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Positive Margins Rates Following Breast-Conserving Surgery for Stage I–III Breast Cancer: Palpable versus Non-Palpable Tumors

Jordan Atkins, BS¹, Fatema Al Mushawah, MD¹, Catherine M. Appleton, MD², Amy E. Cyr, MD¹, William E. Gillanders, MD¹, Rebecca L. Aft, MD, PhD¹, Timothy J. Eberlein, MD¹, Feng Gao, PhD³, and Julie A. Margenthaler, MD¹

¹Department of Surgery, Washington University School of Medicine, St. Louis, MO

²Department of Radiology, Washington University School of Medicine, St. Louis, MO

³Division of Biostatistics, Washington University School of Medicine, St. Louis, MO

Abstract

Background—Margin status is a significant risk factor for local recurrence. We sought to examine whether the method of tumor localization predicted the margin status and the need for re-excision for both non-palpable and palpable breast cancer.

Methods—We identified 358 consecutive breast cancer patients who were treated with breast-conserving therapy (BCT) from 1999–2006. Data included patient and tumor characteristics, method of localization (needle versus palpation), and pathologic outcomes. Descriptive statistics were utilized for data summary and data were compared using Chi-square.

Results—Of 358 patients undergoing BCT, 234 (65%) underwent needle localization for a non-palpable tumor and 124 (35%) underwent a palpation-guided procedure. Patients undergoing palpation-guided procedures were younger and had larger tumors at a more advanced pathologic stage of disease than those undergoing needle localization procedures ($p < 0.05$ for each). Patient race, tumor grade, presence of lymphovascular invasion, biomarker profile, and nodal status were not significantly different between the two groups ($p > 0.05$). Overall, 137 (38%) patients had one or more positive margins; 90 of 234 (38%) who had a needle localization procedure and 47 of 124 (38%) who had a palpation-guided procedure ($p > 0.05$). The number of margins affected did not differ significantly between the two groups.

Conclusion—Although patients with palpable breast cancer had larger tumors than those with non-palpable breast cancer, the incidence and number of positive margins was similar to those who had needle localization for non-palpable tumors. Improved methods of localization are needed to reduce the rate of positive margins and the need for re-excision.

Keywords

Breast Cancer; Margin Status; Needle Localization

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Address Correspondence: Julie A. Margenthaler, MD, FACS, Department of Surgery-WUSM, 660 S. Euclid Ave., Campus Box 8109, St. Louis, MO 63110, Telephone – 314-747-9724, Fax – 314-454-5509, margenthalerj@wudosis.wustl.edu.

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INTRODUCTION

Breast cancer is the most common type of cancer affecting women and a leading cause of death in the United States [1]. The adoption of screening mammography has led to the identification of smaller, often non-palpable, tumors that are amenable to breast-conserving surgical approaches as opposed to mastectomy [2–4]. Breast-conserving therapy (BCT), which includes wide local excision of the tumor followed by irradiation, has become a standard treatment option for women with early-stage invasive breast cancer. Long-term survival following BCT has been shown to be equivalent to that of mastectomy, while also providing an acceptable cosmetic outcome and low morbidity [5–9].

Local recurrence following BCT has been shown to be impacted by a number of patient and tumor characteristics, including patient age, tumor size, tumor grade, and presence of multifocal or multicentric disease [5–11]. However, the strongest predictor of local recurrence remains that of surgical margin status [10–13]. Meric et al. [10] followed 1,043 patients who underwent BCT and found that 12% developed an ipsilateral breast tumor recurrence and 18% developed a systemic recurrence at 8.4 years of median follow-up. Further, ipsilateral breast tumor recurrence was an independent predictor of systemic recurrence and positive margins were an independent predictor of poor disease-specific survival [10]. The median time to develop an ipsilateral breast tumor recurrence may be delayed by the use of adjuvant systemic therapy [13]. In one series of 1,262 patients with Stage I–II breast cancer who underwent BCT, including axillary lymph node dissection and adjuvant radiation, the median interval to development of an ipsilateral breast tumor recurrence was 3.7 years if no adjuvant systemic therapy was administered, 5.0 years after systemic chemotherapy with or without tamoxifen, and 6.7 years after tamoxifen alone [13]. This delay in ipsilateral breast tumor recurrence was observed in patients with close (2 mm) or positive margins; there was no impact on the time to failure for patients with initial negative (>2 mm) margins [13].

