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Research Article

Predictors of Margin Positivity and Re-excision Following Breast-Conserving Surgery: Association with Imaging Findings, Histopathological Characteristics, Microbiological Findings, Therapeutic Management, and Clinical Outcomes

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Abstract: Achieving negative surgical margins during breast-conserving surgery remains paramount to minimizing local recurrence and optimizing oncological outcomes, yet variable rates of margin positivity necessitate secondary re-excision procedures. This prospective observational study evaluated the clinical, radiological, histopathological, microbiological, and therapeutic predictors of margin positivity and subsequent re-excision in three hundred and twenty adult female patients undergoing primary breast-conserving surgery for localized invasive breast carcinoma or ductal carcinoma in situ. Preoperative mammographic and sonographic findings, tumor pathological features, perioperative tissue microbiology, and systemic therapeutic management were analyzed against margin status and re-excision rates. Margin positivity was identified in 22.8% of participants, with 19.4% requiring secondary re-excision procedures. Multivariable logistic regression analysis demonstrated that microcalcifications extending beyond the primary mass on preoperative mammography (OR 3.42, 95% CI 1.84–6.35, $p < 0.001$), presence of an extensive intraductal component (OR 4.15, 95% CI 2.12–8.12, $p < 0.001$), lobular histology (OR 2.86, 95% CI 1.35–6.06, $p = 0.006$), and surgical wound colonization by pathogenic microflora (OR 2.18, 95% CI 1.08–4.41, $p = 0.029$) independently predicted margin

involvement. Conversely, receipt of neoadjuvant systemic therapy was inversely associated with re-excision risk (OR 0.41, 95% CI 0.20–0.84, p = 0.015). Preoperative mammographic microcalcification patterns and extensive intraductal components drive margin positivity, whereas neoadjuvant therapy significantly lowers re-excision requirements. Multimodal risk modeling bridges critical diagnostic gaps, enabling tailored operative planning and reducing secondary surgical burdens.

Keywords: Breast-conserving surgery, surgical margins, re-excision

Introduction

Breast-conserving surgery followed by whole-breast adjuvant radiotherapy represents the primary standard of care for women presenting with early-stage invasive breast carcinoma and localized ductal carcinoma in situ. Clinical trial evidence accumulated over multiple decades has conclusively established that breast-conserving therapy yields overall survival outcomes equivalent to total mastectomy while preserving body image and psychological well-being [1-3]. However, the therapeutic success of breast-conserving surgery relies fundamentally on achieving complete microscopic resection of the primary tumor with negative surgical margins. Inadequate intraoperative margin control increases the risk of local disease recurrence, delays the initiation of necessary adjuvant systemic therapies, and often necessitates secondary surgical interventions ranging from targeted re-excision to completion total mastectomy [1-3]. Despite widespread implementation of standardized margin definitions, re-excision rates following initial breast-conserving procedures exhibit substantial clinical variability across institutional cohorts, placing considerable physiological, emotional, and financial burdens on surgical patients [1-3].

The pathogenic mechanisms driving positive surgical margins after partial mastectomy reflect complex interactions between tumor biology, cellular heterogeneity, spatial architecture, and localized tissue microenvironments [4-6]. Malignant mammary cells frequently extend beyond macroscopically palpable tumor masses via microscopic intraductal extensions, multifocal tumor foci, or peritumoral lymphovascular space invasion [4-6]. In addition, host stroma undergo significant remodeling characterized by altered extracellular matrix deposition, neoangiogenesis, and localized inflammatory responses that obscure tumor-stroma

boundaries during intraoperative resection [4-6]. Inflammatory cellular infiltrates and localized microbial colonization within mammary ductal structures can further modify regional tissue density and alter wound healing kinetics, potentially complicating clear pathological assessment of excised tissue specimens [4-6]. Comprehending how these biological and histopathological factors influence margin clearance is vital for minimizing microscopic residual disease [4-6].

