommendations (48). Therefore, in the era of risk-adapted treatment optimization, the adequacy of margin width and the potential need for further surgery after initial wide local excision should be individualized and based on multidisciplinary consensus.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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