MarginProbe Radiofrequency Spectroscopy with Intraoperative Pathology Assessment: Synergistic, or Redundant?

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Abstract

Background:

Published MarginProbe (MP) data reports $\geq 50\%$ reduction in positive lumpectomy margins. Standard of care (SOC) in our facility uses intraoperative pathologic gross assessment for invasive cancer. We sought to determine if adjunctive use of MP would provide incremental value over gross assessment alone.

Methods:

This is a single-site, single-surgeon retrospective chart review of 86 consecutive lumpectomies with MP from 12/2018–11/2019. Margins were considered positive using SSO/ASTRO “no ink on tumor” consensus guideline for invasive cancer, and SSO/ASTRO/ASCO consensus guideline of 2mm or greater for pure DCIS. Significance was measured using Fisher’s exact two-tailed test.

Results:

76 patients (7 bilateral, 3 unilateral/multi-focal) yielded 86 lumpectomies for inclusion. Mean age was 69.8 and mean tumor size was 1.09cm. 68 invasive cancers were assessed using adjunct MP and gross assessment while 18 DCIS cases utilized MP only. Among all cases, gross assessment alone reduced positive margins from 27.9% to 19.8% (29.2% relative reduction, $p=0.28$). Utilizing both modalities in tandem, positive margins decreased from 27.9% to 9.3% (66.7% relative reduction, $p<0.01$) representing a 46.9% relative reduction versus gross assessment alone.

Main specimen tissue volume was 27.1cc. After gross assessment and MarginProbe evaluation, there was additional excised volume that averaged 2.9 cc. Total averaged excised volume was 33 cc. This compares to the reported 40-60 cc average in multiple studies.

Conclusion:

Adjunctive use of MP with gross assessment maximizes reduction of positive margins during breast conserving surgery while minimizing impact on specimen volumes.

Highlights

Neither this manuscript nor any part of its content is currently under consideration or published in another journal. None of the above authors have any commercial interest in the subject of the study nor a source of any financial or material support.

Synopsis

This study demonstrates the benefits of adjunctive MarginProbe use for intraoperative margin assessment in conjunction with the standard of care during breast conserving surgery. MarginProbe

optimizes reduction of positive margins while minimizing impact on specimen volumes. Use of MarginProbe with intraoperative gross pathologic margin assessment synergistically minimizes positive margin rates in invasive breast cancer and DCIS in the final pathological specimen.

Background

Breast cancer is one of the most common cancers diagnosed in the United States today. Approximately 1 in 8 (12%) women will be diagnosed with invasive breast cancer in her lifetime and 276,000 new cases of breast cancer are expected to be diagnosed in 2020 alone¹. The overall disease-free survival for women with invasive breast cancer has been shown to be equivalent when treated with breast conserving surgery (BCS) in combination with adjuvant radiation versus mastectomy².

The standard of care (SOC) at our institution for BCS includes the use of radioactive seed localization, lumpectomy, specimen X-ray and for invasive cancer only, gross pathologic assessment (GA). Additionally, this study routinely uses the MarginProbe device (Dune Medical Devices Ltd, Caesarea, Israel).

Local recurrence has been shown to be directly related to positive and indeterminate specimen margins obtained at the time of BCS³. The standards used for negative margins as per the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO) and Society of Surgical Oncology were “no ink on tumor” for invasive cancer and 2 mm or greater from tumor for DCIS.

Positive margins have been shown to have a relative risk 15 times higher for ipsilateral breast tumor recurrence when compared to those with negative margins^{4–6}. Reportedly, 11–46% of patients are required to undergo a second operation for re-excision of margins. Multiple operations have risks such as increased infection rates, increased medical costs, increased patient anxiety and poor cosmesis⁷. Therefore, it is crucial to ensure negative margins at the index operation. Microscopic marginal cancer involvement necessitates adjunct techniques to confirm total tumor excision. Current standard of care for BCS at our institution includes radioactive seed localization, lumpectomy, intraoperative specimen X-ray, and (for invasive cancer only) intraoperative gross pathologic assessment (GA) of margins.

