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ORIGINAL ARTICLE – BREAST ONCOLOGY

Margin Assessment and Re-excision Rates for Patients Who Have Neoadjuvant Chemotherapy and Breast-Conserving Surgery

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ABSTRACT

Background. Neoadjuvant chemotherapy (NAC) has enabled more patients to be eligible for breast-conservation surgery (BCS). Achieving negative lumpectomy margins, however, is challenging due to changes in tissue composition and potentially scattered residual carcinoma in the tumor bed. Data regarding BCS after NAC have shown variable re-excision rates. MarginProbe (Dilon Technologies, Newport News, VA, USA) has been shown to identify positive resection margins intraoperatively and to reduce the number of re-excisions in primary BCS, but has not been studied in NAC+BCS cases. This study aimed to investigate the clinicopathologic characteristics, margin status, and re-excision rates for NAC+BCS patients with and without the use of MarginProbe.

Methods. The Institutional Breast Cancer Database was queried for patients who received NAC and had BCS from 2010 to 2019. The variables of interest were demographics, tumor characteristics, pathologic complete response (pCR), MarginProbe use, and re-excision rates.

Results. The study population consisted of 214 patients who had NAC, 61 (28.5 %) of whom had NAC+BCS. The median age of the patients was 53.5 years. A pCR was achieved for 19 of the patients (31.1 %). Of the remaining 42 patients, 9 (21 %) had close or positive margins that required re-excision. Re-excision was associated with a larger residual tumor size ($p = 0.025$) and estrogen receptor (ER)-positive disease before NAC ($p = 0.041$). MarginProbe use was associated with a lower re-excision rate for the patients who had NAC+BCS (6 % vs. 31 %, respectively).

Conclusion. The patients with a larger residual tumor burden and ER-positive disease had a greater risk for inadequate margins at surgery. MarginProbe use was associated with a lower re-excision rate. Techniques to reduce the need for re-excision will support the use of BCS after NAC.

Breast-conserving surgery (BCS) for the treatment of breast cancer generally is associated with better cosmetic outcomes and quality-of-life aspects than mastectomy.[1] The use of neoadjuvant chemotherapy (NAC), previously reserved for locally advanced breast cancer, has been extended to patients with less-extensive high-risk disease. For patients with larger tumors, a good response to NAC may increase their eligibility for BCS.[2–4]

Neoadjuvant chemotherapy can downstage tumors, allow the effectiveness of systemic therapy to be evaluated *in vivo,* and lead to lower volumes of resection.[5,6] In this manner, NAC may expand the population of patients who are candidates for BCS. Studies have shown that breast cancer-specific survival is not influenced by the choice of BCS after NAC, with one study even showing that this group appeared to have better survival than patients undergoing mastectomy without radiation after NAC.[7]

Achieving negative lumpectomy margins, however, may be challenging after NAC due to changes in tissue composition and the potential for residual carcinoma to be scattered in the tumor bed.[8] As such, the rate of ipsilateral breast tumor recurrence (IBTR) and locoregional tumor recurrence (LRR) may be higher than those reported for upfront BCS.[9] The rate of tumor-involved margins after NAC is reported to be 24.7 %.[10,11] Although this is in the

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range of the reported rate for upfront BCS in the past (20–40 %),[12,13] it is higher than what has been more recently reported (10–15 %).[11,14,15] Therefore, addressing the high rate of positive margins is of paramount importance so clinicians can continue offering BCS to NAC patients,.

Multiple approaches have been suggested to reduce the re-excision rate in BCS. The MarginProbe device (Dilon Technologies, Newport News, VA, USA), using radiofrequency spectroscopy, has been shown to identify positive resection margins intraoperatively and to reduce the number of re-excisions in primary BCS.[16–18] However, use of this device use has not been studied previously for patients who have undergone NAC and BCS.

This study aimed to investigate the clinicopathologic characteristics, including margin status and re-excision rates, of the patients who had NAC and BCS with and without the use of MarginProbe at our institution.

METHODS

All patients undergoing definitive breast cancer surgery at NYU Langone Health (New York, NY, USA) are eligible to enroll in the institutional review board (IRB)-approved NYU Breast Cancer Database. Diagnostic and follow-up data are obtained from detailed patient questionnaires and electronic medical chart review.