Preoperative diagnostic imaging plays a pivotal role in delineating tumor extent, evaluating multifocality, and guiding operative resection plans prior to breast-conserving surgery [4-6]. Digital mammography, high-resolution sonography, and dynamic contrast-enhanced magnetic resonance imaging provide complementary anatomical and functional data regarding primary breast lesions [4-6]. Certain imaging phenotypes, such as extensive microcalcifications, pleomorphic architectural distortion, or poorly circumscribed non-mass enhancements, frequently correlate with microscopic tumor dissemination beyond gross surgical margins [4-6]. However, discrepancies between radiological tumor size and definitive pathological dimensions remain common, particularly in dense parenchymal tissue or invasive lobular carcinoma [4-6]. Evaluating specific diagnostic imaging features alongside microscopic pathological metrics offers a superior framework for predicting intraoperative margin clearance [4-6].

Histopathological characteristics of the primary excision specimen represent some of the most critical determinants of surgical margin status and subsequent re-excision requirements [7-8]. Tumor histologic subtype, histologic grade, presence of an extensive intraductal component, lymphovascular invasion, and hormone receptor status significantly impact margin involvement [7-8]. Invasive lobular carcinoma, for instance, exhibits a discohesive growth pattern due to loss of E-cadherin expression, making intraoperative macroscopic assessment of tumor boundaries particularly challenging [7-8]. Similarly, lesions harboring a prominent intraductal component frequently demonstrate subtle microscopic skip lesions along adjacent mammary ducts, increasing the probability of focal margin involvement [7-8]. Establishing how these distinct pathological variables correlate with quantitative margin clearance distance is necessary for refining intraoperative margin assessment techniques [7-8].

Furthermore, perioperative therapeutic strategies—including neoadjuvant chemotherapy, targeted biological agents, and endocrine interventions—exert profound effects on primary tumor volume, tumor margin architecture, and surgical resectability [7-8]. Neoadjuvant systemic therapy often induces significant tumor regression, enabling breast preservation in women who would otherwise require total mastectomy [7-8]. However, patterns of response to neoadjuvant treatment vary, ranging from concentric shrinkage to fragmented cellular residual nests scattered throughout the original tumor bed [7-8]. Understanding the impact of neoadjuvant therapy on surgical margin positivity alongside perioperative factors such as surgical wound microbiology and postoperative wound healing complications remains essential for optimizing multidisciplinary management pathways [7-8].

To address these ongoing challenges, the present prospective observational study was designed to systematically evaluate the clinical, radiological, histopathological, microbiological, and therapeutic predictors of margin positivity and secondary re-excision in patients undergoing breast-conserving surgery [9-10]. By integrating preoperative imaging parameters, definitive pathological metrics, wound microflora characteristics, and systemic treatment variables within a unified analytical framework, this investigation aims to establish independent risk factors for surgical margin involvement and refine risk-stratification models for clinical practice [9-10].

Methodology

This prospective observational cohort study was conducted at Mayo Hospital, Lahore over a continuous twenty-four-month period. Adult female patients aged eighteen years or older with histologically confirmed stage I–III invasive breast carcinoma or localized ductal carcinoma in situ scheduled to undergo primary or post-neoadjuvant breast-conserving surgery were systematically evaluated and prospectively enrolled. Sample size calculation was performed prior to study initiation using Epi Info software. Based on an estimated baseline surgical margin positivity rate of twenty-two percent in patients undergoing partial mastectomy, a confidence level of ninety-five percent, a statistical power of eighty percent, and an anticipated minimum odds ratio of 2.2 for margin involvement among patients presenting with high-risk mammographic microcalcifications or extensive intraductal

components, the minimum required sample size was calculated as three hundred and five patients. To compensate for potential loss to follow-up or incomplete pathological data, a total of three hundred and twenty eligible participants were included in the final analysis cohort. Prior to performing any surgical interventions or diagnostic evaluations, detailed explanations regarding study procedures were provided, and formal verbal informed consent was documented from all participating patients in accordance with ethical standards. The study protocol was approved by the institutional review board.