The MarginProbe is a handheld device that was developed as an adjunct to the current standard of care for the assessment of lumpectomy margins. Using radiofrequency spectroscopy, the device measures the electrical properties such as cellular connectivity, membrane potential and vascularity that differs between normal breast tissue and malignant tissue⁸. This device has been found to be accurate within 1 mm of the margin surface⁶. In a prospective, randomized, controlled multicenter study in which 300 patients were enrolled, the MarginProbe was found to have significantly reduced the re-excision rate by 56%⁹.

The aim of the current study is to assess and compare the predictive value of using the MarginProbe as an adjunct to the current standard of care.

Methods

This study is a retrospective chart review utilizing records from 12/2018–11/2019 from a single site, single surgeon database. No identifiable information was recorded. Inclusion criteria were adult patients over 18 years of age with biopsy-proven DCIS or invasive breast cancer that underwent BCS and had MarginProbe used. Patients with multifocal and bilateral disease were included in the study. Each lumpectomy specimen was assessed independently. Patient sex was neither an inclusion or exclusion criterion.

All patients underwent preoperative localization employing radioactive seed placement. They then underwent a lumpectomy in which all six surfaces of the tissue were delineated (superior, inferior, medial, lateral, anterior and posterior). MarginProbe was then used to assess all six surfaces of the lumpectomy specimen. Additional tissue was excised corresponding to the positive surface. The lumpectomy cavity was not assessed with MarginProbe. The specimens were then assessed using our institutional standards: intra-operative specimen X-Ray followed by intraoperative gross pathologic assessment by in-house pathologists.

The primary outcomes evaluated with this study were the main specimen positive margin rate reported on final pathology and specimen volume. A main specimen with positive margins was identified as having at least one positive margin (prior to further margin excision as directed by GA or MarginProbe assessment). This was compared against the positive margin rate of the final specimen (including additionally excised margins) after GA and MarginProbe assessment.

Statistical significance was performed at $p = 0.05$ and values were compared by Fisher's exact two-tailed test. No missing data were cited.

Results

A total of 76 patients yielded 86 lumpectomies for inclusion. Patient characteristics are listed in Table 1. Sixty-eight invasive cancer specimens were assessed using adjunct MarginProbe and gross assessment while 18 DCIS cases utilized MarginProbe only.

Table 1
Patient Characteristics

Total patients	76
Unilateral, unifocal disease	66 (87%)
Unilateral, multifocal disease	3 (4%)
Bilateral disease	7 (9%)
Invasive cancer	68 (79%)
DCIS	18 (21%)
Mean age $\pm \sigma$ (years)	69.8 $\pm$ 11.4
Mean Tumor size $\pm \sigma$ (cm)	1.09 $\pm$ 0.7
DCIS = Ductal Carcinoma in Situ	

The mean specimen characteristics are listed in Table 2. The average main specimen volume was 27.1 cc. After gross assessment and MarginProbe evaluation, there was additional excised volume that averaged 2.9 cc. Total averaged excised volume was 33 cc. This compares to the reported 40–60 cc average in multiple studies^{5,10,11}.

Table 2
Mean Specimen Characteristics

Main Specimen Volume	27.1 cc
Additional Volume per Shave	2.9 cc
Total Excision Volume	33 cc

Table 3 depicts the reported excision volumes and re-excision rate per tumor size. The mean tumor size in this study was 1.09 cm, yielding a total re-excision rate of approximately 14%. Of these cases, half were due to factors other than false negatives. This includes acting on surgical judgement that was discordant with positive MarginProbe results, or finding extensive DCIS in final pathology of additional shaves despite negative margins of the original specimen.

Table 3
Reported Excision Volumes and Re-Excision Rates per Tumor Size

Study	MarginProbe Used	Mean Tumor Size	Re-excision Rate	Mean Volume
Qafiti et al	Yes	1.09 cm	14%*	33.0 cc
Blohmer et al ⁵	-	-	-	-
- MarginProbe Arm	Yes	1–2 cm**	14.6%	41.3 cc
- Control Arm	No	1–2 cm**	33.7%	-
Schnabel et al ⁸	-	-	-	-
- MarginProbe Arm	Yes	1.7 cm	19.8%	87.5 cc
- Control Arm	No	1.6 cm	25.8%	71.7 cc
Allweis et al ⁹	-	-	-	-
- MarginProbe Arm	Yes	1.8 cm	5.6%	107 cc
- Control Arm	No	1.7 cm	12.7%	94 cc
Rivera et al ⁶	-	-	-	87.5 cc
- MarginProbe Arm (No GA)	Yes	-	14.1%	71.9 cc
- Control Arm (No GA)	No	-	29.9%	
*7% required re-excision due to at least one false negative margin; **Median tumor size; GA = intraoperative gross assessment				

