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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Relationship of Breast Density and Positive Lumpectomy Margins

Jessica C. Gooch, MD[1,2], Esther Yoon, MD[3], Jennifer Chun, MPH[1], Elianna Kaplowitz, MPH[1], Talia Jubas, BA[4], Amber Guth, MD[1], Deborah Axelrod, MD[1], Richard Shapiro, MD[1], Farbod Darvishian, MD[3], and Freya Schnabel, MD[1]

[1]Department of Surgery, Division of Breast Surgery, New York University Langone Medical Center, New York; [2]Department of Surgery, Division of Surgical Oncology, University of Rochester Medical Center, Rochester; [3]Department of Pathology, New York University Langone Medical Center, New York; [4]New York University School of Medicine, New York

ABSTRACT

Background. A positive lumpectomy margin after breast-conserving surgery (BCS) is a significant predictor for ipsilateral cancer recurrence. The MarginProbe, a Food and Drug Administration (FDA)-approved device for intraoperative assessment of lumpectomy margins, is associated with a reduction in re-excision surgery. This study aimed to evaluate the relationship of mammographic breast density (MBD) and clinicopathologic characteristics with margin status in women undergoing BCS with the MarginProbe.

Methods. The institutional database was queried for patients with breast cancer who had BCS with the MarginProbe from 2013 to 2017. Clinicopathologic characteristics were collected. The study defined MBD as less dense (Breast Imaging Reporting and Data System [BI-RADS] A and B) and more dense (BI-RADS C and D). A positive margin was defined as smaller than 1 mm. Pearson Chi square and uni- and multivariate logistic regression were performed.

Results. Of 1734 patients, 341 met the study criteria. The median patient age was 63 years. The patients with higher mammographic density were younger ($p < 0.0001$) and had a lower body mass index (BMI) ($p < 0.0001$). The patients with higher MBD were more likely to present with a palpable mass ($p = 0.0360$). Of the 341 patients, 135 (39.6%) had one or more positive margins on the main specimen, and 101 (74.8%) were converted to final negative margins after the MarginProbe directed re-excisions. Positive final margins were associated with larger tumor size ($p = 0.0242$) and more advanced stage of disease at diagnosis ($p = 0.0255$).

Conclusions. In this study of patients undergoing BCS, breast density was not correlated with the likelihood of a positive margin. The presence of positive final lumpectomy margins was associated with older age and more extensive disease.

More than 250,000 cases of breast cancer are diagnosed annually in the United States, and more than 70% of the patients will elect to undergo breast-conserving surgery (BCS).[1,2] A positive margin after BCS is a significant predictor for ipsilateral cancer recurrence and need for surgical re-excision.[3,4] Typical re-excision rates range from 11 to 46% in various series.[1,3,5–8]

The need for re-excision exposes the patient to the risks of a second procedure, has the potential to worsen cosmetic outcome, and increases the cost to the health care system.[7] Thus, it is desirable to reduce re-excision rates as much as possible.

A variety of methods and devices have been devised to address this issue. Traditional approaches to margins include either routinely shaved margins of all six surfaces of the lumpectomy cavity at the time of the initial surgery or directed re-excision of margins thought to be close based on the combination of the surgeon's judgment and the

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F. Schnabel, MD
e-mail: freya.schnabel@nyumc.org

intraoperative specimen radiograph. Both of these methods have drawbacks, including the potential to miss the area of interest as well as the risk of removing too much tissue and leading to a poorer cosmetic outcome. Intraoperative frozen section and touch-prep techniques also are used but are resource and time intensive and require on-site assistance of an experienced pathologist.[3]