The database was queried for all patients who received NAC and had subsequent BCS from 2010 through 2019. The patients were categorized into two groups according to intraoperative MarginProbe use. The variables included for analysis were age at diagnosis, race, method of presentation, palpability, nipple discharge, extent of disease on imaging, mass on preoperative imaging, multifocality, multicentricity, tumor grade, estrogen receptor (ER) status, and progesterone receptor (PR) status. The extent of disease on preoperative imaging was recorded for each patient.

Most of the patients were imaged with at least two methods. The measurements we report were derived from mammographic reports. The patients received individual chemotherapy regimens as directed by their medical oncologists. Adequate margins were defined by the Society of Surgical Oncology (SSO)/American Society for Radiation Oncology (ASTRO) consensus guideline of no ink on the tumor for invasive carcinoma and the SSO/ASTRO/American Society of Clinical Oncology (ASCO) guideline of 2 mm for ductal carcinoma *in situ* (DCIS).[19,20] Patients with pathologic complete response (pCR) were recorded and excluded from final comparisons.

To test for an association between groups and variables of interest, Pearson's chi-square and Fisher's exact tests were used, with an α of 0.05 was considered to be significant. All missing values were excluded from analysis. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Breast cancer was diagnosed for 214 women enrolled in our institutional breast cancer database who underwent NAC from January 2010 through January 2018. Those who subsequently underwent mastectomy were excluded from the study. Of 61 patients (28.5 %) who underwent BCS after NAC, 19 (31.1 %) had pCR and were excluded from this analysis.

The remaining 42 patients who underwent BCS after NAC had a median age of 51.8 years and a mean follow-up time of 7.35 years (Table 1).

The majority of the women (86 %) initially presented with a palpable mass. Most of the masses (79 %) were detected on self-exam, with the remainder detected by clinicians. Only a minority of patients had screening-detected cancer. White women represented 43 % of the cohort, followed by Hispanic women (24 %), with the remainder divided between Asian (17 %) and African American (17 %) women.

For the majority of the women (57 %), mammography showed heterogeneously dense breasts. Stage 2 disease was found in 48 % and stage 3 disease in 40 % of the women. The findings showed ER-positive tumors in 71 %, PR-positive tumors in 45 %, and human epidermal growth factor receptor 2 (HER2)-positive tumors in 31 % of the cases. The average size of the tumors before NAC was 3.7 cm.

Of the 42 patients who underwent BCS after NAC, 9 (21 %) had close or positive lumpectomy margins that required re-excision. Neither the method of presentation nor the mammographic breast density differed between the women who required re-excision and those who did not. The two groups also did not differ in terms of disease stage.

In the re-excision group, 100 % of tumors were ER-positive, whereas in the group not requiring re-excision, only 64 % of the tumors were ER-positive ($p = 0.041$). All the tumors that required re-excision were moderately differentiated on the final pathology ($p = 0.045$; Table 2). Re-excision was associated with a larger residual tumor size (3.5 vs 1.4 cm in the no re-excision group; $p = 0.025$). MarginProbe use was associated with a lower re-excision rate for the patients with NAC+BCS (6 % vs 31 %, respectively), although this difference did not reach statistical significance.

TABLE 1 Clinical characteristics of patients with and without a re-excision

Variables	Total (n = 42)	%	No re-excision (n = 33)	%	Re-excision (n = 9)	%	p Value
Median age: years (range)	51.8 (29.5–85.8)		54.7 (34.5–85.8)		47.5 (29.5–61.3)		0.064
Race							0.4684
African American	7	17	5	15	2	22	
Asian	7	17	7	21	0	0	
White	18	43	18	55	0	0	
Hispanic	10	24	3	9	7	78	
Palpability							0.312
Non-palpable	6	14	6	18	0	0	
Palpable	36	86	27	82	9	100	
Method of presentation							0.653
Mammogram	5	12	5	15	0	0	
Physical breast exam	4	10	3	9	1	11	
Breast self-exam	33	79	25	76	8	89	
Mammographic breast density							0.808
Entirely fatty	3	7	3	9	0	0	
Scattered Fibroglandular	12	29	10	30	2	22	
Heterogeneously dense	24	57	18	55	6	67	
Extremely dense	3	7	2	6	1	11	
Clinical stage							1.000
2	20	48	15	46	5	56	
3	17	40	14	42	3	33	
4	5	12	4	12	1	11	
Pre-NAC ER							0.041
Negative	12	29	12	36	0	0	
Positive	30	71	21	64	9	100	
Pre-NAC PR							1.000
Negative	23	55	18	55	5	56	
Positive	19	45	15	45	4	44	
Pre-NAC HER2neu							1.000
Negative	29	69	23	70	6	67	
Positive	13	31	10	30	3	33	
Mean pre-NAC Ki-67	24.0 (1.0–90.0)		28.0 (1.0–90.0)		7.9 (1.0–25.0)		0.092
Mean pre-NAC Invasive size: cm (range)	3.7 (0.7–10.0)		3.7 (0.7–10.0)		3.6 (1.2–6.5)		0.927

