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EDITORIAL

Positive surgical margins after breast-conserving surgery for ductal carcinoma in-situ: does histologic grade or estrogen receptor status matter?

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Abstract

Purpose DCIS has been shown to have a higher rate of positive margins following breast-conserving surgery (BCS) than invasive breast cancer. We aim to analyze certain factors of DCIS, specifically histologic grade and estrogen receptor (ER) status, in patients with positive surgical margins following BCS to determine if there is an association.

Methods A retrospective review of our institutional patient registry was performed to identify women with DCIS and microinvasive DCIS who underwent BCS by a single surgeon from 1999 to 2021. Demographics and clinicopathologic characteristics between patients with and without positive surgical margins were compared using chi-square or Student's t-test. We assessed factors associated with positive margins using univariate and multivariable logistic regression.

Results Of the 615 patients evaluated, there was no significant difference in demographics between the patients with and without positive surgical margins. Increasing tumor size was an independent risk factor for margin positivity ($P = < 0.001$). On univariate analysis both high histologic grade ($P = 0.009$) and negative ER status ($P = < 0.001$) were significantly associated with positive surgical margins. However, when adjusted in multivariable analysis, only negative ER status remained significantly associated with margin positivity (OR = 0.39 [95% CI 0.20–0.77]; $P = 0.006$).

Conclusion The study confirms increased tumor size as a risk factor for positive surgical margins. We also demonstrated that ER negative DCIS was independently associated with a higher rate of positive margins after BCS. Given this information, we can modify our surgical approach to reduce rate of positive margins in patients with large-sized ER negative DCIS.

Keywords Ductal carcinoma in situ · Breast conserving surgery · Positive margins · Reoperation

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Introduction

In the Unites Stated (US), approximately 1 in 33 women will be diagnosed with DCIS in their lifetime [1]. The incidence of ductal carcinoma-in-situ (DCIS) increased dramatically after implementation of routine screening in the early 1980s [2]. Subsequently, DCIS comprises 20–25% of newly diagnosed breast cancers, and most DCIS is treated with breast-conserving surgery (BCS) with or without radiotherapy [1–4]. The decision for BCS is based on surgeon's perceived ability to achieve negative surgical margins without compromising cosmesis. Clearing surgical margins with breast-conserving surgery can be challenging because tumor growth can be unpredictable as breast ducts branch into irregular patterns and disease may extend past the mammographic abnormality. As a result, 10–40% of patients who have undergone primary BCS will need additional surgery to clear positive surgical margins [3].

Earlier clinical trials found that high grade DCIS and positive surgical margins after BCS is associated with a higher risk of local recurrence (LR) [5–12]. These factors are further emphasized through the Van Nuys Prognostic Index, which included tumor size, margin width, and nuclear grade are predictors of DCIS local recurrence [13]. The morbidity associated with margin re-excision adds increased health care expenditure and additional burden to the patient [14]. A meta-analysis performed by Marinovich et al. reported an estimated average cost savings of $3,540 per women by avoiding reoperation [14, 15]. In 2014, the Society of Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO) multidisciplinary consensus panel concluded that 2 mm margin minimizes the risk of LR compared with smaller negative margins [16]. Re-excision rates following BCS have improved since the adoption of these guidelines [14, 15, 17, 18]. However, there remains a disproportionate amount of DCIS compared to invasive breast cancer with positive surgical margins [18–22].

Positive margins after BCS for DCIS presents a unique area with potential for care improvement that calls for continued research efforts. When considering breast conservation, the patient and surgeon would benefit from knowledge of specific clinicopathological features of the DCIS that confer an increased risk of a positive surgical margin. Murphy et al. sought to investigate this but found no clinicopathologic variable associated with an increased risk of positive margins in a cohort of 102 women with DCIS [17]. It is important to note that ER negative DCIS representation in that study was modest, comprising only sixteen of the 102 patients [17]. Hassan et al. reported DCIS tumor size greater than 1.55 cm and presence of symptoms associated with positive margins following BCS [19]. There were eighteen of the 258 patients assessed in this study with ER negative DCIS. This begs the question; can we reliably say that ER status is not an independent risk factor with such modest representation of the disease.

The purpose of the present study was to determine whether a significant association exists between the histologic grade or estrogen receptor status of DCIS and the incidence of positive margins after BCS. Secondarily, we aimed to identify additional etiologic factors that have an independent predictive association with positive surgical margins after BCS. We hypothesized that the rate of a positive surgical margin after BCS is increased for patients with either ER negative DCIS, high grade DCIS, or both.

