

Surgical Margins and the Risk of Local-Regional Recurrence Following Mastectomy

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Abstract

Purpose

Following mastectomy for invasive or in situ breast cancer, the significance of close (≤ 2 mm) or positive margins on local-regional recurrence (LRR) remains uncertain. This study aims to estimate the risk of LRR in patients with close or positive mastectomy margins.

Methods

Records of patients undergoing mastectomy between 2013 and 2015 at a single institution were reviewed. Two hundred and thirty-six patients (215 with upfront surgery and 21 with preoperative systemic therapy) who did not receive radiation were included. Competing risk analysis (Fine and Gray) evaluated the association between patient characteristics and LRR (with distant recurrence, other cancer, and death as competing events) for patients with upfront surgery.

Results

At a median follow-up of 8.8 years, 8 patients with upfront surgery had a LRR (8-year LRR: 4.7% (95% CI 1.5%, 7.9%)). The cumulative incidence of LRR at 8-years for patients with a positive margin was 20.0% (95% CI 0–46.4%), close: 7.5% (95% CI 0.3% – 14.7%), negative: 1.8% (95% CI 0% – 4.3%). On univariate analysis, margin status neared but did not achieve statistical significance (global $p = 0.054$). However, positive margins were associated with a significantly increased hazard of LRR compared with negative margins (HR 9.56, 95% CI 1.48–61.96); close margins were associated with a nonsignificant increase in LRR (HR 4.83, 95% CI 0.88–26.58).

Conclusion

Positive surgical margins were associated with LRR. While small sample size limits subgroup analysis, these findings support consideration of margin status as one factor in decisions regarding adjuvant radiation.

Introduction

In patients with breast cancer, the risk of local-regional recurrence (LRR) following mastectomy is primarily driven by the extent of axillary adenopathy [1, 2]. The role of other factors, particularly close or positive surgical margins, remains debated. Margin involvement has been identified as a prognostic factor for local recurrence in some studies [3–5], but not others [6, 7]. Much of the existing literature consists of retrospective series, many of which predate contemporary systemic therapy [8–10].

Recent improvements in both chemotherapy and hormonal therapy have led LRR rates to drop, further calling into question the significance of the surgical margin [11, 12]. Improvements in local recurrence with increasingly effective systemic therapy may be most notable in patients with HER2 positive disease [13, 14]. It is possible that these advances in systemic therapy, and their resultant benefit in LRR, may decrease the impact of a positive margin on LRR in the modern era compared to older published results. Furthermore, the benefit of adjuvant radiation in post-mastectomy patients stratified by margin status has been studied but is unclear based on the available literature. Our study intentionally analyzes patients who did not receive postmastectomy radiation therapy to understand the risk factors for and incidence of LRR in the absence of adjuvant radiotherapy. By identifying factors associated with LRR, this study will help to inform decisions surrounding adjuvant treatment of these patients.

Methods

Electronic medical records of 830 consecutive patients who underwent mastectomy between 2013 and 2015 at Brigham and Women's Faulkner Hospital were retrospectively reviewed. Patients who had prior malignancy (except basal and squamous cell skin carcinoma) within the 5 years prior to mastectomy, received radiation therapy (RT) to the chest wall/thoracic region for cancer at any point in time, were male, had a mastectomy for reasons unrelated to breast cancer, had bilateral breast cancer, and/or had known BRCA 1/2 mutations were excluded. Inclusion criteria included the following: minimum of two years of follow-up visits with either an oncologist or primary care provider from time of diagnosis and age greater than 18 years at the time of breast cancer diagnosis. Data from 236 eligible patients who did not receive radiation was entered into a REDCap project database (Research Electronic Data Capture). The study was approved by the institutional review board.

Clinical and pathologic features were recorded for each patient. They included age, receipt of hormonal and chemotherapy, stage, highest tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER-2) status, presence of positive nodes, lymphovascular invasion (LVI), and multifocal/multicentric status. Follow-up date was obtained from the most recent primary care and/or oncology note that made specific reference to a chest wall exam.

A positive margin was defined as invasive or in situ disease at an inked resection margin. A close margin was defined as invasive or in situ disease within or at 2 mm of an inked resection margin. The primary endpoint was LRR, which was defined as a recurrence in the skin and/or subcutaneous tissues of the ipsilateral chest wall or in the ipsilateral regional lymph nodes. LRR was evaluated by a cumulative-incidence analysis. Competing risk analysis through Fine and Gray methodology evaluated the association between patient characteristics and LRR with other events (distant recurrence, other cancer, and death) as competing events. Given small patient numbers, only patients with upfront surgery were included in the univariate analysis.