At our institution, microscopic margins of >2 to 3 mm are considered sufficient criteria for subsequent adjuvant radiation and BCT. Therefore, patients routinely undergo re-excision of the cavity when histopathology demonstrates evidence of tumor cells that are close to (<2 to 3 mm), but free of, the resection margin. In contrast, a positive margin is defined as histologic confirmation of focal or extensive involvement of one or more margins. Because there is some disagreement as to the necessity of re-excision in patients with negative, but close (2 mm), margins on initial excision, only patients with tumor present at the margin were considered to have “positive” margins in the analysis to determine the impact of the localization techniques utilized. The most common method of localization of a non-palpable breast cancer is by use of a radiologically placed hookwire; this was the only method utilized at our institution during the study period. Palpable tumors may be excised based on palpation alone or by radiologic guidance; radiologic methods of localization were not utilized at our institution for patients with palpable tumors during the study period. We hypothesized that the method of localization would be an independent predictor of a positive margin and the need for re-excision following attempted BCT.

PATIENTS AND METHODS

Institutional review board approval was obtained prior to the commencement of this retrospective study. Written informed consent of patients was not required. Clinical, demographic, and pathologic data from all breast cancer patients treated at our institution are prospectively recorded in a database. We reviewed this database and identified 358 patients who underwent successful BCT for a unifocal Stage I–III invasive breast cancer from 1999–2006. This represented 58% of the total patient population treated during the study period.

Patients were selected who had invasive ductal carcinoma with or without associated ductal carcinoma in situ (DCIS). Patients with DCIS only (Stage 0), invasive lobular carcinoma, or lobular carcinoma in situ (LCIS) were excluded. All patients were diagnosed by pre-operative image-guided needle core biopsy.

The surgical procedures were performed by seven different surgeons with variable years of experience, although breast surgery comprised >50% of each practice. The aim of the surgical excision was complete tumor removal with grossly normal tissue margins of 1 cm. For patients with palpable tumors, this was assessed intraoperatively by the operating surgeon; no radiologic confirmation was obtained on the specimens. For non-palpable tumors, all patients underwent needle localization performed by dedicated breast radiologists on the morning of surgery. A single or multiple (when appropriate) hookwire was placed utilizing mammographic guidance under local anesthesia and sterile technique. The hookwire system was introduced in the most appropriate direction that resulted in the shortest distance to the tumor site. Specimens were retrieved from the operating room in all cases and a specimen radiograph was obtained to document the extent of excision. Additional shave margins were taken at the discretion of the operating surgeon. If surgical margins were positive (tumor present microscopically at the margin), a re-excision was performed in most patients, unless the margin was at the pectoral fascia. The decision for re-excision was left at the discretion of the treating surgeon; the specific reasons for lack of a re-excision in the setting of positive margins was not able to be discerned retrospectively in all cases.

Information on tumor histology and surgical margins was obtained from the original pathology reports. Tumor size was assessed microscopically by our dedicated breast pathologists. The tissue specimen was serially sectioned at 3 to 5 mm intervals in the anteroposterior plane perpendicular to the mediolateral axis and stained by hematoxylin and eosin. Detailed examination was performed, including documentation of the invasive tumor size and the tumor-margin distance for all six margins (anterior, posterior, medial, lateral, superior, and inferior). Focal positivity of a margin was defined as a single, small focus of tumor abutting the margin, typically seen only on one slide (i.e., one 3–5 mm slice of the tissue block). Extensively positive margins were defined by a large area of margin positivity with multiple slides involved or multiple sites along the margin involved.