Eligible participants included adult female patients aged eighteen years or older with unifocal or limited multifocal breast carcinoma undergoing breast-conserving surgery who provided informed consent. Patients were excluded if they met any of the following criteria: presentation with stage IV inflammatory or distant metastatic breast cancer, prior history of ipsilateral breast irradiation or previous ipsilateral breast malignancy, planned primary total mastectomy, active systemic connective tissue disease precluding postoperative radiotherapy, severe uncontrolled systemic comorbidities, or incomplete preoperative imaging or definitive histopathological reports.

All enrolled participants underwent standard preoperative workup, including bilateral diagnostic mammography, high-resolution breast ultrasound, and selective dynamic contrast-enhanced magnetic resonance imaging based on clinical indication. Operative resection was executed using standardized oncoplastic or conventional breast-conserving techniques. Excised surgical specimens were short-stitched and oriented intraoperatively for histological mapping. Intraoperative frozen section analysis or specimen radiography was performed according to institutional standards. Prior to wound closure, aerobic and anaerobic microbiological swab cultures were obtained from the surgical cavity bed to evaluate perioperative tissue microflora colonization. Standardized systemic therapeutic protocols, including neoadjuvant or adjuvant chemotherapy, anti-HER2 targeted therapy, and endocrine therapies, were administered based on multidisciplinary tumor board recommendations.

Pathological evaluation of excised surgical specimens was performed by dedicated breast pathologists. Margins were defined as positive in accordance with international consensus guidelines: for invasive

carcinoma, ink on tumor (0 mm distance) was defined as margin involvement; for ductal carcinoma in situ, a margin clearance of less than 2 mm was categorized as positive. Histopathological parameters evaluated included tumor histological type, nuclear grade, invasive tumor size, extensive intraductal component status, lymphovascular invasion, estrogen/progesterone receptor status, HER2 amplification, and exact quantitative distance from tumor cells to oriented inked surgical margins. Secondary re-excision procedures (re-excision of specific margins or completion mastectomy) were documented across the follow-up period.

Statistical analysis was performed using SPSS version 27.0. Continuous variables conforming to normal distribution were expressed as mean ± standard deviation, whereas categorical variables were reported as absolute frequencies and percentages. Differences between categorical parameters across margin status groups (negative versus positive margins) were evaluated using Pearson's chi-square test or Fisher's exact test where appropriate. Continuous demographic and pathological metrics were compared using independent sample t-tests or one-way analysis of variance (ANOVA). Multivariable binary logistic regression analysis was performed to identify independent biological, radiological, microbiological, and clinical predictors of margin positivity and secondary re-excision, reporting adjusted odds ratios with corresponding ninety-five percent confidence intervals. Statistical significance was defined as a two-sided p-value of less than 0.05

.**Results**

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population According to Surgical Margin Status (n = 320)

Variable	Total Cohort (n = 320)	Negative Margins (n = 247)	Positive Margins (n = 73)	p-value
Age (years)	56.4 ± 11.8	57.1 ± 11.5	54.0 ± 12.6	0.054
Body mass index (kg/m²)	26.8 ± 4.5	26.6 ± 4.3	27.5 ± 5.1	0.142

Variable	Total Cohort (n = 320)	Negative Margins (n = 247)	Positive Margins (n = 73)	p-value
Postmenopausal status, n (%)	204 (63.8%)	162 (65.6%)	42 (57.5%)	0.208
Preoperative tumor size on imaging (mm)	22.4 ± 9.6	20.8 ± 8.7	27.8 ± 10.9	<0.001
Mammographic microcalcifications extending beyond mass, n (%)	88 (27.5%)	51 (20.6%)	37 (50.7%)	<0.001
Receipt of neoadjuvant chemotherapy, n (%)	64 (20.0%)	57 (23.1%)	7 (9.6%)	0.012
Surgical cavity microbial colonization, n (%)	52 (16.3%)	34 (13.8%)	18 (24.7%)	0.029
Secondary re-excision performed, n (%)	62 (19.4%)	4 (1.6%)	58 (79.5%)	<0.001

Table 1 outlines the baseline clinical and demographic characteristics, demonstrating that patients with positive margins presented with larger preoperative imaging dimensions, a higher frequency of extended microcalcifications, lower utilization of neoadjuvant therapy, elevated microbial cavity colonization, and significantly higher rates of secondary re-excision ($p < 0.05$).

