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A novel modality for intraoperative margin assessment and its impact on re-excision rates in breast conserving surgery

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ABSTRACT

Background: A single center retrospective chart review was performed examining the ability of a novel radiofrequency probe (Margin Probe; Dune Medical Devices, Caesarea, Israel) for intraoperative margin assessment to reduce the number of reexcisions in breast-conserving surgery.
Methods: Reexcision rates were evaluated in one-hundred and twenty consecutive patients before and after the institution of the device. Utility of the device was evaluated by comparing intraoperative feedback with postoperative pathology reports.
Results: Two hundred and forty patient subjects were reviewed in total. There was a significant decrease in the re-lumpectomy rate (50%, $p = 0.039$) in the device group without increasing the total volume of tissue resected.
Conclusions: The use of the MarginProbe device as an adjunct to the standard of care resulted in reduction of positive margins after lumpectomy and the number of re-excisions, significantly improving outcomes in breast-conserving surgery at our institution.

Breast conserving-surgery is the standard of care for patients with early stage breast cancer. Current guidelines state that no tumor should extend to the margin of resection. The association between positive margins after lumpectomy and ipsilateral recurrence is well established.[1,2] If clear margins are not obtained, re-excision is the standard of care even in the setting of post-operative radiation.[3,4]

Despite advancement of radiologic and localization technologies the problem of positive margins has not been eliminated. Re-excision rates vary substantially however the recently reported average across multiple institutions was 25%.[5,6] A device (Margin Probe; Dune Medical Devices, Caesarea, Israel) that uses radio-frequency spectroscopy to algorithmically analyze tissues and differentiate between normal and malignant tissue has been approved for use in the United States for several years. It provides a solution for the detection malignant cells that cannot be seen radiographically or palpated.

The MarginProbe is a handheld device that gives immediate feedback allowing the surgeon to make intraoperative decisions to take additional shavings and achieve clear margins. It works by transmitting radiofrequency signals which are reflected back providing a measure of the impedance of the tissue. The reflected signals are analyzed based on algorithms and correlate with a "positive" or "negative" margin which is visualized on a console. The reported sensitivity and specificity is 70–100% and 70–87% respectfully.[7] Several multi-center, prospective, randomized controlled studies revealed encouraging results for both invasive and ductal carcinoma in situ.[8–10]

The purpose of this study was to investigate the utility of this device in a single institution community hospital setting. The re-excision rate before and after use of the device was calculated and the pathological results analyzed against the intraoperative device feedback and decision making. Other variables assessed were the volume of the specimen and the number of additional shavings taken.

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1. Methods

1.1. Study design

After permission was obtained from our institutional review board, data was prospectively collected and a retrospective chart review was performed for patients who underwent breast-conserving surgery at our institution. An A prior power analysis was preformed suggesting the requirement of 240 subjects to achieve a statistical difference in re-excision rates with 120 subjects in each group. A total of 240 consecutive cases were therefore evaluated. All patients were treated with breast-conserving surgery at a single institution by one of two surgeons. Use of the device was discussed with the patient in the clinic preoperatively and signed a consent obtained. The subjects are categorized into two groups. The first group consisting of patients who underwent surgery from October 2014 to September 2015. Margin assessment for this group consisted of the standard of care (SOC). The second group consisted of patients who underwent surgery from October 2015 to October 2016. Margin assessment for this group consisted of the SOC with the adjunctive use of the Marginprobe device. Inclusion criteria included patients over 18 years of age with invasive and ductal carcinoma in situ diagnosed with core needle biopsy. Patients with prior radiotherapy or neoadjuvant chemotherapy were excluded.

1.2. Standard of care

The standard of care consists of use of a localization marker for non-palpable lesions, orientation with a silk suture, intraoperative specimen x-ray, and then clinician specimen palpation and inspection of the cavity. Based on this feedback the surgeon would excise additional shavings.

1.3. Standard of care with adjunctive use of the device

The surgeon excised the specimen in the usual manner and first evaluated the adequacy of resection using with the standard of care as described above. Then the specimen was oriented and then marked with a skin marker to delineate six surfaces. The probe was then used to evaluate each surface. The process takes around 5–20 min depending on the number of shavings taken. The probe is only used on the specimen and is not meant for intracorporeal use. The surgeon would take an additional margin shaving for each "positive" reading. The standard of care was never withheld due to a "negative" reading by the device.