Patients were grouped according to whether they had a non-palpable tumor excised with needle localization or a palpable tumor excised by palpation-guidance. Patient and tumor characteristics, as well as the pathology findings at the initial and re-excision procedures, were recorded. All data were transferred to a single spreadsheet (Excel; Microsoft, Redmond, WA). Descriptive statistics were used to assess frequency distributions between the two groups. Categorical variables and continuous variables were compared between the two groups using chi-squared tests. Statistical analyses were performed using a statistical package SAS (SAS Institutes, Cary, NC). *P* values <0.05 were considered to be statistically significant.

RESULTS

Of 358 patients with Stage I–III invasive breast cancer, 234 (65%) had non-palpable lesions requiring needle localization and 124 (35%) had palpable tumors that were excised with palpation guidance only. Overall, 137 (38%) had positive margins on the final microscopic pathology, including 90 of 234 (38%) who underwent needle localization and 47 of 124 (38%) who had palpation guidance ($p>0.05$). Of the 137 patients with positive margins, 38 (28%) had no further surgical procedures and proceeded to adjuvant therapy. The remaining 99 (72%) underwent re-excision of the cavity, including 68 of 90 (76%) in the needle

localization group and 31 of 47 (66%) in the palpation group. Final re-excision pathology revealed no residual disease in 48 [31 of 68 (46%) in the needle localization group and 17 of 31 (55%) in the palpation group ($p>0.05$)] and residual disease in 51 [37 of 68 (54%) in the needle localization group and 14 of 31 (45%) in the palpation group ($p>0.05$)]. For the 38 patients who did not undergo re-excision for positive margins [22 of 90 (24%) in the needle localization group and 16 of 47 (34%) in the palpation group ($p>0.05$)], a positive deep (pectoralis) margin was identified in 20 of 38 (53%), despite taking tissue to the pectoralis fascia and/or muscle per operative report. The reason for lack of re-excision in the remaining patients was unclear retrospectively. Figure 1 illustrates the pathologic outcomes of all 358 patients.

Table 1 summarizes the patient and tumor characteristics for each group. Patients undergoing palpation-guided procedures were younger (mean age 50.6 ± 4.9 years) compared to patients undergoing needle localization procedures (mean age 61.4 ± 5.4 years) ($p<0.05$). Patients undergoing palpation-guided procedures also had larger tumors and more advanced pathologic stage of disease than those undergoing needle localization procedures ($p<0.01$ and $p<0.05$, respectively). Patient race, tumor grade, presence of lymphovascular invasion, biomarker profile, and nodal status were not significantly different between the two groups ($p>0.05$). Neoadjuvant therapy was utilized in 18 of 358 (5%) of the total group, including 10 of 234 (4%) in the needle localization group and 8 of 124 (6%) of the palpation group.

The number of affected margins was investigated for each patient with a positive margin following initial surgical therapy (Table 2). The number of margins affected did not differ significantly between those patients who had a needle localization versus those who had a palpation-guided procedure ($p>0.05$ for all): 40 (44.4%) versus 24 (51%) with one positive margin, 28 (31%) versus 13 (27.6%) with two positive margins, and 22 (24%) versus 10 (21%) with three or more positive margins, respectively. The most common margin to be affected in both groups was the anterior margin either alone or with other positive margins (47% of the positive margins in the needle localization group and 34% of the positive margins in the palpation group, $p>0.05$). The second most common margin to be affected in both groups was the posterior margin either alone or with other positive margins (25% of the positive margins in the needle localization group and 23% of the positive margins in the palpation group, $p>0.05$).