Materials and methods

Study design

After approval by the institutional review board, we conducted a retrospective review of the clinical practice patient registry. We selected women with pathologically confirmed DCIS or microinvasive DCIS undergoing breast-conserving surgery by a single surgeon from January 1999 to August 2021. Microinvasive DCIS is defined as DCIS with a less than 0.1 cm focus of invasive breast cancer [23]. We elected to include these patients because the recommended surgical margins for BCS are the same in the SSO-ASTRO-ASCO guidelines [16]. A margin of less than 2 mm from DCIS was deemed positive for this analysis. Using the clinical research database, we were able to evaluate both demographic data and clinicopathologic features necessary for our analysis.

Surgical procedure(s)

Breast-conserving surgery was performed by a single surgeon at the institution for all patients by means of either wide excision in case of palpable tumors or needle localized excision for non-palpable DCIS. The operative surgeon used intraoperative breast specimen radiographs to ensure complete removal of the targeted area and associated calcifications. Cavity shave margins or intraoperative frozen section of margins are not routinely performed at our institution.

Participant eligibility criteria

To determine if certain pathologic features influenced the ability to achieve negative surgical margins with BCS, we excluded patients found to have invasive carcinoma greater than 0.1 cm and those with missing reported pathologic tumor characteristics or surgical margin assessment. Independent variables included age, year of surgery, tumor size (in cm), race, histologic grade (low, intermediate, or high), estrogen receptor status (positive vs negative), concurrent oncoplastic surgery (yes, no), and Ki-67 ($\leq 15\%$, $> 15\%$).

Statistical analysis

Demographics and clinical features between subjects with and without positive margin status were compared using chi-square or t-test, as appropriate. Association of clinical and demographic features with margin positivity were assessed using an unconditional logistic regression model. Variables that were significant in univariable analysis were further analyzed in a multivariable logistic regression model to assess which variables are independently associated with margin positivity. Multicollinearity was checked in the adjusted model by ensuring the variance inflation factor was below the acceptable thresholds between the risk factors. All tests were 2-sided and statistical significance set at $P < 0.05$ for all analyses. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute).

Results

From January 1999 and August 2021, 632 patients underwent BCS for DCIS. We excluded 17 patients for missing clinicopathologic features or surgical margins, leaving 615 patients for analysis. Table 1 reports the detailed study cohort demographic and clinicopathologic data. A total of 21 (3%) patients had microinvasive DCIS. We identified 92 of 615 (14.9%) patients with positive surgical margins.

The median patient age at intervention was 62 years [interquartile range (IQR), 38–91] and the cohort was predominantly white. The overall median tumor size was 0.75 cm (IQR, 0.1–5.2). Histologic grade was evenly distributed among the patients. The patients had primarily ER positive DCIS, comprising most of the cohort at 86.7%. Concurrent oncoplastic surgery, namely reduction mammoplasty, was performed in only 6.5% of the operations. A low proliferation index was present among 66.8% of the patients.

We then compared patients with and without positive surgical margins. Three factors were associated with positive margins on univariate analysis. The patients most likely to have positive surgical margins were those with large tumors ($P = < 0.001$), high histologic grade ($P = 0.009$), and ER negative DCIS ($P = < 0.001$). The median tumor size of the patients with positive surgical margins was 1.8 cm, which is three times higher than those with negative surgical margins. Half of the patients with positive surgical margins had high grade DCIS. In addition, the positive surgical margin cohort had almost three times more ER negative DCIS compared to the negative surgical margin cohort (28.3% vs. 10.7% respectively, shown in Table 1). As shown in Table 2, there was no statistical difference between positive margin rates by the following factors: age ($P = 0.137$), year of surgery ($P = 0.396$), race ($P = 0.474$), proliferative index ($P = 0.188$), or concurrent oncoplastic surgery ($P = 0.17$).

ER expression in DCIS is inversely related to the histologic grade [24, 25]. Therefore, we examined the distribution of histological grade by ER status among our patients