The MarginProbe (Dune Medical Devices, Caesarea, Israel), a Food and Drug Administration (FDA)-approved device for intraoperative assessment of lumpectomy margins, has been associated with a reduction in the need for re-excision surgery. The device uses radiofrequency (RF) spectroscopy to detect structural differences in tissue and thus can differentiate between benign and malignant tissues, which have differing physical properties.[3,6] Examination of the lumpectomy specimen at the time of surgery allows for selective resection of positive margins and reduces the need for repeat surgeries. Prior studies have documented the utility of the device for both invasive and in situ disease, with a sensitivity reaching 100% and a specificity reaching 87%.[1] The seminal paper validating use of the MarginProbe noted false-negative rates of 24.8% and 66.1% and false-positive rates of 53.6% and 16.6% in the device and control arms of the study, respectively.[1] Use of the MarginProbe has been associated with no significant increase in volume of tissue removed compared with standard excisions.[1,8]

Breast density is increasingly recognized as a risk factor for breast cancer development and postulated to be a risk factor for the need for margin re-excision, in part because the dense tissue makes the extent of the tumor more difficult to determine at the time of surgery.[5] In addition, the presence of denser tissue has been associated with more extensive disease at the time of diagnosis, which may impede the ability to achieve negative margins at the initial lumpectomy.[5]

This study aimed to evaluate the relationship of breast density and other clinicopathologic characteristics to margin status in a population of women undergoing BCS surgery with intraoperative use of the MarginProbe.

METHODS

After Institutional Review Board (IRB) approval was obtained, the institutional Breast Cancer Database (BCD) was queried for patients who underwent BCS with use of the MarginProbe device from 2013 to 2017. At our institution, use of the MarginProbe during BCS is at the discretion of the operating surgeon. Patients who underwent neoadjuvant chemotherapy were excluded, as were patients without residual disease at the final surgical excision and patients with incomplete information.

The variables of interest included breast density, patient and tumor characteristics, and the results of preoperative breast imaging. Re-excision surgery was defined as a return to the operating room for a subsequent procedure after the initial index operation to obtain clear margins. If missing, clinical and demographic variables were supplied by manual chart review.

Mammographic breast density (MBD) was defined according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) breast composition categories as follows: A (the breasts are almost entirely fatty), B (there are scattered areas of fibroglandular density), C (the breasts are heterogeneously dense, which may obscure small masses), and D (the breasts are extremely dense, which lowers the sensitivity of mammography).[9] The patients then were grouped into less dense (BI-RADS A and B) and more dense (BI-RADS C and D) for analysis purposes.

The definition of a positive margin in ductal carcinoma in situ (DCIS) changed during the study period after publication of the Society of Surgical Oncology, the American Society for Radiation Oncology, and the American Society of Clinical Oncology (SSO–ASTRO–ASCO) joint consensus guidelines for margin width in BCS for DCIS in 2016.[10] However, to maintain a consistent definition for the purposes of this study, margin positivity for both DCIS and invasive disease was defined as 1 mm or smaller. This also maintained consistency with the definition used in the MarginProbe pivotal trial.[1]

The main lumpectomy specimen was defined as the initial tissue specimen excised, targeting the index lesion. Final margin status was defined as the conclusion of the surgery, taking into consideration any additional margins excised after removal of the main specimen with direction from the MarginProbe device. If missing on the initial pathology reports, the margin status of the main specimen was supplied by supplemental slide review by the study pathologists (E.Y. and F.D.).

Intraoperatively, MarginProbe assessment is performed in accordance with the protocol outlined in the pivotal trial.[1] Briefly, the probe is applied sequentially to each of the six surfaces of the main lumpectomy specimen (lateral, superior, medial, inferior, anterior, and deep). The probe provides a series of positive and negative readings. Margins with positive readings are subjected to a shaved margin re-excision. These margins are then oriented and sent to pathology for final analysis. The additional shaved margins are not interrogated further with the MarginProbe. Statistical analyses included Pearson's Chi square tests and logistic regression.