DISCUSSION

BCT, which includes wide local excision of the primary breast tumor followed by adjuvant radiation therapy, has become the standard therapy for early breast cancer with long term survival that is comparable to mastectomy [5–9]. Several large randomized trials have been conducted in the past forty years to study the long term outcome of BCT, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 which was initiated in 1976 and included 1851 stage I and II breast cancer patients who were randomized to lumpectomy alone, lumpectomy with radiation therapy, or total mastectomy [5]. These results have been corroborated in 5 major prospective, randomized controlled trials in Europe and North America, including the Italian trial [6], the European Organization for Research and Treatment of Cancer (EORTC) 10801 trial [7], the French trial [8], the National Cancer Institute (NIH) trial [9], and the Danish trial [14].

What remains unclear from these previous trials is the definition of an adequately negative margin and the best method to achieve such margins. Achieving an adequate margin is critical as the strongest predictor of local recurrence remains that of surgical margin status [10–13]. Freedman et al. reported their association between a positive margin and the risk of

an ipsilateral breast tumor recurrence after BCT and found that a negative margin that is >2 mm results in a lower risk of local recurrence (7 % at 10 years) compared with close or positive margins (12% and 14% at 10 years, respectively) [13]. In the current study, nearly 40% of our patients required re-excision and this rate did not vary between those who had a needle localization procedure versus those who had a palpation-guided procedure, despite the fact that those patients undergoing palpation-guided procedures had significantly larger tumors. The re-excision rates we observed are similar to those reported in previous studies [15–17].

Interestingly, there were a sub-group of patients (24% in the needle localization group and 34% in the palpation group) who had positive margins but did not undergo re-excision. Nearly half of these had positive deep (pectoralis) margins and the surgeon did not return for re-excision presumably because they felt that no further tissue could be taken based on the description of tissue taken to the depth of the pectoralis fascia and/or muscle. We were unable to determine the rationale in the remaining patients, but this rate is consistent with that seen in previous studies [13, 18].

Multiple factors have been reported to be associated with margin positivity, including patient age. Jobsen et al. reported their 5- and 10-year local recurrence rates as 3.1% and 6.9%, respectively, for negative margins versus 5.6% and 12.2%, respectively, for positive margins. However, the 5-year local recurrence rates for women <40 years was 8.4% for negative margins and 36.9% for positive margins, suggesting that free margins are particularly important for this unique sub-group of patients [18]. A variety of tumor factors have also been reported to be associated with a positive margin status, including large tumor size, multifocality, presence of extensive in situ component, lobular histological type, and positive axillary nodal status [17, 19–22]. Although patients undergoing palpation-guided procedures were younger with larger tumors and more advanced stages of disease, none of these patient or tumor characteristics were independent predictors of positive margins in our study.

Multiple methods of pre- and intra-operative techniques have been proposed to help decrease the risk for a positive pathologic margin. Needle localization remains the most popular technique for intraoperative guidance in patients with non-palpable tumors [23, 24]. One disadvantage of needle localization is that it does not provide a three-dimensional view of the various tumor edges. Mazouni et al. reviewed their experience with lumpectomy specimen radiographs and found that a radiological margin <5 mm and lesion multifocality were the only risk factors for close pathological margins [25]. Despite this, re-excision rates with needle localization remain high. All of the patients in the current study who had non-palpable tumors underwent needle localization-guided lumpectomy, and 38% of patients had compromised margins despite localization.

Others have advocated the use of intraoperative ultrasound as an effective method to localize non-palpable breast cancers and to decrease re-excision rates [26–28]. Thompson et al. compared the use of needle localization versus hematoma-directed ultrasound-guided localization of the core biopsy cavity in a group of 186 patients undergoing lumpectomy for benign and malignant lesions [29]. Margin positivity was significantly higher (73%) in the needle localization group compared to the ultrasound-guided group (22%) [29]. Ultrasound-guided lumpectomy has recently been adopted at our institution for palpable and select non-palpable lesions. However, it was not utilized in the time period of this study. Its ability to reduce the need for re-excision is the topic of future research at our institution.