Time to event was defined as the time from the date of mastectomy to the date of LRR, distant recurrence, other cancer, or death, whichever occurred first. Patients without any events were censored

at the date of last disease assessment.

Results

Patients were analyzed in two separate cohorts: patients with upfront surgery (n = 215) and those with preoperative treatment (n = 21). The median follow-up after mastectomy among patients still alive was 8.8 years (range 0.8–11.6 years) for patients with upfront surgery and 8.4 years (range 1.4–11.5 years) for the neoadjuvant cohort, which included chemotherapy and/or hormonal therapy. Table 1 summarizes patient and tumor characteristics. Among the upfront surgery patients, 98 (45.6%) had invasive ductal carcinoma (IDC), 69 (32.1%) ductal carcinoma in situ (DCIS) only, 13 (6.0%) invasive lobular carcinoma, 24 (11.2%) mixed invasive histology, and 11 (5.1%) other. Most patients in both cohorts had pathologically node-negative disease, specifically 172 (80.0%) of patients undergoing upfront surgery and 20 (95.2%) of patients receiving neoadjuvant therapy. The most common tumor subtype in both groups was ER or PR positive, HER2 negative. Overall, 17 patients with upfront surgery and one patient with neoadjuvant therapy had additional skin removed. Location of the additional tissue and impact on possible margin status was not specified in the patient records and was therefore not recorded.

Table 1
Patient Characteristics

	Upfront Surgery	Neoadjuvant Therapy
	n (%)	n (%)
Number of Patients	215	21
Age at Mastectomy (years)		
Median (Range)	53 (24, 87)	47 (29, 76)
Highest Tumor Grade		
1	49 (22.8%)	0
2	93 (43.3%)	7 (33.3%)
3	73 (34.0%)	14 (66.7%)
Mastectomy Histologic Type		
IDC	98 (45.6%)	15 (71.4%)
Pure DCIS ¹	69 (32.1%)	2 (9.5%)
ILC	13 (6.0%)	3 (14.3%)
Mixed	24 (11.2%)	1 (4.8%)
Other	11 (5.1%)	-
Clinical T Stage		
T0	-	0
T1	-	4 (19.0%)
T2	-	14 (66.7%)
T3	-	3 (14.3%)
Clinical N Stage		
N0	-	18 (85.7%)
N1	-	1 (4.8%)
N2	-	0
NX	-	2 (9.5%)
Path T Stage		
¹ One patient with IDC and one patient with mixed histology on core prior to neoadjuvant chemotherapy. Only residual DCIS found on final mastectomy		

	Upfront Surgery	Neoadjuvant Therapy
	n (%)	n (%)
Tis	50 (23.3%)	3 (14.3%)
T0	0	4 (19.0%)
T1	125 (58.1%)	9 (42.9%)
T2	37 (17.2%)	4 (19.0%)
T3	2 (0.9%)	1 (4.8%)
T4	1 (0.5%)	0
Path N Stage		
N0	182 (84.7%)	20 (95.2%)
N1	21 (9.8%)	0
N2	1 (0.5%)	1 (4.8%)
Nx	11 (5.1%)	0
Number of Nodes Removed		
0	15 (7.0%)	0
1	81 (37.7%)	9 (42.9%)
2	58 (27.0%)	5 (23.8%)
3	25 (11.6%)	5 (23.8%)
≥ 4	36 (16.7%)	2 (9.5%)
Number of Positive Nodes		
0	172 (80.0%)	20 (95.2%)
1	34 (15.8%)	0
2	7 (3.3%)	0
3	1 (0.5%)	0
≥ 4	1 (0.5%)	1 (4.8%)
Largest Positive Node (among Positive Nodes)		
Macrometastases	14 (32.6%)	1 (100.0%)
¹ One patient with IDC and one patient with mixed histology on core prior to neoadjuvant chemotherapy. Only residual DCIS found on final mastectomy		