TABLE 1 Patient characteristics by main specimen and final margin status

Variable	Main specimen margins			Final margins		
	Positive (n = 135) n (%)	Negative (n = 206) n (%)	p value	Positive (n = 51) n (%)	Negative (n = 290) n (%)	p value
Median age at diagnosis: years (range)	64 (29–84)	62.5 (36–93)	0.9401	66 (30–88)	62.5 (29–93)	0.2206
BMI (kg/m^2)			0.7391			0.2477
Underweight ($\leq$ 18)	1 (0.7)	2 (0.9)		1 (2.0)	8 (0.7)	
Normal (18–24)	57 (42.2)	76 (36.9)		22 (43.1)	111 (38.3)	
Overweight (25–29)	35 (25.9)	64 (31.1)		10 (19.6)	89 (30.7)	
Obese (30+)	42 (31.1)	64 (31.1)		18 (35.3)	88 (30.3)	
Race			0.4725			0.4713
White	94 (69.6)	157 (77.0)		42 (84.0)	209 (72.3)	
Black	14 (10.4)	14 (6.9)		2 (4.0)	26 (9.0)	
Asian	14 (10.4)	18 (8.8)		3 (6.0)	29 (10.0)	
Hispanic	13 (9.6)	15 (7.3)		3 (6.0)	25 (8.7)	
Method of presentation			0.0597			0.4137
Breast exam	40 (29.6)	37 (18.0)		16 (31.4)	61 (21)	
Mammography	87 (64.4)	158 (77.1)		33 (64.7)	212 (73.4)	
Ultrasound	6 (4.4)	8 (3.9)		2 (3.9)	12 (4.2)	
MRI	2 (1.5)	2 (1.0)		0 (0)	4 (1.4)	
Palpable mass	48 (35.6)	40 (19.5)	0.0010[a]	18 (35.3)	70 (24.2)	0.0960
Mammographic density						0.4564
BI-RADS A&B	67 (49.6)	110 (53.7)		22 (56.9)	148 (51.2)	
BI-RADS C&D	68 (50.4)	95 (46.3)	0.4669	29 (43.1)	141 (48.5)	
Stage at diagnosis			0.0247[a]			0.0122[a]
0	23 (17.3)	36 (18.2)		7 (14.0)	52 (18.5)	
1	68 (51.1)	126 (63.6)		25 (50.0)	169 (60.1)	
2	39 (29.3)	35 (17.7)		15 (30.0)	59 (21.0)	
3	3 (2.3)	1 (0.5)		2 (4.0)	1 (0.4)	
Invasive grade			0.8642			0.5219
Low	13 (12.0)	22 (14.2)		6 (14.0)	29 (13.2)	
Intermediate	61 (56.5)	87 (56.1)		21 (48.8)	127 (57.7)	
High	34 (31.5)	46 (29.7)		16 (37.2)	64 (29.1)	
Histology			0.7241			0.8920
DCIS	24 (17.8)	40 (19.4)		8 (15.7)	56 (19.3)	
IDC	89 (65.9)	141 (68.5)		36 (70.6)	194 (66.9)	
ILC	14 (10.4)	17 (8.3)		4 (7.8)	27 (9.3)	
Other invasive	8 (5.9)	8 (3.9)		3 (5.9)	13 (4.5)	
Size (cm)			< 0.0001[a]			0.0040[a]
< 1	35 (26.5)	91 (45.1)		9 (17.7)	117 (41.3)	
1–2.5	64 (48.5)	94 (46.5)		30 (58.8)	128 (45.2)	
> 2.5	33 (25.0)	17 (8.4)		12 (23.5)	38 (13.4)	
ER status			0.8534			0.6486
Positive	121 (89.6)	185 (90.2)		45 (88.2)	261 (90.3)	
Negative	14 (10.4)	20 (9.8)		6 (11.8)	28 (9.7)	
PR status			0.8682			0.4843
Positive	105 (77.8)	161 (78.5)		38 (74.5)	228 (78.9)	
Negative	30 (22.2)	44 (21.5)		13 (25.5)	61 (21.1)	

TABLE 1 continued

Variable	Main specimen margins			Final margins		
	Positive (n = 135) n (%)	Negative (n = 206) n (%)	p value	Positive (n = 51) n (%)	Negative (n = 290) n (%)	p value
HER2/neu status			0.8493			0.2908
Positive	15 (11.1)	19 (9.2)		8 (2.4)	26 (9.0)	
Negative	94 (69.6)	146 (70.9)		35 (68.6)	205 (70.7)	
Unknown	26 (19.3)	41 (19.9)		8 (15.7)	59 (20.3)	
Re-excision performed	23 (17)	10 (4.9)	0.0002[a]	31 (60.8)	2 (0.7)	< 0.0001[a]

