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SHORT COMMUNICATION

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Margin assessment before intraoperative radiotherapy during breast conserving surgery—Does the addition of MarginProbe decrease the need for addition of fractionated whole breast radiation?

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Abstract

When performing Breast Conserving Surgery (BCS) with Intraoperative Radiation Therapy (IORT), positive resection margin necessitates not only re-lumpectomy—but also the addition of fractionated whole breast radiation. This retrospective study of 106 patients undergoing BCS and IORT aims to evaluate intraoperative margin assessment use in our center, and the contribution of the MarginProbe device (MP) to achieving negative surgical margins. Eleven out of 106 lumpectomy specimens had a total of 17 margins positive for tumor cells. Intraoperative gross pathology identified 6 (43%) involved margins, MarginProbe detected 8 (50%), and their combined use allowed for detection of 12 (70.5%) involved margins. In conclusion, the adjunctive use of intraoperative gross pathology and MarginProbe reduced the number of lumpectomies with positive resection margins by more than 50%, decreasing the need for re-lumpectomy and the addition of whole breast radiation.

KEYWORDS

breast conservation, intraoperative radiotherapy, MarginProbe, surgical margins

1 | INTRODUCTION

Radiation therapy following BCS is associated with a significant reduction in breast tumor recurrence and an increase in overall survival.[1] However, traditional whole breast irradiation is associated with short- and long-term side effects and requires multiple sessions. The length of therapy leads to increased medical costs, negative effect on short-term quality of life and an overall decrease in compliance.[2] Intraoperative Radiation Therapy (IORT) is an alternative to whole breast multi-fraction radiation. As shown in the TARGIT trial,[3] in selected patients with early breast cancer IORT is non-inferior to whole breast irradiation in terms of local recurrence and disease specific morbidity mortality. IORT is also associated with lower mortality from cardiovascular causes and other cancers, and less radiotherapy-related skin complications.[3-5] It is estimated that almost 50% of T1-2 N0 patients could be eligible for IORT.[5]

Inadequate resection of early-stage breast cancer during breast-conserving surgery (BCS) is a major risk factor for ipsilateral breast tumor recurrence. After final pathological evaluation of the surgical specimen, up to 25% of patients treated with breast conserving surgery undergo re-excision to attain clear surgical margins.[6] Re-lumpectomy is associated with increased surgical complications, patient distress, negative cosmetic outcome, increase in medical costs, and delay in adjuvant treatment for all patients. When undergoing IORT, positive resection margin mandate not only re-lumpectomy, but also completion of whole breast irradiation.

Surgeons often use different intraoperative modalities to try and evaluate the resection margin status and re-resect any involved

margin at the time of the index surgery. Modalities that are commonly used include: intraoperative gross pathological examination, cytology and frozen-section analysis, intraoperative imaging such as ultrasound or specimen radiography, and use of universal cavity margin shaving.[7] The selection of which modality to use is left to the surgeon discretion based on consideration such as center availability and expertise, and personal experience and preference. Each of the intraoperative modalities has its limitations. In general, both intraoperative pathology and intraoperative radiology are user-dependent, time-consuming and may require the involvement of a staff member from discipline other than surgery. Universal cavity shaving may lead to unnecessary tissue excision, thereby having a negative impact on cosmesis.[8,9]

In an effort to improve existing techniques, there has been a growing interest in the use of additional intraoperative margin assessment modalities. MarginProbe (Dune Medical Devices Ltd) is an intraoperative margin assessment device based on radiofrequency spectroscopy, which can be used as an adjunctive tool to current standard of care practices. Malignant cell changes, such as membrane depolarization, increase in nuclear-to-cytoplasmic ratio and neo-angiogenesis, cause an alteration in the electromagnetic signature of the malignant tissue which is detected by the MP. The probe is sensitive to malignant tissue at specimen surface up to a depth of 0.1 cm. Previous studies showed a reduction of the re-excision rate when using MarginProbe.[10-13]

2 | MATERIALS AND METHODS

This study is a retrospective single-arm study of all the patients who underwent BCS and IORT at the Meir Medical Center Breast Unit, Kfar Saba, Israel, between January 2014 and February 2017. The final version of the clinical protocol was approved by the institutional review board.

2.1 | Participants

Patients eligible for IORT were 55 years or older, with a single foci of invasive ductal carcinoma no larger than 2.5 cm. All the tumors were ER-positive and Her2-negative on preoperative biopsy, with clinically uninvolved lymph nodes.

2.2 | Intraoperative margin assessments modalities

The following methods for intraoperative margin assessments were available in our institution:

1. Gross macroscopic examination by the staff pathologist on call.
2. Intraoperative specimen radiography.
3. Margins assessment using MarginProbe.

TABLE 1 Tumor characteristics

Tumor characteristics	
Size (mean, mm)	12.2
Tumor grade	
1	22 (20.7%)
2	57 (54.3%)
3	14 (12.7%)
Other[a]	13 (12.3%)
Receptor status	
ER+	106 (100%)
PR+	89 (84%)
Her2+	2 (1.9%)
Ki 67% (average, range)	11 (1-30)
Lymph nodes status	
Negative for metastasis	93 (87.7%)
Positive for metastasis	13 (12.3%)

[a]Other—Mucinous carcinoma, Invasive lobular carcinoma, unknown.

