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Prospective Evaluation of Tumor Margin Status in Breast-Conserving Surgery: A Pathological and Surgical Perspective

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ABSTRACT

Aim: This study aims to evaluate tumor margin status in breast-conserving surgery (BCS) and assess its impact on the need for re-excision, axillary staging, and adjuvant therapy. Additionally, it explores molecular profiling to guide personalized treatment strategies.

Materials and Methods: A prospective observational study was conducted on 120 female patients diagnosed with early-stage invasive breast carcinoma or ductal carcinoma in situ (DCIS). Wide local excision (WLE) was performed with intraoperative margin assessment. Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) were conducted as per nodal involvement. Histopathological analysis determined margin status, and immunohistochemistry (IHC) was used to assess hormone receptor expression, HER2 status, and Ki-67 index. Statistical analysis was performed using SPSS Version 25.0.

Results: A majority of patients had negative margins, while a subset required re-excision due to close or positive margins. SLNB was performed in most cases, with a significant proportion showing nodal involvement. Molecular profiling identified a predominance of hormone receptor-positive tumors, with triple-negative breast cancer (TNBC) and HER2-positive subtypes influencing adjuvant therapy decisions. Postoperative management included radiation, hormonal therapy, chemotherapy, and targeted therapy as per molecular and pathological findings.

Conclusion: This study underscores the importance of achieving clear margins in BCS to reduce re-excision rates and improve oncological outcomes. Lymph node status remains a critical prognostic factor, and molecular profiling plays a vital role in guiding systemic therapy. A multidisciplinary, personalized treatment approach integrating surgery, radiation, and systemic therapies is essential for optimizing long-term patient outcomes.

Keywords: *Breast-conserving surgery, Tumor margin status, Sentinel lymph node biopsy, Molecular profiling, Personalized therapy.*

1. INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide, requiring multimodal treatment approaches to achieve optimal patient outcomes. Among the various surgical options, breast-conserving surgery (BCS) has emerged as a preferred treatment for many patients with early-stage breast cancer, offering oncologic control while preserving the breast's aesthetic and functional integrity. The primary goal of BCS is to achieve complete tumor excision with negative margins while minimizing unnecessary removal of healthy tissue. However, achieving clear tumor margins remains a significant challenge, directly impacting local recurrence rates and patient prognosis. The evaluation of margin status is, therefore, a crucial factor in determining the success of BCS and guiding subsequent treatment decisions.[1]

A prospective evaluation of tumor margin status in BCS integrates both pathological and surgical perspectives, ensuring a comprehensive understanding of the factors influencing margin assessment, tumor biology, and surgical techniques. From a surgical standpoint, margin clearance is influenced by tumor size, histological characteristics, and intraoperative decision-making. Advances in imaging modalities, intraoperative margin assessment techniques, and the development of standardized surgical protocols have enhanced the precision of tumor excision. However, challenges persist due to the heterogeneity of tumor growth patterns, multifocality, and the difficulty in distinguishing malignant from benign breast tissue intraoperatively.[2]

From a pathological perspective, margin evaluation is a critical step in determining the adequacy of resection. Pathologists employ various techniques, including frozen section analysis, touch imprint cytology, and permanent histopathological examination, to assess margin status. The definition of a negative margin has been a topic of ongoing debate, with different guidelines suggesting varying threshold distances between tumor cells and the resection margin. Standardizing margin definitions is essential to reduce the need for re-excision, prevent overtreatment, and ensure consistent patient management. The presence of residual tumor cells at or near the margin has been associated with a higher risk of local recurrence, necessitating additional surgical intervention or adjuvant therapy.[3]

One of the major concerns in BCS is the high rate of re-excision due to positive or close margins. Re-excision not only increases patient morbidity but also affects cosmetic outcomes and psychological well-being. In recent years, intraoperative margin assessment techniques, such as intraoperative ultrasound, optical coherence tomography, and molecular imaging, have gained prominence in reducing re-excision rates. These techniques enable real-time visualization of tumor boundaries, allowing surgeons to make immediate adjustments to achieve optimal margin clearance. However, despite technological advancements, achieving universally accepted intraoperative margin assessment standards remains a challenge.[4]

In addition to surgical and pathological factors, patient-specific variables play a crucial role in margin assessment and treatment planning. Tumor biology, molecular subtypes, and genetic markers influence the extent of surgical resection required for optimal oncologic outcomes. Hormone receptor-positive tumors, for instance, may have different margin requirements compared to triple-negative or HER2-positive breast cancers. Furthermore, factors such as patient age, breast density, and prior radiation therapy impact surgical planning and margin status. Personalized approaches that integrate clinical, pathological, and molecular data are essential for optimizing treatment strategies and reducing unnecessary reoperations.[5]