1.4. Pathology and tissue volumes

Specimens were then sent for permanent pathological analysis. A positive margin was considered disease extending to the margin of resection. The decision to re-operate was determined by our institutional treatment paradigms which take into consideration the surgeon and oncologists recommendations as well as patient preferences. Intraoperative decision to take additional shavings based on the standard of care and feedback from the device was then compared to pathological data. For each surface the margin status and distance was noted. Tissue dimensions were used to calculate the specimen volume using the Ellipsoid formula: $\pi/6 \times L \times W \times D$.

1.5. Data analysis

For all statistical analysis, groups were defined by patient treatment status as SOC or SOC plus device. Group comparisons involving categorical outcome variables were conducted using chi-square tests, whereas those involving numeric outcomes were conducted using independent samples t-tests. All statistical analyses were conducted using SAS 9.4.

2. Results

A total of 240 cases were reviewed with 120 in each group. Table 1 addresses patient demographics and tumor characteristics. Although there were some differences between the two groups none of them were found to be statistically significant (all p-values > 0.05).

The course for all 240 patients is outlined in Fig. 1 and results summarized in Table 2. After excision of the main specimen a total of 25 patients had positive margins in the SOC group compared with 35 in the device group (Fig. 1, phase I). After shavings were taken significantly more margins were cleared in the device group than the SOC group (Fig. 1, phase II). After removal of the main specimen a total of 95 patients had negative margins in the SOC group compared with 85 in the device group (Fig. 1, phase I). Of those with negative main specimen margins 3 patients in the SOC group and 10 patients in the device group were found to have malignancy in the shavings (Fig. 1, phase III). All patients with positive margins not cleared by the main specimen or margin shavings underwent a reexcision procedure. There were 18 relumpectomies (15%) in the SOC group and 7 (5.8%) in the device group (Fig. 1, phase IV) ($p = 0.20$). The conversion to mastectomies was the same in the two groups 4 (3.3%). The total reexcision rate was 18.2% in the SOC group compared with 9.2% in the device group ($p = 0.039$).

Table 2 also demonstrates the volume of the main specimen was smaller in the device group by 9.2 cc ($p = 0.32$). The number of shavings taken did increase significantly from 0.5 shavings per case to 2.0 shavings per case (p=<0.001). This resulted in similar total volumes on average between the groups. The total volume was not significantly changed ($p = 0.974$).

3. Discussion

This study found that the adjunctive use of the MarginProbe in breast-conserving surgery lead to a decrease in positive margins

Table 1
Descriptive statistics for device and control groups.

Characteristic	SOC (N = 120)	SOC + Device (N = 120)
Age, years, mean (SD)	65.0 (11.6)	65.1 (9.4)
Race, *n* (%)		
African American	20 (16.7%)	12 (10.0%)
White	99 (82.5%)	104 (86.7%)
Other	1 (0.8%)	4 (3.3%)
BMI, kg/m^2, mean (SD)	30.3 (7.4)	30.4 (6.7)
Diagnosis, *n* (%)		
Invasive ductal	90 (75.0%)	94 (78.3%)
Invasive lobular	13 (10.8%)	10 (8.3%)
Mixed invasive	0 (0.0%)	3 (2.5%)
Ductal carcinoma-in situ	15 (12.5%)	12 (10%)
Receptor Status, *n* (%)		
ER positive	103 (85.8%)	101 (84.2%)
PR positive	91 (75.8%)	91 (75.8%)
HER2 positive (invasive only)	17 (16.0%)	11 (10.0%)
HER2 triple negative	11 (9.2%)	14 (11.7%)
Preoperative Imaging, *n* (%)		
Mammogram	120 (100.0%)	120 (100.0%)
MRI	21 (17.5%)	34 (28.3%)
Tumor Size, cm, mean (SD)	1.4 (1.0)	1.5 (1.1)

SOC standard of care, SD standard deviation, BMI body mass index, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, MRI magnetic resonance imaging.