BMI body mass index, *MRI* magnetic resonance imaging, *BI-RADS* Breast Imaging Reporting and Data System, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ER* esterogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[a]Significant at the $p = 0.05$ level

TABLE 2 Main and final margin status

	Final margins positive	Final margins negative	Total
Main specimen			
Positive margins	34	101	135
Negative margins	17	189	206
Total	51	290	341

RESULTS

The search strategy identified 341 patients with complete information who underwent BCS with use of the MarginProbe between 2013 and 2017. There were 23 patients in group A (7%), 154 patients in group B (45%), 148 patients in group C (44%), and 15 patients in group D (4%). The median age for the full cohort was 63 years (range, 29–93 years). Positive margins on the main lumpectomy specimen were associated with larger tumor size ($p < 0.0001$), more advanced stage at diagnosis ($p = 0.0247$), presence of a palpable mass ($p = 0.0010$), and greater chance of a subsequent re-excision procedure ($p = 0.0002$) (Table 1).

The patients with higher MBD were younger ($p < 0.0001$), had a lower BMI ($p < 0.0001$), and included a higher proportion of Asian women and a lower proportion of African American women ($p < 0.0001$). The patients with higher MBD were more likely to present with a palpable mass ($p = 0.0360$). No relationship was found between MBD and histology, tumor size, or the presence of a positive margin in the main or final specimen (Table 3).

Of the 341 patients, 135 (39.6%) had at least one positive margin on the main lumpectomy specimen. Intraoperative MarginProbe interrogation and directed re-excision of margins left only 51 patients with a positive final margin. Use of the MarginProbe converted 101 patients (75% of those with a positive main specimen margin) to a negative final margin at the conclusion of the surgical procedure. Interestingly, additional tissue was removed from the lumpectomy cavity in patients whose the main specimen was found to have negative margins, resulting in positive final margins for 17 patients (Table 2). The distribution of MBD did not differ significantly among the 51 patients with a positive final margin ($p = 0.4564$) (Table 3).

Positive final margins were associated with larger tumor size ($p = 0.0023$) and more advanced stage of disease at diagnosis ($p = 0.0122$) (Table 1). When logistic regression was performed to identify variables associated with positive main specimen margin status, the only significant finding was tumor size larger than 2.5 cm on both the uni- and multivariate models ($p = 0.0024$) (Table 4). When logistic regression of final margin status was performed, the most significant finding was that larger tumor size ($p = 0.0242$) and higher tumor stage ($p = 0.0255$) were associated with positive final margin status (Table 4). The main and final margin positive statuses also were analyzed on the basis of whether the tumor was palpable or not, and no relationship between MBD and palpability was noted (Table 5).

DISCUSSION

In our study of patients undergoing BCS, MBD was not correlated with the likelihood of a positive margin after use of the MarginProbe. This is encouraging because it reinforces the effectiveness of this device for any woman undergoing lumpectomy regardless of tumor or patient

TABLE 3 Selected variables by BI-RADS breast density

Variable	BI-RADS A&B (n = 177) n (%)	BI-RADS C&D (n = 163) n (%)	p value
Median age at diagnosis: years (range)	65 (38–88)	59 (29–93)	< 0.0001[a]
Race			< 0.0001[a]
White	135 (76.7)	116 (71.6)	
Black	22 (12.5)	6 (3.7)	
Asian	7 (4.0)	25 (15.4)	
Hispanic	12 (6.9)	15 (9.3)	
BMI (kg/m^2)			< 0.0001[a]
Underweight (≤ 18)	1 (0.56)	2 (1.23)	
Normal (18–24)	49 (27.7)	84 (51.53)	
Overweight (25–29)	47 (26.6)	52 (31.9)	
Obese (30+)	80 (45.2)	25 (15.34)	
Palpable mass	37 (20.9)	50 (30.86)	0.0360[a]
Histology			0.1853
DCIS	27 (15.25)	37 (22.7)	
IDC	124 (70.0)	105 (64.4)	
ILC	15 (8.5)	16 (9.8)	
Other invasive	11 (6.2)	5 (3.1)	
Size (cm)			0.8298
< 1	68 (39.3)	58 (36.3)	
1–2.5	79 (45.7)	78 (48.7)	
> 2.5	26 (15.0)	24 (15.0)	
Main specimen margins			0.4669
Positive	67 (37.9)	68 (41.7)	
Negative	110 (62.1)	95 (58.3)	
Final margins			0.4564
Positive	29 (16.4)	22 (13.5)	
Negative	148 (83.6)	141 (86.5)	
Re-excision performed	20 (11.3)	13 (8.0)	0.3010