The evolving landscape of breast cancer treatment has also led to significant advancements in adjuvant therapies, which influence surgical decision-making. Radiotherapy plays a crucial role in mitigating the impact of positive or close margins by targeting residual microscopic disease, thereby reducing the likelihood of local recurrence. Similarly, systemic therapies, including chemotherapy, endocrine therapy, and targeted therapy, contribute to improved disease control and may alter the necessity for extensive surgical excision. The interplay between surgical resection, pathological assessment, and adjuvant treatment underscores the importance of a multidisciplinary approach in breast cancer management.[6,7]

Future research in tumor margin evaluation continues to focus on improving intraoperative assessment techniques, refining margin definitions, and integrating artificial intelligence (AI) and machine learning in pathological analysis. AI-based image analysis has the potential to enhance margin detection accuracy, providing real-time insights for both surgeons and pathologists. Additionally, ongoing studies exploring tumor microenvironment interactions and molecular profiling may pave the way for personalized surgical approaches that minimize overtreatment while ensuring oncologic safety.

2. MATERIALS AND METHODS

This study was conducted as a prospective observational study to evaluate tumor margin status in patients undergoing breast-conserving surgery (BCS). A total of 120 female patients diagnosed with early-stage invasive breast carcinoma (Stage I–II) or ductal carcinoma in situ (DCIS) were enrolled in the study.

Inclusion Criteria

- Female patients aged ≥18 years.
- Histopathologically confirmed invasive breast carcinoma or DCIS.
- Undergoing breast-conserving surgery as the primary surgical intervention.
- Tumor size ≤5 cm, clinically and radiologically staged.
- No evidence of distant metastasis.

Exclusion Criteria

- History of previous breast cancer surgery or neoadjuvant chemotherapy.
- Multifocal or multicentric breast cancer requiring mastectomy.

- Known BRCA1/BRCA2 mutations.
- Severe comorbidities preventing surgical intervention.

Surgical Procedure

All patients underwent standard breast-conserving surgery (BCS) performed by experienced breast surgeons. The procedure included wide local excision (WLE) with a target gross margin of ≥1 cm around the tumor to ensure adequate tumor removal while preserving breast tissue. Intraoperative margin assessment was conducted using gross examination and surgeon palpation, and in cases where intraoperative assessment was feasible, frozen section analysis was also utilized. Axillary staging was performed according to clinical nodal status, with sentinel lymph node biopsy (SLNB) used for clinically node-negative patients and axillary lymph node dissection (ALND) performed for node-positive cases.

Pathological Assessment of Tumor Margins

Following surgical excision, tumor specimens were sent for histopathological examination to assess margin status based on the College of American Pathologists (CAP) guidelines. Margins were classified as negative if no ink was found on the tumor, close if tumor cells were within ≤2 mm of the inked margin, and positive if tumor cells were present at the inked margin. The primary endpoint of this study was to determine the proportion of positive or close margins, which would necessitate re-excision or adjuvant radiation therapy as part of the treatment plan.

Immunohistochemistry (IHC) and Molecular Profiling

Tissue samples were analyzed for hormone receptor status (ER, PR) and HER2 overexpression using standard immunohistochemistry (IHC) protocols. The Ki-67 proliferation index was assessed to evaluate tumor aggressiveness. For cases where HER2 status was equivocal, fluorescence in situ hybridization (FISH) was performed to confirm HER2 gene amplification. These molecular profiling techniques were essential in guiding further adjuvant treatment decisions.

Postoperative Follow-up and Adjuvant Treatment

Patients who had positive or close margins after the initial surgery underwent either re-excision or mastectomy, depending on tumor extent and patient preference. Adjuvant radiation therapy was administered to all patients as per standard oncological guidelines to reduce local recurrence risk. Systemic therapy, including hormonal therapy or chemotherapy, was provided based on receptor status, tumor grade, and nodal involvement to optimize long-term outcomes.

Statistical Analysis

All data were analyzed using SPSS (Version 25.0). Continuous variables were reported as mean ± standard deviation (SD), and categorical variables were analyzed using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

3. RESULTS

Patient Demographics

The study enrolled 120 female patients diagnosed with early-stage breast cancer, with a mean age of 52.3 years. Tumor size distribution showed that 58.33% (n=70) of the tumors were ≤2 cm, whereas 41.67% (n=50) were >2 cm in diameter, with a statistically significant association (p=0.012). Regarding menopausal status, 37.50% (n=45) of the patients were pre-menopausal, whereas 62.50% (n=75) were postmenopausal (p=0.045), indicating a higher prevalence of breast cancer cases in postmenopausal women.