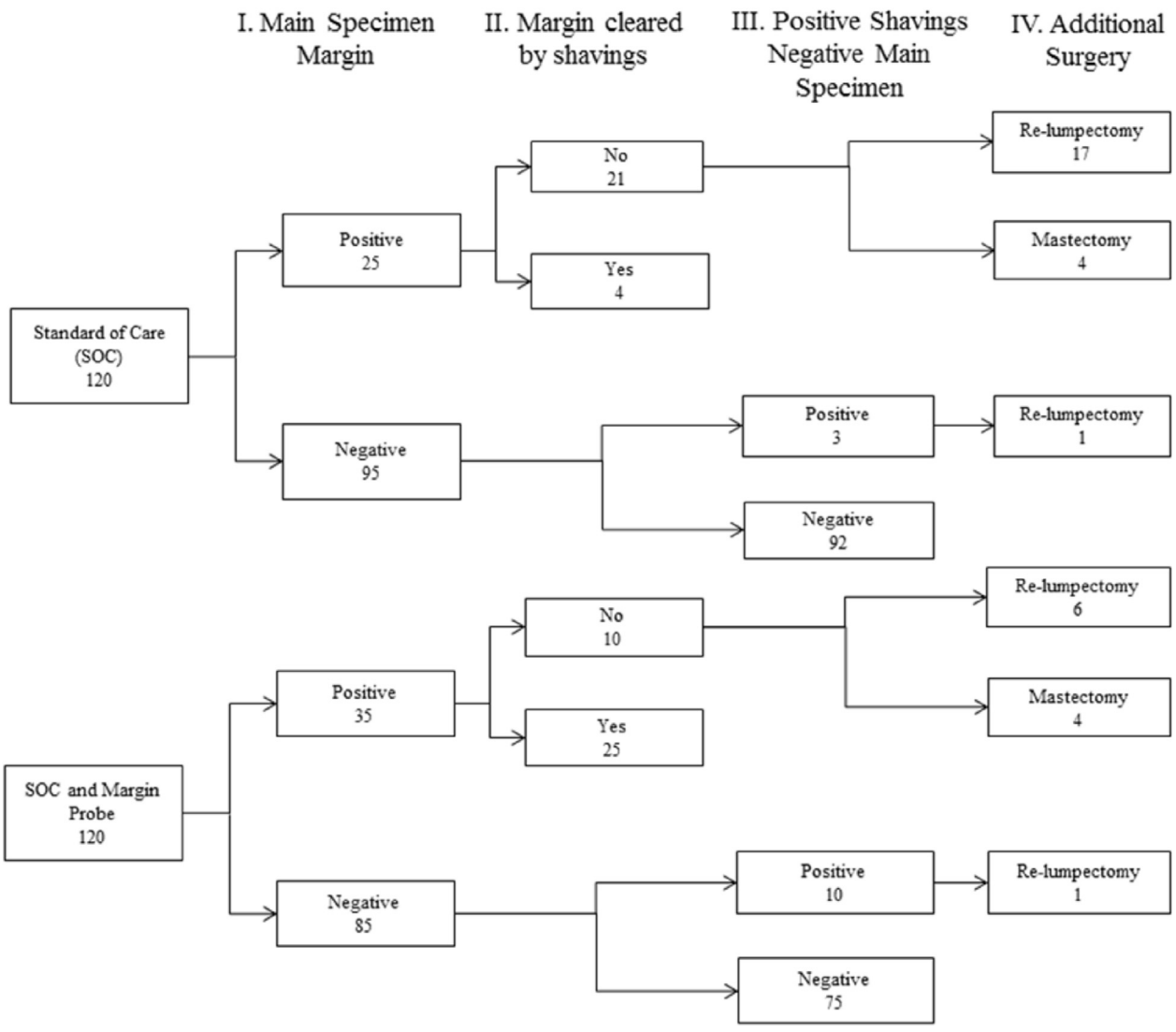

Fig. 1. Margin outcomes for all patients.

($p = 0.039$). This was achieved with the addition of only 1.5 margin shavings per case. The main specimen volume was smaller in the device group which may have led to a higher number of positive margins on the main specimen. After shavings were taken the total volume excised was similar between the two groups ($p = 0.974$).

The most significant finding was that re-lumpectomies were decreased by 61% in the device group. In the device group 71% of positive margins on the main specimen were cleared by shavings compared to 16% in the standard of care group.

In some cases, malignant cells were detected in the shavings after the main specimen was determined to have negative margins. These "skip lesions" were identified in both groups, but were more

Table 2
Outcome comparison between SOC and SOC + device groups.