The decision which methods to use was left at the discretion of the surgeon performing the operation. All surgeries were performed by one of 4 dedicated breast surgical oncology surgeons.

2.3 | Surgical margins

Margins were defined as 6 faces of a cube. Marginal shavings were named according to the face of the cavity they were taken from. The final lumpectomy specimen includes the main lumpectomy and any additional margin shavings. Free margins are defined according to the SSO/ASTRO consensus as no tumor cells on resection margin ("'no ink on tumor"). Margin assessment was not performed on the shaving margins.

2.4 | Data collection

Data of the patients who underwent IORT during the relevant dates were retrieved from local registrations and entered to an Excel database. Data collected include demographic information, operative report (detailing the margin assessment modality used and addition of margin shavings), final histopathology report, and the postoperative and routine follow-up clinic visits.

3 | RESULTS

One hundred and six patients underwent IORT during the study. Mean age was 67.2 years. Tumors' pathology and immunohistochemistry are displayed in Table 1. Preoperative biopsy results were refuted in two cases in which final pathology showed invasive lobular carcinoma and in two cases who were found to be HER2-positive.

Average volume of the main lumpectomy specimen was 46 cc. Additional margin shaving was performed in 79 cases (74.5%). The average number of margin shavings added per case was 1.68 (range 0-6). Average volume of final specimen (including shavings) was 56.7 cc.

One margin assessment modality was used in 20 operations (19%), two modalities were used in 82 (77%) and 3 modalities in 4 (4%). MarginProbe was used for margin assessment in 89 operations (84%), gross pathology in 67 (63%), and specimen radiography in 40 operations.

3.1 | Margin status and Intraoperative margin assessment

For the main lumpectomy specimen, R0 resection (margins negative for residual tumor cells) was achieved in 95 cases (89.6%). After performing the additional intraoperative shavings, 6 cases were converted to R0 on final specimen. 5 cases (4.7%) had an R1 resection on the final specimen (Figure 1). Out of these 5 R1 resections, 2 were identified intraoperatively. In one case, the MP detected margin was not resected, and in the second, the margin shaving was R1 as well.

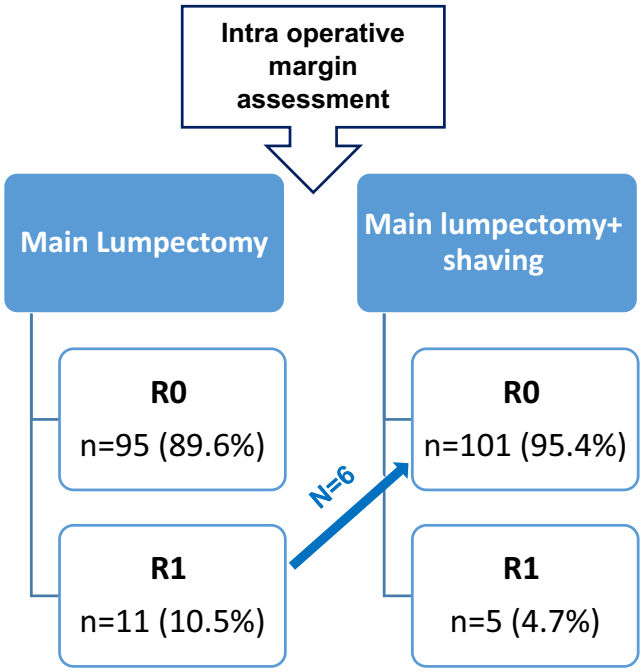

FIGURE 1 Margin status according to final pathology results

Out of the 11 cases with R1 resection on main lumpectomy, MarginProbe was used in 10, Intraoperative pathology was used in 9, and specimen radiography was used in one. These 11 cases had a total of 17 involved margins, as more than one margin can be involved per specimen.

Sixteen positive margins, proven by final postoperative pathology, were examined by the MarginProbe device which detected 8 of them. Fourteen positive margins were grossly examined by pathology during the operation, out of which 6 were identified. One lumpectomy with positive margin had specimen radiography, which failed to show involved margin. Two of the positive margins were identified both by MarginProbe and by intraoperative pathology. The adjunct use of pathology and MP allowed for detection of 12 out of 17 positive margins (70.5%), and 8 out of 11 cases (72.7%) (Table 2).

MarginProbe's false positive rate was 0.7, and false negative rate was 0.1. The MP device showed high specificity (96%), but low sensitivity (13%). No significant difference was found between total specimen volume with or without the use of MarginProbe (57.2 vs 54.6 cc, P = .65). No correlation was found between positive MarginProbe readings and tumor Grade (P = .72), Tumor size (P = .41) or KI67 proliferation marker (P = .74).

3.2 | Treatment and outcome

All patient received adjuvant hormonal therapy. Thirteen patients underwent additional external radiation due to tumor metastasis to axillary lymph nodes.