Table 4 lists the positive margin rates of the initially excised specimen and compares this to the positive margin rates in the final pathology after the SOC and MarginProbe (MP) were utilized. Among all cases, gross assessment alone reduced positive margins from 27.9–19.8% (29.2% relative reduction, $p = 0.28$). Utilizing both gross assessment and MarginProbe, positive margins decreased from 27.9–9.3% (66.7% relative reduction, $p < 0.01$) representing a 46.9% relative reduction versus gross assessment alone. Similar trends were noted in subgroup analysis of invasive cancers. MarginProbe (MP) demonstrated significant reduction in PMR compared to main specimen when used as adjunct to SOC in all cases and in invasive cancer. Although positive margins decreased by 66.7% in the DCIS subgroup, a larger dataset would be needed to reach statistical significance.

Table 4
Positive Margin Rates and Relative Reduction Rates

All Lumpectomies (N = 86)	PMR (%)	RR (%)	p
Main Specimen	27.9	-	-
SOC	19.8	29.2	0.28
SOC + MP	9.3	66.7	< 0.01*
Invasive Cancer (N = 68)	PMR (%)	RR (%)	p
Main Specimen	22.1	-	-
SOC	11.8	46.7	0.17
SOC + MP	7.4	66.7	0.03*
DCIS (N = 16)	PMR (%)	RR (%)	p
Main Specimen	50	-	-
SOC	50	-	-
SOC + MP	16.7	66.7	0.08
SOC: Standard of Care; PMR: Positive Margin Rate; RR = Relative Reduction compared to Main Specimen PMR; (*) = statistically significant (p<0.05); PPV = Positive Predictive Value; NPV = Negative Predictive Value			

Of the 68 cases of invasive cancer, 14 of the lumpectomies were identified to have at least 1 positive margin on final pathology. Ten of the 14 (71%) were identified intra-operatively utilizing gross assessment and MarginProbe. Three of the 14 were identified only by MarginProbe intraoperatively, 2 were identified only by gross assessment intraoperatively, and 5 were identified by both MarginProbe and gross assessment (Fig. 1).

The performance of each margin assessment modality in invasive cancer was evaluated. The MarginProbe sensitivity was found to be 63.6%, compared to gross assessment being 40.9%. The negative predictive value of MarginProbe was 97.2% compared to gross assessment at 96.3%. The increase in sensitivity of positive margins applying MarginProbe came at the cost of a reduction in specificity; MarginProbe 68% and gross assessment 81.5%. Positive predictive value of MarginProbe found to be 9.7% and 10.6% with gross assessment. This is outlined in Table 5.

Table 5
MarginProbe Statistical Characteristics

(N = 68)	MP	GA
Sensitivity	63.6%	40.9%
Specificity	68.0%	81.5%
PPV	9.7%	10.6%
NPV	97.2%	96.3%
MP = MarginProbe; GA = Gross Assessment; PPV = Positive Predictive Value; NPV = Negative Predictive Value		

Table 6
Cost and Benefit of MarginProbe when Used Routinely with Standard of Care in Invasive Cancer Cases

(n = 68)	With MarginProbe	Without MarginProbe
Added Per-Case Cost (x 68 cases)	\$68,000	\$0
Cases with Postoperative Residual Cancer	4 (5.9%)	7 (10.3%)
Cases with Negative Margins	64 (94.1%)	61 (89.7%)
Average cost of re-excisions (\$4792)¹⁵ x Residual Cancer Cases	\$19,168	\$33,544
Cumulative Cost	\$87,168	\$33,554

Discussion

Breast conserving surgery is an established treatment approach to invasive breast cancer and DCIS. When used with adjuvant radiation, it has shown to have equivalent long-term outcomes with total mastectomy. Positive margins are associated with ipsilateral breast tumor recurrence. Therefore, every effort should be made to obtain negative margins. Current standard of care for intraoperative assessment of margins at our institution includes radioactive seed localization, specimen X-ray and gross pathological assessment of margins for invasive cancer by in-house pathologists. Unfortunately, up to 40% of patients must undergo re-excision to obtain negative margins⁴⁻⁶. Our study demonstrates that using MarginProbe as an adjunct for intraoperative assessment of specimen margins results in a statistically significant reduction in positive margin rates during breast conserving surgery for invasive cancer. Furthermore, we characterize and compare the accuracy of both gross assessment and MarginProbe at a single institution. MarginProbe similarly reduces positive margins when used routinely in DCIS, however, a larger dataset would be required to reach statistical significance for this subset of patients.