	Upfront Surgery	Neoadjuvant Therapy
	n (%)	n (%)
Micrometastases	10 (23.3%)	0
Isolated Tumor Cells (ITC)	19 (44.2%)	0
LVI		
Present	31 (17.3%)	1 (6.3%)
Absent	148 (82.7%)	15 (93.8%)
Unknown	36	5
ER/PR/HER2		
ER or PR Positive, HER2 Positive	15 (8.0%)	5 (23.8%)
ER or PR Positive, HER2 Negative	140 (74.9%)	9 (42.9%)
ER and PR Negative, HER2 Positive	21 (11.2%)	1 (4.8%)
Triple Negative	11 (5.9%)	6 (28.6%)
Unknown	28	0
Other Characteristics		
Multifocal or Multicentric Disease	87 (40.5%)	4 (19.0%)
Received Pre-op Chemotherapy	-	19 (90.5%)
Received Pre-op Hormonal Therapy	-	5 (23.8%)
Received Adjuvant Chemotherapy	37 (17.2%)	4 (19.0%)
Received Adjuvant Hormonal Therapy	134 (62.3%)	15 (71.4%)
Received Anti-HER2 Therapy among HER2 Positive	14/37 ² (37.8%)	6/6 (100.0%)
¹ One patient with IDC and one patient with mixed histology on core prior to neoadjuvant chemotherapy. Only residual DCIS found on final mastectomy		

² One patient had HER2 positive disease but “ER/PR/HER2” status was unknown due to missing ER/PR status.

Margin status at any location (superficial, deep, or both) was determined for our cohort as seen in Table 2. Patients were divided into six detailed margins categories: Positive Invasive & Positive DCIS, Positive Invasive only, Positive DCIS only, Close Invasive or Close DCIS, Close Both, and Negative/Other. Patients with Positive and Close margins were placed in the respective "Positive" category. For our analysis, patients were further divided into three margin categories: positive (tumor at inked margin),

close (margin ≤ 2 mm), and negative (> 2 mm). In this categorization, patients with any positive margin are listed as positive, while those with only close are listed as close. These categories included invasive or in situ disease at the superficial, deep, or nipple margin.

Table 2
Overall Margin Status

Margin Status¹	Upfront Surgery		Neoadjuvant	
	n	%	n	%
Positive Invasive & Positive DCIS	2	0.9%	0	
Positive Invasive	3	1.4%	1	4.8%
Positive DCIS	9	4.2%	0	
Close Both	15	7.0%	0	
Close Invasive or Close DCIS	43	20.0%	2	9.5%
Negative	141	65.6%	18	85.7%
Other ²	2	0.9%	0	
Margin Status³	n	%	n	%
Positive	14	6.5%	1	4.8%
Close	58	27.0%	2	9.5%
Negative/Other	143	66.5%	18	85.7%
¹ Margin status anywhere				
² Both cases are in the “no neoadjuvant treatment” cohort; one with no superficial margin assessment and negative deep margin; the other with superficial negative, deep negative, and nipple not evaluated (with nipple sparing mastectomy)				
³ Margin status anywhere, DCIS or invasive disease,3 categories				

For patients with upfront surgery, the closest margin was positive in 14 (6.5%), close in 58 (27.0%), and negative in 143 (66.5%). For the smaller cohort of patients with neoadjuvant therapy, the closest margin was positive in 1 (4.8%), close in 2 (9.5%), and negative in 18 (85.7%). Table 3 presents the cumulative incidence of LRR by margin status. At a median follow-up of 8.8 years, 8 patients with upfront surgery had LRR (8-year LRR: 4.7% (95% CI 1.5%, 7.9%)). The cumulative incidence of LRR at 8-years for positive margin was 20.0% (95% CI 0–46.4%), close: 7.5% (95% CI 0.3% – 14.7%), and negative: 1.8% (95% CI 0% – 4.3%). The 5-year cumulative incidence of LRR was: Positive: 0%, Close: 7.5% (95% CI 0.3%, 14.7%), and Negative/Other: 0.7% (0%, 2.1%).

Table 3
Cumulative Incidence¹ of LRR by Margin Status

All	Upfront Surgery	Neoadjuvant Therapy
	N = 215	N = 21
Total number of patients with LRR	8	1
Positive	2/14	0/1
Close	4/58	1/2
Negative/Other	2/143	0/18
5-year cumulative incidence of LRR (95% CI)		
Positive	0%	0%
Close	7.5% (0.3%, 14.7%)	NA ²
Negative/Other	0.7% (0%, 2.1%)	0%
8-year cumulative incidence of LRR (95% CI)		
Positive	20.0% (0%, 46.4%)	0%
Close	7.5% (0.3%, 14.7%)	NA ²
Negative/Other	1.8% (0%, 4.3%)	0%

¹ Distant recurrence, other cancer and death were considered as competing events in this analysis.