Variable	SOC (N = 120)	SOC + Device (N = 120)	Difference	*p*
Positive margins after initial surgery, *n* (%)	22 (18.3%)	11 (9.2%)	50.0%	0.039
Additional Surgery, *n* (%)				
Due to main specimen positive margin	21 (17.5%)	10 (8.3%)	52.3%	0.034
Due to shavings positive margin	1 (0.8%)	1 (0.8%)	0.0%	0.999
Additional surgery Type, *n* (%)				
Re-lumpectomy	18 (15.0%)	7 (5.8%)	61.1%	0.020
Mastectomy	4 (3.3%)	4 (3.3%)	0.0%	0.999
Number of shavings, mean (SD)	0.5 (0.6)	2.0 (1.4)	1.5	<0.001
Volume of tissue removed, ml, mean (SD)				
Main specimen	50.8 (37.8)	41.6 (27.3)	−9.2	0.032
Shavings	3.4 (7.4)	11.9 (12.7)	8.5	<0.001
Total	53.6 (38.5)	53.5 (32.0)	−0.1	0.974

SOC standard of care, SD standard deviation; *p*-values reflect chi-square tests all categorical outcome variables and independent sample t-tests for all numeric variables.

frequent in the device group. In the standard of care group three skip lesions were identified and one patient required a re-lumpectomy because tumor extended to the new margin. In the device group ten skip lesions were identified and again only one patient required a re-lumpectomy. This suggests utility of the MarginProbe in detecting extent of disease not detected by pathological analysis.

The rate of conversion to mastectomy was consistent in both groups. The small number of patients did not lend this group to statistical analysis however the observation was made that the patients who were converted to mastectomies had larger tumors and lobular histology. In several shavings the MarginProbe correctly detected the positive margin; however the tumor spread to the edge of the additional shaving. This group represents a subset of patients who strongly desire a lumpectomy but are be considered borderline in meeting criteria for breast conservation.

Obtaining negative margins continues to be a challenge for surgeons today. Intraoperative margin assessment is a dynamic field that is continuing to grow with new technology and new application of established technology. It was not the purpose of this study to directly compare the use of the probe to other forms of intraoperative margin assessment but to describe our experience with the MarginProbe device. However, some points of comparison can be discussed and proposed as topics of future study.

Some institutions have achieved excellent outcomes lowering the re-excision rate to under 4% with the application of frozen section analysis.[12] Although some non-tertiary facilities have successfully applied frozen section to their practice of margin assessment it requires a robust pathology department and resources and which may not be practical for all. While older studies showed no difference in reexcision rates when applying full cavity shavings a recent high powered randomized prospective study has supported the utility of routine cavity shaving.[11,13] Some points of comparison to consider are full cavity shaving requires 6 routing margin shavings while in this study 2.5 shavings were taken on average without increasing the total excised volume. This could have implications for operative time, volume of the specimen and cosmetic outcome, and increased work burden for the pathology department. Intraoperative use of ultrasound while it is cost effective and shown utility in decreasing reexcision rates has limitations when attempting to evaluate DCIS and lesions less likely to be visualized with this technology.[14,15] The previous barrier to comparison of intraoperative margin assessment methods has been the paucity of high power studies directed at evaluating the individual techniques.[15] As more quality studies have been published it would be beneficial to review and compare the different techniques.

No cost analysis was performed for this study. Considering the significant decrease in reexcisions which save not only costly reoperations but also stress for the patient and delay in adjuvant therapies we have determined the cost of the device is worthwhile and we continue to use it routinely in practice. A cost analysis will be performed as we collect more data which could provide insight not only in comparison to our previous standard of care but other margin assessment techniques.

4. Conclusion

This study showed the utility of the MarginProbe in detecting positive margins intraoperatively and allowed us to significantly improve the quality of care provided at our institution by decreasing our re-excision rate without increasing the total volume of excision. Real-time assessment of margin status lowers the necessity for re-operations improving oncologic and aesthetic outcomes, preventing delay in adjuvant treatment, and relieving additional stress for the patient. This benefits not only the patient but the health system as a whole.

Conflict of interest

None.

Disclosure

There is no disclosure of any commercial interest or financial support.

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