Addition of the MarginProbe for breast conserving surgery was intended to increase the sensitivity of detecting positive margins. In our patients, MarginProbe was more sensitive than gross pathologic assessment. An additional margin was taken when either demonstrated a positive margin. Forty-two percent more true positive invasive cancer margins were identified with both GA and MarginProbe used in tandem than with GA use alone.

Moreover, the use of the MarginProbe does not add considerably to the final excision volume. The amount of breast tissue excised correlates to decreased patient satisfaction and cosmesis^{12,13}. Although cosmesis was not directly evaluated in this study, the findings suggest that utilizing the MarginProbe does not dramatically affect total excision volume; in our patients with average tumor size of 1.2 cm, the mean additional margin volume was approximately 5.9 cc.

MarginProbe has been quoted to cost between \$700 and \$1700 per case¹⁴. At our institution, MarginProbe costs approximately \$1000 per case. In 68 invasive cancer cases, approximately 3 patients were spared re-excision surgery with routine usage of MarginProbe, 4 left the operating room with residual cancer, and 7 had positive margins that were identified and addressed successfully intraoperatively independent of MarginProbe. Table 6 compares the theoretic cost and benefit of MarginProbe to a standard of care without MarginProbe had it not been used in our patients.

This analysis confirms the use of the MarginProbe as a valuable adjunct to the current standards of breast conserving surgery despite a significant added cost. In 68 cases, \$14,376 in re-excision costs were saved using MarginProbe (averaged at \$211 per case) at the expense of an additional \$1000 per case. The benefits are seen in the 4.4% who were spared re-excision, the associated risk of breast deformity, added anxiety, and the risk of ipsilateral breast tumor recurrence. Whereas each institution and surgeon must make a calculated decision on the value of MarginProbe, these benefits may be worth the investment.

Conclusion

This study demonstrates the benefits of adjunctive MarginProbe use for intraoperative margin assessment in conjunction with the standard of care. MarginProbe optimizes reduction of positive margins during breast conserving surgery while minimizing impact on specimen volumes. Use of MarginProbe with intraoperative gross pathologic margin assessment synergistically minimizes positive margin rates in invasive breast cancer and DCIS in the final pathological specimen. Re-excision cost savings do not outweigh the cost of MarginProbe, however the benefit of reduced re-excision rates among other patient benefits make routine use—or at least selective use—of MarginProbe an option worth considering.

Abbreviations

MP = MarginProbe

SOC = Standard of care

BCS = Breast conserving surgery

GA = Gross pathological assessment

ASCO = American Society of Clinical Oncology

ASTRO = American Society for Radiation Oncology

SSO = Society of Surgical Oncology

DCIS= Ductal Carcinoma In Situ

Declarations

Funding:

There is no disclosure of any financial support

Competing Interests:

Author Layton declares that she has no conflict of interest. Author Qafiti declares that he has no conflict of interest. Author McDonald declares that she has no conflict of interest.

Ethical Approval and Consent to Participate:

All procedures performed in this study which involved human participants were in accordance with the ethical standards of Boca Raton Regional Hospital and Lynn Cancer Institute Research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent:

According to local guidelines from our institution, neither approval from the ethics committee nor informed consent from the study populations is required for retrospective chart reviews provided that adequate methods were used to protect patient confidentiality.

Authors' Contributions:

Dr. McDonald designed and carried out the study. Drs. Qafiti, Layton and McDonald contributed to the analysis of the results and writing of the manuscript.

Consent to Publication:

The authors consent to publication of this study

Availability of Data and Materials:

All data generated or analyzed during this study are included in this published article

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Figures

Figure 1

Intraoperative Margin Assessment of Invasive Cancer; MP = MarginProbe; GA = gross assessment.