NAC, neoadjuvant chemotherapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor

DISCUSSION

The use of NAC in the treatment of breast cancer has provided the opportunity to prioritize systemic treatment for patients at risk for metastatic spread and allow assessment of *in vivo* response to therapy. Based on individual tumor response, the use of NAC has converted many BCS-ineligible patients to BCS eligibility.

Response to NAC depends on a variety of factors, particularly tumor subtype, with triple-negative and HER-2/neu-positive tumors most likely to demonstrate response to treatment. The current study found that patients with a larger residual tumor burden and ER-positive disease were at an increased risk for inadequate margins at the time of BCS.

The literature on risk factors for positive margins in BCS after NAC includes small retrospective series, but the reported results are mostly similar to our findings.[21–23] In one study of 69 patients treated with BCS after NAC, the re-excision rate was 32 % (n = 22) compared with 17 % for their primary BCS group.[23] Lobular carcinoma and ER-positive tumors were found to have a significantly higher rate of re-excision (100 % vs 42 %, respectively).[23]

TABLE 2 Tumor characteristics of patients with and without a re-excision

Variables	Total (n = 42)	%	No re-excision (n = 33)	%	Re-excision (n = 9)	%	p Value
Path stage							0.195
0	3	7	3	9	0	0	
1	15	36	13	40	2	22	
2	15	36	12	36	3	33	
3	7	17	3	9	4	45	
4	2	5	2	6	0	0	
Histologic grade							**0.045**
Well-differentiated	3	7	3	9	0	0	
Moderately Differentiated	27	64	18	55	9	100	
Poorly differentiated	12	29	12	36	0	0	
Lymphovascular invasion (LVI)							0.067
Yes	14	33	10	30	4	45	
No	25	60	22	67	3	33	
Multifocality							0.257
No	23	55	20	61	3	33	
Yes	19	45	13	39	6	67	
Mean post-NAC Invasive size (cm)	1.8 (0–9.7)		1.4 (0.0–6.0)		3.5 (0.8–9.7)		**0.025**
MarginProbe							0.119
No	26	62	18	55	8	89	
Yes	16	38	15	45	1	11	

Bold indicates meeting statistical significance threshold ($p < 0.05$)

NAC neoadjuvant chemotherapy

In our cohort, all the tumors were of the invasive ductal subtype, so we were unable to make observations on lobular carcinoma after NAC. In another study of 71 BCS cases after NAC, the risk of positive margins was significantly higher for cancers with an initial size larger than 5 cm, low tumor grade, and hormone receptor-positive status.[21] Although it may be reasonable to assume that larger tumor size would increase the risk of tumor-involved margins, another study of 97 patients found that an initial ultrasound tumor size of 27 mm or smaller was independently associated with tumor-involved margins (p = 0.045).[22] The authors' rationale for thinking smaller tumor size leads to increased positive margins was that the smaller tumors tended to be the luminal type in their study, and findings have found NAC to be less effective in the treatment of that breast cancer subtype.[24]

Findings from these published reports generally are compatible with the literature on risk factors for involved margins in upfront BCS for invasive carcinoma. A Dutch retrospective study analyzing more than 25,000 cases of upfront BCS for invasive carcinoma found that a tumor size larger than 2 cm and positive ER status both were strongly associated with involved margins.[25] This body of literature also reports HER2-positive tumors to be a risk factor for positive margins. However, because neoadjuvant HER2-targeted chemotherapy can lead to pCR rates reaching 60 %,[26] HER2 positivity is not a reported risk factor for positive margins after NAC. Recognizing that HER2-targeted NAC is highly effective, HER2 positivity is not seen as a risk marker for patients with residual disease,. Alternatively, ER-positive tumors do not respond as robustly to NAC, rarely achieve pCR, and may contribute to increased risk for positive margins after BCS. This is compatible with the association of ER-positivity and increased re-excision in our study. Therefore, tumor subtype should be an intraoperative consideration for the surgeon when assessing and delineating margins.

