

Factors Associated With Positive Margins in Women Undergoing Breast Conservation Surgery

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Abstract

Objective: To identify factors predicting positive margins at lumpectomy prompting intraoperative reexcision in patients with breast cancer treated at a large referral center.

Patients and Methods: We reviewed all breast cancer lumpectomy cases managed at our institution from January 1, 2012, through December 31, 2013. Associations between rates of positive margin and patient and tumor factors were assessed using χ^2 tests and univariate and adjusted multivariate logistic regression, stratified by ductal carcinoma in situ (DCIS) or invasive cancer.

Results: We identified 382 patients who underwent lumpectomy for definitive surgical resection of breast cancer, 102 for DCIS and 280 for invasive cancer. Overall, 234 patients (61.3%) required intraoperative reexcision for positive margins. The reexcision rate was higher in patients with DCIS than in those with invasive disease (78.4% [80 of 102] vs 56.4% [158 of 280]; univariate odds ratio, 2.80; 95% CI, 1.66-4.76; $P < .001$). Positive margin rates did not vary by patient age, surgeon, estrogen receptor, progesterone receptor, or ERBB2 status of the tumor. Among the 280 cases of invasive breast cancer, the only factor independently associated with lower odds of margin positivity was seed localization vs no localization ($P = .03$).

Conclusion: Ductal carcinoma in situ was associated with a higher rate of positive margins at lumpectomy than invasive breast cancer on univariate analysis. Within invasive disease, seed localization was associated with lower rates of margin positivity.

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For patients with cancer undergoing breast-conserving surgery, negative margins are important for local control because positive margins are associated with a higher risk of local recurrence.¹⁻³ The Society of Surgical Oncology—American Society for Radiation Oncology—American Society of Clinical Oncology consensus guidelines define a 2-mm tumor-free margin for ductal carcinoma in situ (DCIS) and no tumor on ink for invasive breast cancer as adequate margins.^{4,5} Patients with positive margins are advised to undergo reexcision of margins, usually requiring a second operation. Reoperation for margin reexcision occurs in approximately 10% to 40% of all women undergoing lumpectomy for breast cancers.⁶⁻¹¹

At our institution, we routinely use intraoperative pathologic assessment with

frozen-section margin analysis to reach negative margin status within the original operation. Margins identified as positive intraoperatively are excised within the same operation. The aim of this study was to identify risk factors for positive margins within this practice because identification of factors associated with need for reexcision/reoperation may inform the practice of breast conservation surgery and minimize reoperation rates.

PATIENTS AND METHODS

After institutional review board approval, we identified patients with DCIS or invasive breast cancer who elected to undergo breast-conserving surgery at Mayo Clinic in Rochester, Minnesota, between January 1, 2012, and December 31, 2013, from a prospectively maintained breast surgery database. All cases

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were retrospectively reviewed for patient, surgeon, and tumor factors. It is standard practice at our institution for all breast specimens to be evaluated by intraoperative frozen-specimen pathologic examination. If margins are positive, they are reexcised, and the new margin is again evaluated by intraoperative frozen-section analysis. Pathology reports were concurrently reviewed by 2 pathologists (M.G.K., G.L.K.) to confirm intraoperative margin status. Slides were reviewed in 25 cases that had no specific mention of final margin status. A positive margin was defined for this analysis as “tumor on ink” (cancer detected on the inked margin of the specimen) for both DCIS and invasive disease. Close margins (<2 mm) were counted as negative. Associations between rates of positive margin and patient-tumor factors were assessed with univariate χ^2 tests or Fisher exact tests (as applicable) and univariate and adjusted multivariate logistic regression, both overall and stratified by diagnosis (DCIS or invasive breast cancer). Multivariate models included statistically significant variables from univariate analyses as well as selected clinically significant variables. Multivariate logistic regression was used to model the rate of having a positive margin. Independent variables included were estrogen receptor (ER)—positive status (yes [$\geq 1\%$ cells stained positive] vs no), progesterone receptor (PR)—positive status (yes [$\geq 1\%$ cells stained positive] vs no), age (>50 vs <50 years), surgeon (6 individual surgeons), grade (I, II, or III), tyrosine receptor kinase 2 (ERBB2; formerly, HER2) status (positive, negative, or missing), Ki-67 (missing, <15%, $\geq 15\%$), neoadjuvant therapy (chemotherapy, hormonal, or none), localization (seed, wire, intraoperative ultrasound, or none), clinical tumor stage (Tis, T1, T2, T3), and diagnosis category (DCIS, invasive lobular carcinoma, invasive ductal carcinoma, invasive mammary carcinoma, or other). The α level was set at .05 for statistical significance. Analyses were performed using SAS statistical software, version 9.4 (SAS Institute).

RESULTS

We identified 382 women who underwent lumpectomy for treatment of breast cancer during the study period: 102 for DCIS and 280 for invasive cancer. Overall, 238

(62.3%) had positive margins, and 234 (61.3%) underwent intraoperative reexcision (80 of 102 [78.4%] with DCIS and 158 of 280 [56.4%] with invasive cancer; univariate odds ratio, 2.80; 95% CI, 1.66-4.76; $P < .001$). Of all 382 patients, 4 (1.0%) had negative margins at completion of the lumpectomy based on intraoperative pathologic analysis but were found to have positive margins on final pathologic examination. Two of these 4 patients underwent a second operation for margin reexcision, with additional disease identified in the reexcised margin in both cases. Final margin status in these 2 cases after reexcision lumpectomy was negative. The 2 cases with positive final margins that did not have a reoperation were a 72-year-old with a separate small focus of DCIS at the superior margin and an 82-year-old with a focus of invasive disease. Both patients received adjuvant radiation.

We further evaluated factors associated with positive margins separately for patients with DCIS and invasive disease. Among the 102 DCIS cases, there was no statistical difference between positive margin rates by any of the factors evaluated by univariate analysis: tumor stage, ER ($P = .33$), PR ($P = .76$), or ERBB2 status ($P = .09$), surgeon ($P = .62$), age 50 years or older or less than 50 years ($P = .11$), localization technique ($P = .63$), or DCIS grade ($P = .33$) (Table 1). On multivariate analysis, there were no greater odds of positive margins with patient age (odds ratio [OR], 3.22; 95% CI, 0.87-11.95; $P = .08$), ER status (OR, 3.32, 95% CI, 0.35-31.85; $P = .30$), PR status (OR, 1.03; 95% CI, 0.12-8.79; $P = .98$), or tumor grade (grade II vs grade I: OR, 1.05; 95% CI, 0.29-3.77; $P = .94$; grade III vs grade I: OR, 3.19; 95% CI, 0.70-14.49; $P = .13$) (Table 2). Although localization technique was considered clinically significant and was intended to be included in both stratified multivariate models, we could only include it in the invasive model because the DCIS model with localization would not converge.

Among the 280 cases of invasive breast cancer, factors associated with a positive margin on univariate analysis included tumor Ki-67 and method of localization (Table 1). Of the patients who underwent wire-localized excision, 35 of 58 (60.3%) had positive

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