Table 2. Histopathological Characteristics and Biomarker Profiles Stratified by Surgical Margin Clearance

Pathological Parameter	Negative Margins (n = 247)	Positive Margins (n = 73)	Total Cohort (n = 320)	p-value
Invasive Ductal Carcinoma, n (%)	192 (77.7%)	45 (61.6%)	237 (74.1%)	0.007

Pathological Parameter	Negative Margins (n = 247)	Positive Margins (n = 73)	Total Cohort (n = 320)	p-value
Invasive Lobular Carcinoma, n (%)	26 (10.5%)	17 (23.3%)	43 (13.4%)	0.005
Ductal Carcinoma In Situ alone, n (%)	29 (11.7%)	11 (15.1%)	40 (12.5%)	0.456
Pathological Tumor Size (mm)	21.2 ± 8.9	28.6 ± 11.4	22.9 ± 9.9	<0.001
Histologic Grade 3, n (%)	74 (30.0%)	33 (45.2%)	107 (33.4%)	0.017
Extensive Intraductal Component present, n (%)	38 (15.4%)	31 (42.5%)	69 (21.6%)	<0.001
Lymphovascular Invasion present, n (%)	56 (22.7%)	28 (38.4%)	84 (26.3%)	0.008
Estrogen Receptor Positive, n (%)	191 (77.3%)	54 (74.0%)	245 (76.6%)	0.554
HER2 Gene Amplified, n (%)	48 (19.4%)	17 (23.3%)	65 (20.3%)	0.473
Triple Negative Subtype, n (%)	38 (15.4%)	14 (19.2%)	52 (16.3%)	0.443

Table 2 displays the primary pathological parameters, showing that invasive lobular histology, high histologic grade, presence of an extensive intraductal component, larger pathological size, and positive lymphovascular invasion were significantly associated with surgical margin involvement ($p < 0.05$).

Table 3. Multivariable Logistic Regression Analysis of Independent Predictors for Surgical Margin Positivity and Re-excision

Predictor Variable	Odds Ratio	95% Confidence Interval	p-value
Mammographic microcalcifications extending beyond mass	3.42	1.84 – 6.35	<0.001
Presence of Extensive Intraductal Component	4.15	2.12 – 8.12	<0.001
Invasive Lobular Carcinoma histology	2.86	1.35 – 6.06	0.006
Pathological tumor size >20 mm	2.34	1.21 – 4.53	0.011
Surgical cavity microbial colonization	2.18	1.08 – 4.41	0.029
Receipt of Neoadjuvant Systemic Therapy	0.41	0.20 – 0.84	0.015

Table 3 summarizes the multivariable logistic regression model, establishing that extensive intraductal components, extended microcalcifications, lobular histology, tumor size over 20 mm, and cavity microflora colonization independently increased the risk of positive margins, whereas neoadjuvant systemic therapy exerted a significant protective effect.

Discussion

The findings of this prospective observational study demonstrate that surgical margin positivity and subsequent re-excision following breast-conserving surgery are strongly influenced by a distinct combination of preoperative imaging features, definitive histopathological characteristics, surgical microenvironment factors, and systemic therapeutic strategies. In this cohort of three hundred and twenty patients, initial margin positivity occurred in 22.8% of cases, leading to a overall secondary re-excision rate of 19.4%. These empirical results align closely with published international benchmarks, reinforcing that achieving microscopic clear margins remains a complex challenge requiring careful consideration of multidisciplinary risk factors [11-12].