Despite advances in systemic therapies and increasing rates of pCR, the uptake of BCS after NAC has not increased. In the landmark study, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, despite a pCR rate of 26 %, uptake of BCS increased only from 60 % in the adjuvant therapy group to 67 % in the group receiving NAC.[27]

More recently, the Cancer and Leukemia Group B (CALGB) 40603 trial, which considered NAC in stages 2 and 3 triple-negative breast cancer (TNBC), published a surgical companion study investigating the rate of BCS eligibility and uptake.[28] They reported a 42 % rate of conversion from BCS ineligibility to BCS eligibility. However, only 68 % of the eligible patients underwent BCS.[28] Similar numbers were reported from the

BrighTNess trial, in which 75 patients (53 %) converted to BCS eligibility after NAC, but only 42 (56 %) of the eligible patients elected to undergo BCS.[3] It appears that inability to obtain clear margins has not been an obstacle because the CALGB study reported that 93 % of the patients who chose BCS were successful.

Undoubtedly, patients considering the choice between BCS and mastectomy after NAC weigh concerns other than the potential need for re-excision. An accurate assessment must be made to determine a patient's risk for in-breast recurrence and/or development of a secondary primary breast cancer, particularly in the context of a germline mutation.[28] Also, the reliability of imaging after NAC is important when clinicians are evaluating who is BCS-eligible after NAC.

Studies have shown limitations in the ability of MRI and other imaging methods to correlate with pathologic response after NAC and pCR, with MRI both over- and underestimating residual disease.[29–31] Nevertheless, findings have shown the superiority of MRI over clinical exam, mammography, and ultrasound (US), with an accuracy of about 74 %.[30–32] Therefore, suitable patients should be counseled according to their personal risk profile in conjunction with breast MRI imaging to encourage BCS when they are eligible.

At our institution, we have shown a reduction in re-excision rates for BCS. For upfront BCS, the literature supports MarginProbe as an intraoperative adjunct for assessment of lumpectomy margins. A prospective randomized trial demonstrated a significant reduction in the re-excision rates of patients who underwent BCS for non-palpable disease when MarginProbe was used.[17]

The MarginProbe device functions by using radiofrequency spectroscopy to detect differences between normal and malignant tissue.[33] Our study found that the use of MarginProbe was associated with a lower re-excision rate for BCS after NAC (6 % in the MarginProbe group vs 31 % in the group that did not use the device). This difference did not achieve statistical significance, likely due to the small number of cases. Future studies with more patients may provide the statistical power to support this difference.

The literature shows that a surgeon's ability to detect positive margins intraoperatively is limited. A variety of other techniques for intraoperative margin assessment are under investigation. Options range from routine intraoperative frozen section to an array of more novel techniques. The Cosmetic Outcome of the Breast After Lumpectomy Treatment (COBALT) study evaluated the use of intraoperative ultrasound and found that tumor-involved margins were decreased by 14 % in ultrasound-guided BCS.[34] Studies also are investigating optical coherence tomography (OCT), an optical analog to ultrasound, that uses near-infrared light to penetrate the specimen surface and detect differences in tissue morphology up to 2 mm below the surface.[35,36] Massachusetts General Hospital is investigating a protease-activated fluorescent imaging system that intraoperatively detects elevated fluorescent signaling from tumor cells in both the specimen and lumpectomy cavity.[37] The optimal method for intraoperative margin assessment will provide quick and accurate information in a non-tissue-destructive manner. Methods to increase the success of primary breast-conserving procedures and reduce re-excision rates will support BCS in the post-NAC population.

The current study had several limitations. First, it was a single-institution retrospective study with a relatively small sample. The proportion of patients that elected to undergo BCS after NAC was small (n = 61, 28.5 %), and the rationale for the choice of mastectomy for the majority of the other cases was not known. Nevertheless, the results of this study may be useful in helping surgeons provide better counsel for patients on the results of BCS after NAC and make use of intraoperative techniques to increase the rate of adequate lumpectomy margins with a single surgical procedure. Accurate intraoperative margin assessment, by reducing re-excision rates, supports the performance of BCS, both upfront and after NAC. In our hands, the MarginProbe has been an effective tool and should lead to increased use of BCS after NAC for appropriate patients.

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