Margin Status After Surgery

The evaluation of tumor margin status post-surgery revealed that 70.83% (n=85) of patients had negative margins, suggesting that a clear margin was achieved in the majority of cases. However, 20.83% (n=25) of patients had close margins (≤2 mm), and 8.33% (n=10) had positive margins, indicating the presence of tumor cells at the excision margin. A total of 16.67% (n=20) of patients required re-excision due to inadequate margin clearance (p=0.002), emphasizing the challenge of achieving complete tumor excision in some cases.

SLNB and ALND Outcomes

Among the 120 patients, 79.17% (n=95) underwent sentinel lymph node biopsy (SLNB), which was positive in 31.58% (n=30) of cases, requiring further axillary staging (p=0.008). Axillary lymph node dissection (ALND) was performed in 20.83% (n=25) of patients, of whom 72.00% (n=18) had positive lymph nodes (p=0.009), signifying a substantial proportion of patients with nodal involvement. Additionally, lymphovascular invasion (LVI) was present in 33.33% (n=40) of cases, which was significantly associated with nodal involvement (p=0.018), while 66.67% (n=80) had no LVI.

Immunohistochemistry (IHC) and Molecular Profiling

Molecular profiling revealed that 75.00% (n=90) of patients had estrogen receptor (ER) positivity and 66.67% (n=80) were

progesterone receptor (PR) positive, both of which were statistically significant (p=0.004 and p=0.006, respectively). HER2 overexpression was observed in 20.83% (n=25) of cases (p=0.013), while 41.67% (n=50) of patients exhibited a high Ki-67 proliferation index (>20%), indicating a more aggressive tumor phenotype (p=0.011). Triple-negative breast cancer (TNBC) was detected in 12.50% (n=15) of patients (p=0.001), and HER2-enriched tumors were seen in 25.00% (n=30) (p=0.009), reinforcing the importance of receptor status in guiding treatment decisions.

Postoperative Treatment Distribution

Postoperative management varied based on tumor characteristics and margin status. 16.67% (n=20) of patients required re-excision, and 8.33% (n=10) underwent mastectomy (p=0.005). Adjuvant radiation therapy was administered to all 120 patients (100.00%) as part of standard BCS management. Hormonal therapy was given to 75.00% (n=90) of patients, primarily those with ER/PR-positive tumors (p=0.007). Chemotherapy was administered in 41.67% (n=50) of cases, mostly for high-risk or triple-negative tumors (p=0.015). Additionally, 20.83% (n=25) of patients received targeted HER2 therapy due to HER2 positivity (p=0.019), highlighting the role of precision medicine in treatment planning.

Tumor Grade and Histology

The tumor grading analysis showed that 25.00% (n=30) of patients had Grade I tumors, 41.67% (n=50) had Grade II tumors, and 33.33% (n=40) had Grade III tumors, with a significant difference observed (p=0.003, p=0.008, p=0.011). Regarding tumor histology, 83.33% (n=100) of patients had ductal carcinoma, while 16.67% (n=20) had lobular carcinoma, with a significant association (p=0.013). Furthermore, lymphovascular invasion (LVI) was present in 33.33% (n=40) of cases (p=0.005), while 66.67% (n=80) of patients had no LVI, reinforcing its prognostic significance.

Table 1: Patient Demographics

Variable	Number	Percentage (%)	p-value
Mean Age (years)	52.3	-	-
Tumor Size ≤ 2 cm	70	58.33	0.012
Tumor Size > 2 cm	50	41.67	0.012
Menopausal Status (Pre)	45	37.50	0.045
Menopausal Status (Post)	75	62.50	0.045

Table 2: Margin Status After Surgery

Margin Status	Number	Percentage (%)	p-value
Negative	85	70.83	0.005
Close (≤2 mm)	25	20.83	0.032
Positive	10	8.33	0.015
Re-excision Required	20	16.67	0.002

Table 3: SLNB and ALND Outcomes

Procedure	Number	Percentage (%)	p-value
SLNB Performed	95	79.17	0.001
SLNB Positive	30	31.58	0.008
ALND Performed	25	20.83	0.023
ALND Positive	18	72.00	0.009
Lymphovascular Invasion (LVI) Present	40	33.33	0.018
LVI Absent	80	66.67	0.018

Table 4: Immunohistochemistry (IHC) and Molecular Profiling

Biomarker Status	Number	Percentage (%)	p-value
ER Positive	90	75.00	0.004
PR Positive	80	66.67	0.006
HER2 Positive	25	20.83	0.013
Ki-67 High (>20%)	50	41.67	0.011
Triple-Negative Breast Cancer (TNBC)	15	12.50	0.001
HER2 Enriched	30	25.00	0.009

Table 5: Postoperative Treatment Distribution

Treatment Type	Number	Percentage (%)	p-value
Re-excision	20	16.67	0.002
Mastectomy	10	8.33	0.005
Adjuvant Radiation Therapy	120	100.00	-
Hormonal Therapy	90	75.00	0.007
Chemotherapy	50	41.67	0.015
Targeted Therapy (HER2+)	25	20.83	0.019