BI-RADS Breast Imaging Reporting and Data System, *BMI* body mass index, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma

[a]Significant at the p = 0.05 level

characteristics. Use of the MarginProbe resulted in a 62% rate for conversion of positive main specimen margins to negative final margins after directed re-excision. This real-world use of the device has resulted in lumpectomy margin salvage rates exceeding those of previously published studies.[1,6–8]

The patients left with positive margins after directed cavity shavings showed no significant difference in distribution of MBD. In a previously published abstract, MBD was suggested to be an independent risk factor for positive margins.[11] However, with the addition of the MarginProbe in the current study, the effect of MBD seems to have been abrogated. In a second abstract by Police et al.,[12] increasing MBD was associated with an increasing level of patient benefit from use of the MarginProbe to achieve clear margins.

Positive final margins were associated with larger tumor size and more advanced stage of disease at diagnosis. This is in keeping with previous literature, which has noted factors such as increased proportion of DCIS, tumor size, multifocality, and nodal status as variables that may increase the risk of positive resection margins.[5] Our study showed no relationship of invasive and in situ histology types to risk of positive final margins, suggesting that the MarginProbe also performed well in this population. We also noted that in 17 patients whose surgeon elected to take additional tissue shavings despite negative Margin Probe readings, the final margins were positive for disease. This also was seen in the pivotal trial and may reflect the frequency of noncontiguous disease discovered in the breast.[1]

TABLE 4 Logistic regression modeling on positive main specimen and final margin status