Radioguided occult lesion localization (ROLL) is another developing technique in tumor localization [30]. It utilizes the injection of a radioisotope into the tumor under ultrasound or

stereotactic guidance and the use of a hand-held gamma probe intraoperatively to direct resection. Van Esser et al. utilized this technique in 31 patients; 5 patients (16%) required re-excision, including 2 with margins positive for in situ disease only [30]. Krekel et al. retrospectively reviewed the rate of positive margins in 201 patients who underwent either needle localization-guided lumpectomy, ultrasound-guided lumpectomy, or ROLL [31]. The rate of positive margins for invasive cancer was significantly lower in the ultrasound-guided group (3.7%) compared to the needle localization group (21.3%) and the ROLL group (25%), suggesting that ultrasound-guidance may be the best method for localization overall [31]. In fact, there is an ongoing prospective, multicenter, randomized controlled trial (the COBALT trial) that aims to assess the efficacy of ultrasound-guided versus palpation-guided lumpectomy in patients with palpable early-stage primary invasive breast cancer [32]. The primary outcomes include volume of the lumpectomy specimen, margin status, cosmetic outcomes, and quality of life.

Some authors advocate the use of systematic “shave” margins intraoperatively, reporting a reduction in re-excision rates from ~50% without shave margins to 7–20% with shave margins [33, 34]. However, it is unclear whether this strategy represents a reliable predictor of the completeness of resection and whether it will translate into good rates of local control. This uncertainty likely reflects the variation in the groups studied, variability in the techniques themselves, and the criteria defining close margins. Shave margins are used at the discretion of the surgeon at our institution. It is unclear from this retrospective analysis how this may have impacted our results. However, given that our positive margin rates were equivalent between the two groups, we believe that the use or non-use of shave margins in selected patients is unlikely to account for significant differences in the final results.

Intraoperative pathologic assessment using either frozen section or touch prep analysis has also been proposed as a mechanism to reduce positive margins. The diagnostic accuracy of frozen section has been reported to be as high as 86%, with a sensitivity that varies between 83–91% [35, 36]. Lower observed sensitivity for smaller lesions, risk of compromising the pathologic specimens, and time needed for pathologic assessment have largely limited the usefulness of this modality. Touch prep analysis is an alternative method of intraoperative assessment which has been reported to be quicker than frozen section, but the sensitivity has been widely variable and ranging between 75–96% [37, 38]. This decreased accuracy which is potentiated by drying and cautery artifacts have limited its widespread use. Neither frozen section nor touch prep analysis are used at our institution; all tissue is submitted for permanent histology.

This study has a number of limitations. It is a retrospective analysis, and it is difficult to interpret the complex decision-making surrounding the selection of patients who underwent re-excision compared to those who did not. We analyzed only patients with true positive margins (tumor present microscopically at the margin) for this reason so that we could evaluate the two localization methods in patients with similar pathologic findings. In addition, pathologist interpretation of margins is a subjective one that may vary by institution. A further limitation of this study is that we did not specifically address the presence or absence of residual disease as being invasive or in situ. We recognize that the presence of ductal carcinoma in situ may impact our results. Dillon et al. studied the impact of the percentage of in situ component in the original needle core biopsy with the likelihood of obtaining a positive or close margin on the final breast-conserving surgical specimen [22]. They found that if patients had only invasive disease on the core biopsy that the compromised margin rate was 23%, but that this was significantly higher at 39% when patients had either an invasive component with accompanying in situ disease or ductal carcinoma in situ only [22]. We are unable to determine the impact of associated in situ disease retrospectively, but we would anticipate that both groups would have similar rates of

such associated disease. In addition, we did exclude Stage 0 to compensate for the unique difficulties surrounding breast conservation in this group of patients.

Despite these limitations, the current study highlights the difficulty surrounding breast conservation procedures. We were surprised to find that the rate of positive margins was similar between patients who had smaller, non-palpable tumors and those who had larger, palpable tumors. However, this study illustrates the need for more accurate pre- and intraoperative assessment of margins in order to aid the breast surgeon in performing the best possible wide local excision so that the rates of positive margins, re-excisions, and local recurrences are minimized.