² Not computable due to insufficient follow-up time for the two patients.

As referenced in the addendum, among patients with upfront surgery, 8 patients had LRR. From this cohort, 5 patients had chest wall recurrence; one patient had chest wall, supraclavicular node, and axillary node recurrence; two patients had axillary recurrences. Only two patients had positive lymph nodes. Among those with neoadjuvant therapy, one patient had a LRR, which was an axillary lymph node recurrence, at 26 months. This patient had close DCIS at the deep margin.

The univariate analysis for patients with upfront surgery is presented in Table 4. On univariate competing-risk analysis, margin status was not significantly associated with LRR based on an $\alpha = 0.05$ level (global $p = 0.054$). However, compared with negative margins, positive margins were associated with a significantly higher risk of LRR (HR 9.56, 95% CI 1.48, 61.96), whereas close margins showed an observable but non-significant increase in LRR (HR 4.83, 95% CI 0.88, 26.58).

Table 4

Associations between Time to LRR and Patient Characteristics for Upfront Surgery Cohort¹

Age at Mastectomy (year)	Hazard Ratio (95% CI)	P value
		0.81
≤ 50	Ref.	
> 50	0.84 (0.21, 3.33)	
Tumor Grade at Mastectomy		< .0001
1	Ref.	
2	NA ²	
3	NA ²	
Mastectomy Histologic Type		< .0001
IDC	Ref.	
Pure DCIS	0.47 (0.10, 2.31)	
Mixed, ILC, Other	NA ³	
Path T Stage		0.63
Tis	Ref.	
T1	2.39 (0.30, 19.3)	
T2/T3/T4	1.24 (0.08,19.45)	
Path N Stage		0.62
N0	Ref.	
N1/N2	1.68 (0.21, 13.31)	
Number of Nodes Removed		0.31
0–1	Ref.	
> 1	0.48 (0.12, 1.97)	
Number of Positive Nodes		0.65
0	Ref.	
≥ 1	1.45 (0.30, 7.08)	

¹ Competing risk analysis; distant metastasis, other cancer and death are considered as competing events (univariable analysis)

Age at Mastectomy (year)	Hazard Ratio (95% CI)	P value
		0.81
LVI		0.09
Present	3.55 (0.82, 15.47)	
Absence	Ref.	
ER/PR/HER2 ⁴		< .0001
ER or PR Positive, HER2 Positive	Ref.	
ER or PR Positive, HER2 Negative	NA ⁵	
ER and PR Negative, HER2 Positive	NA ⁵	
Triple Negative	1.00 (0.43, 2.31)	
Multifocal or Multicentric Disease		0.63
No	Ref.	
Yes	1.40 (0.36, 5.48)	
Margin Status (Anywhere)		0.054
Positive	9.56 (1.48, 61.96)	
Close	4.83 (0.88, 26.58)	
Negative/Other	Ref.	
¹ Competing risk analysis; distant metastasis, other cancer and death are considered as competing events (univariable analysis)		

² Hazard ratios could not be computed as no LRRs were observed among patients with tumor grade 1 at mastectomy.

³ Hazard ratio could not be computed as no LRRs were observed in the “Mixed, ILC, Other” category.

⁴ Patients with ER/PR/HER2 status unknown were excluded from the analysis of this covariate.

⁵ Hazard ratios could not be computed as no LRRs were observed in the reference group (ER or PR positive, HER2 positive).

Table 5 presents patients by margin status combinations with at least two margins reported. The most common combination was superficial negative, deep negative (n = 130, 60.5%) for patients undergoing upfront surgery and 16 (76.25%) receiving neoadjuvant systemic therapy. The location of the positive

margin was also examined. From the upfront surgery cohort, 13 patients had positive superficial margins; of these patients, 2 (15.4%) developed a LRR at 90 and 92 months, respectively. One patient had a positive deep margin and did not experience recurrence. Among the 21 patients receiving neoadjuvant systemic therapy, one had a positive (superficial, invasive) margin and two had close margins (deep invasive, deep DCIS). One patient with a close deep margin had a LRR at 26 months. Table 6 demonstrates the distribution of first events.