Preoperative mammographic imaging parameters emerged as powerful early indicators of margin involvement. Specifically, the presence of microcalcifications extending beyond the main tumor mass conferred more than a three-fold increase in the odds of positive

surgical margins on multivariable analysis. Microcalcifications frequently reflect malignant intraductal epithelial proliferation extending into adjacent ductal networks far beyond the central palpable or ultrasonographically visible mass. These radiological findings support recent diagnostic studies highlighting that failure to adequately incorporate mammographic calcification boundaries into preoperative localized surgical mark-up routinely leads to under-resection of subclinical intraductal disease [13-14].

Histopathological evaluation confirmed that extensive intraductal components and invasive lobular histology serve as primary pathological drivers of margin involvement. The presence of an extensive intraductal component increased the odds of positive margins more than four-fold, representing the strongest independent pathological predictor in the multivariable model. Intraductal disease frequently exhibits discontinuous skip lesions along the mammary duct tree, preventing accurate macroscopic margin estimation during lumpectomy. Similarly, invasive lobular carcinoma exhibited a significantly higher rate of margin positivity compared to invasive ductal carcinoma, driven by its characteristic infiltrative single-file growth pattern and lack of desmoplastic stromal reaction. These pathological observations agree with comprehensive oncological studies confirming that lobular histology and intraductal extension mandate larger excision margins and careful intraoperative margin assessment [15-17].

An intriguing finding of this investigation was the statistically significant association between surgical cavity microbial colonization and increased surgical margin positivity. Patients demonstrating intraoperative bacterial colonization within the resection cavity exhibited higher odds of positive surgical margins. Perioperative microflora proliferation and localized tissue inflammation can alter surgical planes, induce microvascular engorgement, and complicate frozen section or gross pathological evaluation. While microbial colonization may also reflect longer operative times or larger surgical wounds, these biological observations warrant further research into how localized tissue microenvironments influence intraoperative margin assessment and wound healing [15-17].

Conversely, receipt of neoadjuvant systemic therapy exerted a significant protective effect against margin positivity, reducing the odds of re-excision by more than fifty percent. Neoadjuvant chemotherapy induces primary

tumor downsizing, clear tumor bed fibrosis, and eradication of subclinical micro-metastatic foci, thereby improving the feasibility of achieving clear microscopic margins during partial mastectomy. This protective association aligns with clinical trial data demonstrating that neoadjuvant treatment effectively converts previously ineligible or high-risk surgical candidates into successful breast-conservation candidates with low re-excision requirements [18-20].

Integrating preoperative imaging microcalcification patterns, invasive tumor histology, extensive intraductal component status, and neoadjuvant response profiles into a standardized preoperative risk score offers significant clinical utility. Identifying high-risk patients prior to surgery allows operative teams to implement targeted strategies, such as wire- or seed-guided localization of microcalcifications, routine cavity margin shaving, or intraoperative specimen radiographies. Tailoring the surgical approach based on individual risk profiles minimizes secondary re-excision procedures, avoids delays in adjuvant therapy, and reduces patient psychological distress [18-20].

Strengths of this study include its prospective design, standardized margin definitions, thorough pathological mapping, and novel inclusion of intraoperative cavity microbiological profiling alongside classical radiological and pathological metrics. Potential limitations include the single-center setting and the lack of long-term ten-year local recurrence tracking, which was beyond the immediate scope of this surgical margin evaluation. Future multi-center investigations incorporating advanced radiomics and real-time intraoperative margin imaging modalities are recommended to further refine margin assessment protocols [18-20].

Conclusion

Mammographic microcalcifications, extensive intraductal components, lobular histology, and cavity microbial colonization independently drive surgical margin positivity, whereas neoadjuvant therapy significantly reduces re-excision rates. Preoperative risk-stratification models combining radiological and histopathological parameters fill key diagnostic gaps, allowing tailored operative planning and reducing secondary surgical interventions.

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