Table 1 Univariate analysis of patient and tumor variables

Characteristic	Overall* ($n = 615$)	Patients with positive surgical margins ($n = 92$)	Patients with negative surgical margins ($n = 523$)	P value**
Age; median (IQR)	62 (53–70)	60 (51–67)	63 (53 – 71)	0.137
Year of surgery; median (IQR)	2016 (2012–2018)	2016 (2012–2018)	2016 (2013–2018)	0.396
Tumor size, cm; median (IQR)	0.75 (0.30–1.40)	1.80 (1.10–3.00)	0.60 (0.30–1.10)	< 0.001
Race, n (%)				
White	495 (80.5%)	70 (76.1%)	425 (81.3%)	0.474
Black	89 (14.5%)	17 (18.5%)	72 (13.8%)	
Others	31 (5.0%)	5 (5.4%)	26 (4.9%)	
Histological grade, n (%)				
Low	146 (23.7%)	13 (14.1%)	133 (25.4%)	0.009
Intermediate	241 (39.2%)	33 (35.9%)	208 (39.8%)	
High	228 (37.1%)	46 (50.0%)	182 (34.8%)	
Estrogen receptor status, n (%)				
Positive	553 (86.7%)	66 (71.7%)	467 (89.3%)	< 0.001
Negative	82 (13.3%)	26 (28.3%)	56 (10.7%)	
Oncoplasty, n (%)				
Yes	40 (6.5%)	3 (3.3%)	37 (7.1%)	0.170
No	574 (93.5%)	89 (96.7%)	485 (92.9%)	
Proliferation indices, n (%)				
> 15	204 (33.2%)	36 (39.1%)	168 (32.1%)	0.188
≤ 15	411 (66.8%)	56 (60.9%)	355 (67.9%)	

*17 patients with missing data were excluded from the analysis

**Comparing patients with and without positive surgical margins

IQR Interquartile range

Statistical significance set at $P < 0.05$ for all analyses

Table 2 Multivariate logistic regression analysis

Covariate	Unadjusted Odds ratio (95% CI)	*P*	Adjusted* Odds ratio (95% CI)	*P*
Age, per year increase	0.99 (0.97–1.01)	0.138	0.98 (0.96–1.002)	0.08
Year of surgery	0.99 (0.96–1.03)	0.720		
Tumor size, per cm increase	2.60 (2.10–3.22)	< 0.001	2.57 (2.06–3.21)	< 0.001
Race				
White vs. Black	0.70 (0.39–1.25)	0.228		
Others vs. Black	0.81 (0.27–2.43)	0.713		
Histological grade				
G3 vs. G1	2.59 (1.34–4.98)	0.005	1.06 (0.47–2.36)	0.896
G2 vs. G1	1.62 (0.82–3.20)	0.161	1.28 (0.60–2.77)	0.525
Laterality (left vs. right)	1.12 (0.72–1.74)	0.630		
Estrogen receptor status (positive vs. negative)	0.30 (0.18–0.52)	< 0.001	0.39 (0.20–0.77)	0.006
Oncoplasty (yes vs. no)	0.44 (0.13–1.46)	0.182		
Proliferation indices (> 15 vs. ≤ 15)	1.36 (0.86–2.15)	0.189		

*Multivariable analysis adjusted for age, tumor size, histological grade and estrogen receptor status

AUC of the adjusted model was 0.826 (95% CI 0.781, 0.870)

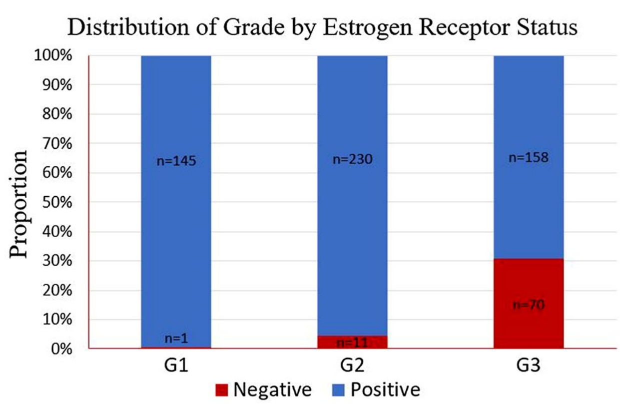

Fig. 1 Distribution of grade by estrogen receptor status

and identified a significant trend (Fig. 1). There was a proportional increase in ER negative DCIS across histological grades (0.68%, 4.6%, and 30.7% for low, intermediate, and high; respectively, $P = < 0.001$). These factors were checked for multicollinearity and found to be acceptable for multivariable analysis.

Multivariable logistic regression was able to highlight two factors which were predictive of margin positivity. When adjusted, the factors independently associated with higher odds of positive surgical margins were increasing tumor size (odds ratio 2.57, 95% CI 2.06–3.21, $P = < 0.001$) and negative ER status (odds ratio 0.39, 95% CI 0.20–0.77, $P = 0.006$) on multivariate analysis (Table 2). The AUC of the adjusted model was 0.826 (95% CI 0.781, 0.870). Therefore, the predicted probability of a positive surgical margin following breast-conserving surgery for DCIS is influenced by both tumor size and ER negative status. For every centimeter increase in tumor size there was 2.57 times risk of positive margins. ER negative disease was an independent risk factor for positive surgical margins with an almost four-fold risk by our analysis, which was statistically significant. We plotted the estimated risk of positive margins depicted in Fig. 2.