Table 5
Margin Status Combinations

Margin Status (detailed)	Upfront Surgery		Neoadjuvant	
	n	%	n	%
Superficial Neg, Deep Neg	130	60.5%	16	76.2%
Superficial Neg Deep Neg Nipple Neg	10	4.7%	2	9.5%
Superficial Neg Deep Close Inv	4	1.9%	1	4.8%
Superficial Neg Deep Close DCIS	5	2.3%	1	4.8%
Superficial Neg Deep Close DCIS Deep Close Inv	3	1.4%		
Superficial Close Inv Deep Neg	3	1.4%		
Superficial Close Inv Deep Close Inv	2	0.9%		
Superficial Close DCIS Deep Neg	17	7.9%		
Superficial Close DCIS Deep Close DCIS	5	2.3%		
Superficial Close DCIS Superficial Close Inv Deep Neg	7	3.3%		
Superficial Pos Inv Deep Neg	1	0.5%	1	4.8%
Superficial Pos Inv Superficial Close DCIS Deep Neg	2	0.9%		
Superficial Pos DCIS Deep Neg	2	0.9%		
Superficial Pos DCIS Superficial Close DCIS Deep Neg	2	0.9%		

Table 6
Distribution of First Events

	Upfront Surgery	Neoadjuvant Therapy
	n	n
LRR	8	1
Distant	7	3
Other Cancer	14	0
Death	2	0
Censored	184	17

Discussion

In this study of patients who underwent mastectomy without radiation, there was a higher cumulative incidence of LRR at 8 years in patients with positive surgical margins compared to patients with negative margins. Furthermore, the association between margin status and LRR was significant for positive compared to negative margins. These findings corroborate multiple retrospective series and meta-analyses that demonstrated higher rates of LRR among patients with positive margins [8, 10]. Our study closely resembles that of Childs and colleagues (2012), whose study of women who underwent mastectomy without radiation found that those with positive margins had a 5-year LRR of 6.2%, compared to 1.5% for close margins (≤ 2 mm) and 1.9% for negative margins ($p = 0.04$) [15]. While limited by a small number of events, our study contributes to a growing pool of literature demonstrating an association between positive surgical margins and risk of local-regional recurrence.

Notably, the overall risk of LRR was low in our study cohort. In our series, 8 patients with upfront surgery had a LRR and one patient with neoadjuvant treatment had a LRR. The overall low risk of LRR in the modern era was most recently demonstrated by a randomized controlled trial by Kunkler and colleagues [16]. This group randomized patients with intermediate risk breast cancer and mastectomy to receive radiation. They found that the 10-year chest-wall recurrence was 2.5% without radiation. Furthermore, this study found that women who received radiation did not have a higher overall survival than women who did not receive radiation.

The low recurrence rate observed in this cohort, even among patients with positive margins, may partially reflect the widespread use of modern systemic therapy, including endocrine therapy, chemotherapy, and HER2-directed therapy. While not directly evaluated in our study, the role of adjuvant systemic therapy in reducing LRR has been demonstrated in prior work. A study by Glorioso and colleagues found that closer surgical margins were associated with increased local recurrence, while adjuvant endocrine therapy independently reduced recurrence risk [8]. Another study conducted by McBride and colleagues demonstrated how improvements in LRR correlate with modern treatment advances [17]. This team studied rates of LRR in 1027 women with 1–3 positive axillary nodes following

mastectomy in an early (1978–1997) and a late (2000–2007) cohort which was characterized by the widespread use of more advanced treatments including taxane chemotherapy and aromatase inhibitors. Ultimately, LRR was 9.5% among women not receiving radiation in the early cohort (1978–1997), compared to 2.8% among the more recent patients with advanced treatments (2000–2007). As systemic therapy continues to improve, the role of mastectomy margins in guiding treatment decisions will need to be continuously re-assessed.