Variable	Univariate OR (95% CI)	*p* value	Multivariate[a] OR (95% CI)	*p* value
Main specimen margins				
Age	1.00 (0.98–1.01)	0.6604	1.00 (0.97–1.02)	0.6253
Race				
White	Ref	Ref	Ref	Ref
Black	1.67 (0.76–3.66)	0.1995	1.60 (0.67–3.78)	0.2922
Asian	1.30 (0.62–2.73)	0.4905	1.33 (0.58–3.01)	0.5121
Hispanic	1.45 (0.66–3.18)	0.3561	1.61 (0.69–3.75)	0.2729
Mammographic density				
BI-RADS A&B	Ref	Ref	Ref	Ref
BI-RADS C&D	1.18 (0.76–1.82)	0.4670	1.24 (0.74–2.08)	0.4225
BMI (kg/m^2)				
Underweight ($\leq$ 18)	0.67 (0.06–7.53)	0.7431	0.83 (0.07–9.82)	0.8852
Normal (18–24)	Ref	Ref	Ref	Ref
Overweight (25–29)	0.73 (0.43–1.25)	0.2485	0.72 (0.40–1.29)	0.2718
Obese (30+)	0.88 (0.52–1.47)	0.6141	0.87 (0.48–1.60)	0.6588
Stage				
0	Ref	Ref	Ref	Ref
1	0.85 (0.46–1.54)	0.5818	1.023 (0.53–1.99)	0.9365
2	1.74 (0.87–3.49)	0.1163	1.33 (0.60–2.95)	0.4796
3	4.69 (0.36–47.88)	0.1920	4.68 (0.32–51.21)	0.2067
Size (cm)				
< 1	Ref	Ref	Ref	Ref
1–2.5	1.77 (1.07–2.93)	0.026[b]	1.59 (0.92–2.75)	0.0962
> 2.5	5.05 (2.50–10.20)	< 0.0001[b]	3.6 (1.58–8.32)	0.0024[b]
Final margins				
Age	1.02 (1.00–1.04)	0.2486	1.01 (0.98–1.04)	0.6314
Race				
White	Ref	Ref	Ref	Ref
Black	0.38 (0.09–1.68)	0.2023	0.47 (0.10–2.14)	0.3253
Asian	0.52 (0.15–1.77)	0.2916	0.50 (0.13–1.91)	0.3076
Hispanic	0.60 (0.17–2.07)	0.4161	0.66 (0.18–2.39)	0.5271
Mammographic density				
BI-RADS A&B	Ref	Ref	Ref	Ref
BI-RADS C&D	0.80 (0.44–1.45)	0.4570	0.83 (0.41–1.69)	0.6033
BMI (kg/m^2)				
Underweight ($\leq$ 18)	2.52 (0.22–29.05)	0.458	2.35 (0.19–29.16)	0.5051
Normal (18–24)	Ref	Ref	Ref	Ref
Overweight (25–29)	0.57 (0.26–1.26)	0.1632	0.41 (0.16–1.03)	0.0571
Obese (30+)	1.03 (0.52–2.04)	0.9279	0.83 (0.38–1.83)	0.6383
Stage				
0	Ref	Ref	Ref	Ref
1	1.10 (0.45–2.69)	0.8362	0.88 (0.33–2.35)	0.8037
2	1.89 (0.72–5.00)	0.1996	1.12 (0.40–3.25)	0.8326
3	22.29 (2.03–244.87)	0.0111[b]	19.97 (1.44–276.47)	0.0255[b]
Size (cm)				
< 1	Ref	Ref	Ref	Ref
1–2.5	3.05 (1.39–6.69)	0.0055[b]	2.64 (1.14–6.15)	0.0242[b]

TABLE 4 continued

Variable	Univariate OR (95% CI)	*p* value	Multivariate[a] OR (95% CI)	*p* value
> 2.5	4.11 (1.61–10.49)	0.0032[b]	2.90 (0.94–9.02)	0.0651

OR odds ratio, *CI* confidence interval, *BI-RADS* Breast Imaging Reporting and Data System, *BMI* body mass index

[a]Adjusted for age, race, mammographic density, stage, size, and BMI

[b]Significant at the $p = 0.05$ level

TABLE 5 Logistic regression of main specimen and final margin status (palpable vs. nonpalpable finding)

Variable	Palpable finding				Nonpalpable finding			
	Univariate OR (95% CI)	*p* value	Multivariate[a] OR (95% CI)	*p* value	Univariate OR (95% CI)	*p* value	Multivariate[a] OR (95% CI)	*p* value
Main specimen margin status								
Mammographic density								
BI-RADS A&B	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
BI-RADS C&D	1.58 (0.67–3.73)	0.2937	1.52 (0.42–5.53)	0.5239	0.95 (0.57–1.61)	0.8590	1.14 (0.62–2.09)	0.6725
Final specimen margin status								
Mammographic density								
BI-RADS A&B	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
BI-RADS C&D	0.68 (0.24–1.94)	0.4729	0.95 (0.22–4.02)	0.9422	0.79 (0.37–1.66)	0.5318	0.79 (0.33–1.89)	0.5950

OR odds ratio, *CI* confidence interval, *BI-RADS* Breast Imaging Reporting and Data System

[a]Adjusted for age, race, mammographic density, stage, size, and body mass index (BMI)

CONCLUSION

The current study demonstrated the utility of the MarginProbe device in a heterogeneous cohort of patients from our institution with both invasive and in situ disease. Patients who desire breast conservation benefit from addition of the MarginProbe device, which reduces the potential need for additional surgical procedures to achieve optimal margins. It is well established that a proportion of patients with positive margins after BCS opt to undergo completion mastectomy. Use of the MarginProbe supports the successful performance of a breast-conserving approach for women with breast cancer and may help to alleviate the burden of this disease for both the patient and the health care system.

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