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Figure 1. Outcomes of 358 patients undergoing breast-conserving surgical therapy using either a needle localization technique or palpation guidance.

Table 1
Patient and Tumor Characteristics for 358 Patients Undergoing Breast-Conserving Therapy Using Palpation-Guidance for Palpable Tumors (n=124) or Needle Localization for Non-Palpable Tumors (n=234) According to Margin Status

	Positive margins n=137 (38%)				Negative margins n=221 (62%)			
	Palpation N=47 (34%)		Needle localization N=90 (66%)		Palpation N=77 (35%)		Needle localization N=144 (65%)	
	N	%	N	%	N	%	N	%
Age*								
<50	21	45%	21	23%	24	31%	32	22%
50	26	55%	69	77%	53	69%	112	78%
Race								
African American	14	30%	18	20%	22	29%	31	21%
Caucasian	32	68%	69	77%	54	70%	109	76%
Other	1	2%	3	3%	1	1%	4	3%
Stage*								
I	19	41%	52	58%	33	43%	102	71%
II	24	51%	32	36%	40	52%	38	26%
III	3	6%	4	4%	1	1%	2	2%
Unknown	1	2%	2	2%	3	4%	2	1%
Tumor size [^]								
T1	29	62%	69	77%	52	68%	122	85%
T2	13	28%	17	19%	24	31%	18	12%
T3	4	9%	1	1%	0	0%	0	0%
Unknown	1	1%	3	3%	1	1%	4	3%
Nodal status								
0	30	64%	58	65%	45	58%	114	79%
1	17	36%	30	33%	29	38%	28	20%
2	0	0%	2	2%	0	0%	2	1%
Unknown	0	0%	0	0%	3	4%	0	0%
Grade								

	Positive margins n=137 (38%)				Negative margins n=221 (62%)			
	Palpation N=47 (34%)		Needle localization N=90 (66%)		Palpation N=77 (35%)		Needle localization N=144 (65%)	
	N	%	N	%	N	%	N	%
I	7	15%	23	26%	16	21%	46	32%
II	24	51%	36	40%	34	44%	64	44%
III	16	34%	31	34%	27	35%	30	21%
Unknown	0	0%	0	0%	0	0%	4	3%
LVI								
Present	13	28%	16	18%	18	23%	22	15%
Absent	34	72%	73	81%	58	76%	119	83%
Unknown	0	0%	1	1%	1	1%	3	2%
ER Status								
Positive	37	79%	70	78%	57	74%	118	82%
Negative	10	21%	20	22%	19	25%	24	17%
Unknown	0	0%	0	0%	1	1%	2	1%
PR Status								
Positive	28	60%	60	67%	54	70%	99	69%
Negative	18	38%	30	33%	22	29%	43	30%
unknown	1	2%	0	0%	1	1%	2	1%
Her/2neu Status								
Amplified	13	28%	24	27%	26	34%	36	25%
Non-amplified	28	60%	58	64%	32	41%	92	64%
Unknown	6	12%	8	9%	19	25%	16	11%

LVI = Lymphovascular invasion; ER = estrogen receptor; PR = progesterone receptor

* P<0.05

^ P<0.01

Table 2

Positive Margin Details for 137 Patients Undergoing Breast-Conserving Therapy Using Palpation-Guidance for Palpable Tumors (n=47) or Needle Localization for Non-Palpable Tumors (n=90)

<i>Number of positive margins</i>	Palpation N=47		Needle Localization N=90	
	N	%	N	%
<i>1</i>	24	51%	40	45%
<i>2</i>	13	28%	28	31%
<i>3</i>	4	9%	13	15%
<i>4</i>	1	2%	5	5%
<i>5</i>	0	0%	1	1%
<i>6</i>	0	0%	0	0%
<i>Not specified</i>	5	10%	3	3%