Completion of treatment for the R1 patients was decided on after oncological consultation. Two of the patients underwent re-lumpectomy, and all 5 patients completed whole breast irradiation.

Postoperative complications included seroma in the surgical cavity (13 patients requiring needle drainage of the breast cavity) and wound infection (3 patients admitted for IV antibiotics).

Two patients died during follow-up: one from metastatic ovarian cancer and one from ruptured aortic aneurysm. No breast recurrences were diagnosed during the follow-up period.

4 | DISCUSSION

Margin involvement in BCS is a well-established risk factor for tumor recurrence. R1 resection raises the need for additional treatment, usually by re-lumpectomy. Furthermore, the finding of positive

TABLE 2 Detection of R1 margins intraoperatively

Intraoperative modality	Number of positive margins tested intraoperatively	Number of positive margins detected intraoperatively
MarginProbe	16	8 (50%)
Pathology	14	6 (43%)
Radiography	1	0
Both MarginProbe and Pathology	17	12 (70.5%)

resection margins on BCS combined with IORT also mandates the addition of external whole breast irradiation, negating the benefits of IORT. In the TARGIT trial, 6.8% of patients had to undergo re-excision and whole breast irradiation because of involved margins.[3] Due to these implications, this study reviews intraoperative margin assessment modalities during BCS and IORT and their effect on recognition and resection of involved margins.

Looking at the data retrospectively, we could compare the information from the final pathology report with the intraoperative margin detection of the various modalities used in our center.

The intraoperative detection rate of positive margins was 50% for MarginProbe and 43% for intraoperative gross pathology. Importantly, MarginProbe and intraoperative pathology had a synergetic effect and their combined use allowed for a detection rate of 70.5% of the positive margins—higher than each modality by itself.

MP showed a high specificity, but a low sensitivity. A higher sensitivity would have allowed for less cavity shaving and therefore less tissue volume loss. However, with an average of 1.68 shaving per specimen in the cohort, it could be a reasonable price to pay for the high specificity provided by the device. This is especially true when compared with technique such as cavity shaving, for which 6 shavings are performed per specimen.

The use of both intraoperative modalities comes at a price. Intraoperative gross pathology requires having a pathologist on call is user-dependent and adds additional time to the surgery. MarginProbe use has been shown to add approximately 5 minutes to the operation time,[11] requires implementation of the probe, and adds additional cost to the operation. These extra expenses are probably negligible when compared with the costs required to treat patients with R1 lumpectomies.

Study limitations include its retrospective non-randomized nature, and multiple surgeons and pathologists involved. The relatively small number of participants and the low incidence of positive margins make the results underpowered. The local practice of using gross pathology for margin assessment makes it less generalizable for surgeons using other intraoperative margin assessment modalities. Bigger, randomized controlled trials are needed to examine the role of intraoperative margin assessment, and specifically MarginProbe, before performing IORT.

5 | CONCLUSION

The adjunct use of gross pathology and the MarginProbe device had a synergetic effect on detecting R1 margins intraoperatively. Our results suggest that their combined use allows for better assessment of lumpectomy margins during the index surgery before performing IORT.

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REFERENCES

1. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366(9503):2087-2106.
2. Shah C, Vicini F, Wazer DE, Arthur D, Patel RR. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy*. 2013;12(4):267-277.
3. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet*. 2010;376(9735):91-102.
4. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014;383(9917):603-613.
5. Ziouèche-Mottet A, Houvenaeghel G, Classe JM, et al. Eligibility criteria for intraoperative radiotherapy for breast cancer: study employing 12,025 patients treated in two cohorts. *BMC Cancer*. 2014;14:868.
6. Buchholz T, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. *J Clin Oncol*. 2014;32(14):1502-1506.
7. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. *Ann Surg Oncol*. 2009;16(10):2717-2730.
8. Harness JK, Giuliano AE, Pockaj BA, Downs-Kelly E. Margins: a status report from the annual meeting of the American society of breast surgeons. *Ann Surg Oncol*. 2014;21(10):3192-3197.
9. St John ER, Al-Khudairi R, Ashrafian H, et al. Diagnostic accuracy of intraoperative techniques for margin assessment in breast cancer surgery: a meta-analysis. *Ann Surg*. 2017;265(2):300-310.
10. Allweis TM, Kaufman Z, Lelcuk S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. *Am J Surg*. 2008;196(4):483-489.
11. Schnabel F, Boolbol SK, Gittleman M, et al. A randomized prospective study of lumpectomy margin assessment with use of MarginProbe in patients with nonpalpable breast malignancies. *Ann Surg Oncol*. 2014;21(5):1589-1595.
12. Blohmer JU, Tanko J, Kueper J, Groß J, Völker R, Machleidt A. MarginProbe reduces the rate of re-excision following breast conserving surgery for breast cancer. *Arch Gynecol Obstet*. 2016;294(2):361-367.
13. Karni T, Pappo I, Sandbank J, et al. A device for real-time, intraoperative margin assessment in breast-conservation surgery. *Am J Surg*. 2007;194(4):467-473.

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