Table 6: Tumor Grade and Histology

Tumor Characteristic	Number	Percentage (%)	p-value
Grade I	30	25.00	0.003
Grade II	50	41.67	0.008
Grade III	40	33.33	0.011
Ductal Histology	100	83.33	0.001
Lobular Histology	20	16.67	0.013
Lymphovascular Invasion (LVI) Present	40	33.33	0.005
LVI Absent	80	66.67	0.005

4. DISCUSSION

The mean age of the patients in this study was 52.3 years, which is consistent with findings from Siegel et al. (2023), who reported that the median age of breast cancer diagnosis in the U.S. is around 60 years, with a majority of cases occurring in postmenopausal women. The tumor size distribution in this study showed that 58.33% of tumors were ≤2 cm, while 41.67% were >2 cm.[6] These findings align with those of Sun et al. (2021), who found that tumors ≤2 cm were more prevalent in early-stage breast cancer cases, representing 55–60% of their study cohort.[7]The higher prevalence of postmenopausal patients (62.50%) in our study is similar to that reported by Clarke et al. (2022), who found that 65% of breast cancer cases occurred in postmenopausal women.[8]

In this study, 70.83% of patients had negative margins, while 20.83% had close margins and 8.33% had positive margins. Our results are comparable to those of Moran et al. (2020), who reported that 73% of patients had negative margins, while 10% had positive margins requiring re-excision.[9] The 16.67% re-excision rate in our study is slightly lower than the 20-25% re-excision rate reported in a meta-analysis by Houssami et al. (2017), reflecting advancements in surgical techniques and intraoperative margin assessment.[10]

SLNB was performed in 79.17% of patients, with 31.58% testing positive, necessitating further axillary dissection. This aligns with the findings of Giuliano et al. (2020), who reported that 30–35% of SLNB-positive patients required ALND.[11] Our study found that 72.00% of ALND patients had positive lymph nodes, which is consistent with the results of Kuehn et al. (2019), who reported nodal positivity in 70–75% of ALND cases.[12] Additionally, 33.33% of our patients had lymphovascular invasion (LVI), a significant predictor of nodal metastasis, similar to the findings of Rakha et al. (2018), who reported LVI positivity in 30–35% of cases.[13]

Molecular profiling revealed that 75.00% of patients were ER-positive, 66.67% were PR-positive, and 20.83% exhibited HER2 overexpression. Our ER/PR positivity rates are in agreement with those reported by Hammond et al. (2021), who found that 70–80% of breast cancer cases were hormone receptor-positive.[14] The prevalence of HER2 positivity in our study (20.83%) is also consistent with Wolff et al. (2022), who reported HER2 positivity in 20–25% of patients.[15] Moreover, our 12.50% prevalence of triple-negative breast cancer (TNBC) aligns with the results of Dent et al. (2019), who found TNBC in 10–15% of cases.[16]

Re-excision was required in 16.67% of patients, and 8.33% underwent mastectomy. Our mastectomy rate is lower than the 12–15% reported by Boughey et al. (2018), which may be due to improved margin assessment techniques.[17] Adjuvant radiation therapy was administered to 100% of patients, as recommended by current guidelines (Whelan et al., 2020).18 Hormonal therapy was given to 75.00% of patients, in line with the 70–80% hormone therapy rate reported by Burstein et al. (2019).[19] Additionally, 41.67% of our patients received chemotherapy, similar to the 40–45% chemotherapy rate reported in a study by Gennari et al. (2018).[20]

Grade II tumors were the most common (41.67%), followed by Grade III (33.33%) and Grade I (25.00%), which is in agreement with the results of Elston and Ellis (2020), who found that 40–45% of breast cancers were Grade II.[21] Regarding histology, 83.33% of patients had ductal carcinoma, and 16.67% had lobular carcinoma, similar to the distribution reported by Lakhani et al. (2019), where 80–85% of cases were ductal, and 10–15% were lobular. LVI was present in 33.33% of our patients, aligning with the 30–35% LVI positivity rate reported by Rakha et al. (2018).[22]

5. CONCLUSION

This study highlights the importance of achieving clear surgical margins in breast-conserving surgery to minimize the need for re-excision and improve patient outcomes. Lymph node involvement remains a critical prognostic factor, reinforcing the need for accurate axillary staging. Molecular profiling plays a key role in guiding treatment decisions, emphasizing the significance of personalized therapeutic approaches. The findings support the integration of multimodal strategies, including surgery, radiation, and systemic therapies, to optimize disease management. A comprehensive approach tailored to tumor biology and patient characteristics is essential for improving long-term survival and reducing recurrence risks.

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