Although univariate analysis revealed that high histologic grade was significant, after adjusting for age, tumor size, histologic grade, and ER status, histologic grade no longer showed a correlation. Multivariate logistic regression models showed no greater odds of positive margins with high grade (odds ratio 1.06, 95% CI 0.47–2.36, $P = 0.896$) or intermediate grade DCIS (odds ratio 1.28, 95% CI 0.60–2.77, $P = 0.525$). The increase in proportion of negative ER DCIS as grade increases partly explains why both ER status and grade were associated with margin positivity on univariate analysis. However, when adjusted in multivariable analysis, only ER status remained significant.

Discussion

The conclusions from our study are two-fold. First, we confirmed that the size of DCIS ($P = < 0.001$) was an independent risk factor for positive surgical margins after BCS as previously reported [19]. We also demonstrated a new finding, in that ER negative DCIS ($P = 0.006$) was independently associated with a higher rate of positive margins after BCS. Future investigation into why estrogen receptor status impacts surgical margins is warranted. As tumor genomic

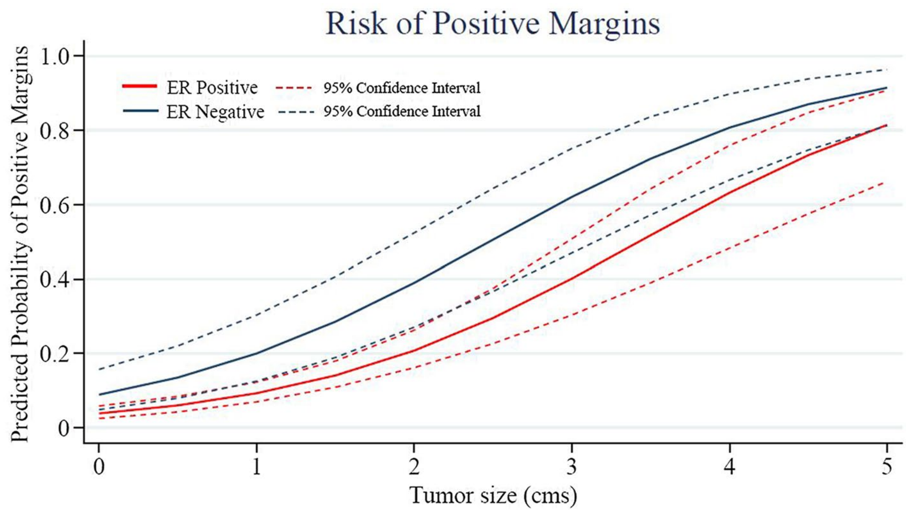

Fig. 2 Estimated risk of positive margins from multivariable logistic regression

research advances, we may gain a better understanding of this phenomenon [26–28].

The result of this study provides two variables which are available preoperatively, namely ER status and tumor size, which can help surgeons guide patients during counseling sessions regarding their potential risk for positive surgical margins and additional surgery. American Society of Breast Surgeons (ASBrS) recommends consideration of cavity shave margins for invasive cancer only [29]. Surgeons who routinely perform cavity shave margins may not benefit from the conclusions of this investigation. For those that do not perform cavity shave margins in their practice, the results of this study suggest there may be a potential role for consideration of cavity shave margins in patients with larger-sized, ER negative DCIS. A prospective randomized trial utilizing this approach can be performed to validate our findings.

Studies looking at reduction in reoperation rates in the United States quote $18.8 million annual cost savings by avoiding re-excision [14]. Practice changes based on our findings can not only further reduce the patient's financial burden but also overall healthcare expenditures.

Study limitation

This is a retrospective review performed at a single academic institution. Also, the limitation of a single surgeon experience is both an advantage and a limitation, as it eliminates the variability or surgical technique. Pathologic assessment variability allows for potential bias [30].

Author contributions TD, MG, LBW, and LRF: contributed to the study concept and design. Material preparation, data collection and analysis were performed by AO, MM, AW, and LRF. LRF: wrote the manuscript with significant contributions by all authors. All authors read and approved the final manuscript.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Requests should be made to Lucy B. Wallace, MD: Lucy.Wallace@BSWHealth.org.

Declarations

Conflict of interest This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval This retrospective study involving human participants was in accordance with the ethical standards of the institution and/or national research committee and in line with the principles of the Declaration of Helsinki. Approval was granted by the review boards of Baylor Scott and White Research Institute.

Informed consent This study used only unidentifiable patient information, and no informed consent was required.

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