We are unable to deduce from our results whether radiation would provide meaningful benefit for patients with close or positive surgical margins, as eligible patients did not receive adjuvant RT. Some prior literature suggests that radiation might be especially beneficial for those with close or positive margins. Behm and colleagues (2013) conducted an analysis of 2300 patients with invasive breast cancer who received either breast conserving surgery or mastectomy and found that an involved margin or close margins were associated with increased risk of LRR (HR 2.72, 95% CI 1.30–5.69), with risks of LRR being particularly high among those not receiving radiation [18]. A recent retrospective study by Sasada and colleagues (2024) found that in patients with positive margins, 7-year cumulative incidences of local recurrence were 1.9% and 12.6% with and without radiation therapy, respectively (adjusted hazard ratio, 0.17; 95% CI, 0.04–0.80) [19]. However, as patients received adjuvant RT based on clinician recommendation, the relationship between receipt of RT and local recurrence can't be determined definitively. A study by Childs and colleagues (2012) concluded that although patients with positive mastectomy margins had a significantly higher rate of LRR than those with close or negative margins, the absolute risk of LRR was low overall. They concluded that the absolute benefit of postmastectomy radiation is therefore likely to be small [15]. Another study by Truong and colleagues (2004) found that in their cohort of patients with age > 50 years, T1 tumors, grade I/II disease, and absence of LVI, no patients developed a LRR, even patients with positive margins. They also showed that post-mastectomy RT did not improve distant relapse, breast cancer-specific or overall survival rates [20]. While the absolute risk of LRR in patients with positive margins in our cohort of patients who did not receive RT may suggest a potential benefit from radiation, more studies are needed to clarify the role of radiation for patients with positive surgical margins.

There are several limitations to our study. First, small sample sizes limited analysis; as a result, multivariate analysis was not possible. Only eight local-regional recurrence events occurred among patients undergoing upfront surgery, limiting the precision of hazard ratio estimates and resulting in wide confidence intervals. Furthermore, it is possible that clinicians selected uniquely low risk patients to not receive adjuvant RT in this retrospective cohort. Therefore, our cohort of patients with close or positive margins may represent a more favorable group as compared to all patients with close or positive mastectomy margins due to selection bias (which may also have contributed to relatively low recurrence rates). Systemic therapy was not standardized, was at the discretion of the medical oncologist, and likely changed throughout the time period of the study. In terms of pathology, the volume of disease at or close to the margin, which may impact the risk of LRR, was not assessed. The clinical significance of superficial margin involvement of mastectomy specimens and whether pathologists should evaluate this margin remains a matter of controversy; unfortunately, given the small number of patients with

superficial margin involvement and the few events in this subgroup, we could not address this issue in our study population. For patients in our study who had additional tissue removed, it is unclear whether this removal addressed the margin or not. Finally, our cohort included patients who underwent re-excision, which limited our ability to assess where additional tissue was taken from, and whether it addressed the margin.

Conclusion

In this modern cohort of patients undergoing mastectomy without postmastectomy radiation, positive surgical margins were associated with higher cumulative incidence of local-regional recurrence compared with negative margins, with close margins showing a nonsignificant trend in the same direction. However, absolute recurrence rates were low overall. Our findings suggest that margin status should be considered in the multifactorial decision surrounding whether to treat with adjuvant radiation. This is especially important as the margin status is not always surgically actionable, as it is not easy to ascertain the re-excision target, nor is doing this necessarily surgically feasible. However, this work emphasizes the need for larger studies to better assess the utility of radiation in patients with close or positive surgical margins treated in the modern era.

Declarations

Funding

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Competing Interests

Within the past three years, Jennifer Bellon was a paid educational consultant for Varian and previously served as an editor for UpToDate. Stuart Schnitt has served on the advisory boards of Ibex Medical Analytics, 4D Path, and Precise Dx. The remaining authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Jordan Tralins and Laura Warren conceived and developed the study, with contributions from Jennifer Bellon to study design and methodology. Jordan Tralins, Summer Westover, and Emma Mayette contributed to data collection and chart review. Jennifer Bellon contributed to study design, coder training, and review of the study data. Yu-Hui Chen performed the statistical analysis. Jordan Tralins drafted the manuscript, with input and guidance from Laura Warren and Jennifer Bellon. Stuart Schnitt and Faina Nakhliis provided expert input from breast pathology and breast surgery, respectively, and contributed to the review and editing of the manuscript throughout the study. Laura Warren and Jennifer Bellon provided critical review and intellectual input throughout the study and manuscript development.

All authors reviewed and edited the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to Protected Health Information but may be available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. This study received IRB approval by the Dana-Farber Cancer Institute Institutional Review Board (DFCI IRB) under protocol DFCI 21-24.

Consent to Participate

Given the retrospective design of this study, the requirement for individual informed consent was waived by the IRB (protocol DFCI 21-24).

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