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A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery

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KEYWORDS:
Breast cancer;
Breast-conserving surgery;
Intraoperative margin assessment;
Surgical margins;
Lumpectomy;
Positive margins

Abstract

BACKGROUND: This randomized, double-arm trial was designed to study the benefit of a novel device (MarginProbe, Dune Medical Devices, Caesarea, Israel) in intraoperative margin assessment for breast-conserving surgery (BCS) and the associated reduction in reoperations.

METHODS: In the device group, the probe was applied to the lumpectomy specimen and additional tissue was excised according to device readings. Study arms were compared by reoperation rates and by correct surgical reaction confirmed by histology.

RESULTS: Three hundred patients were enrolled. Device use was associated with improved correct surgical reaction, defined as additional re-excision in all histologically detected positive margins, with tumor within 1 mm of inked margin. The repeat lumpectomy rate was significantly reduced by 56% in the device arm: 5.6% versus 12.7% in the control arm. There were no differences in excised tissue volume or cosmetic outcome.

CONCLUSIONS: Intraoperative use of the MarginProbe for positive margin detection is safe and effective in BCS and decreases the rate of repeat operations.

Complete removal of tumor with clear margins during breast-conserving surgery (BCS) for breast cancer is one of the major goals of the operation. Failure to obtain clear margins is one of the leading risk factors for local recurrence.[1–7] However, since microscopic involvement of the margins is not readily assessable intraoperatively, finding

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tumor close to or at the margin of a lumpectomy specimen by permanent histology is not an unusual event. Reoperation for positive margins after BCS may be necessary in up to 50% of cases,[8–11] and is associated with patient discomfort, increased costs, and poorer cosmetic outcome. National Comprehensive Cancer Network guidelines[12] suggest that positive lumpectomy margins require reoperation, and standard practice is that it is unacceptable to have tumor cells directly at the margin of the excised specimen.[13] However, there is no consensus regarding the required distance of tumor from the cut edge[1,14] and positive/close margins may be defined anywhere between tumor at the inked margin to tumor within 5 mm of the inked margin.[10,13,15] Patients not amenable to margin-free lumpectomy should undergo mastectomy.[12]

As many as 54% of main lumpectomy specimens will have positive or close margins,[16–18] requiring re-excision. Intraoperative information regarding the presence of tumor at or near the margin enables the surgeon to excise additional tissue immediately, minimizing the need for reoperation. Intraoperative assessment based on palpation alone is highly inaccurate and frozen section or touch prep cytology for margin assessment are time-consuming and imprecise.[2,19] A new device (MarginProbe, Dune Medical Devices, Caesarea, Israel) that can detect tumor cells at or close to the margin of resection has been developed. When previously studied intraoperatively in a blinded fashion,[20] the device detected all positive margins in 86% (19/22) of pathologically positive lumpectomy specimens from 57 patients.

The device is intended to be applied to the main lumpectomy specimen immediately upon excision, which is when the surgeon decides if any additional tissue needs to be re-excised. We sought to assess real-time intraoperative use of the device in a randomized controlled manner.

The study was designed to assess the safety of the device and its effectiveness versus a control group in increasing the likelihood of a correct intraoperative surgical reaction during lumpectomy procedures. In addition, the impact of device use on reoperation rates, excised tissue volume, and cosmetic outcome were studied.

Materials and Methods

Study design and patient selection

Subjects were enrolled at 11 institutions in a prospective, multicenter, randomized, controlled, institutional review board–approved study. All patients were scheduled to undergo BCS for treatment of invasive and/or pre-invasive breast cancer. Patients were excluded if they had received neoadjuvant chemotherapy, had prior surgical procedures or implants in the ipsilateral breast, or were participating in other clinical trials that might interfere with the protocol or device measurements. All patients were at least 18 years of age, and were capable of giving informed consent.

Subjects were randomized into 2 arms: with or without device use. In both arms surgeons were allowed to use any standard of care (SOC) intraoperative methods to evaluate margin status such as palpation, specimen imaging, and intraoperative gross and/or microscopic pathology assessment. Pathology data were collected for the primary lumpectomy and all repeat ipsilateral surgical procedures within 6 months. Pathology data included specimen dimensions, oriented histological margin distance for each of the 6 specimen aspects, as well as microscopic evaluation for tumor presence and margin width of all re-excised margin specimens. Cosmetic evaluation was performed at baseline, 7–30 days, and 3–6 months following surgery by an observer unaware of the patient's randomization assignment. A symmetry-based scale[2] was used for assessment as follows:

1. Excellent: treated breast almost identical to untreated breast
2. Good: minimal difference between the treated and untreated breasts
3. Fair: obvious difference between treated and untreated breasts
4. Poor: major functional and esthetic sequelae in treated breast.

Device description

The MarginProbe is used for intraoperative margin assessment. The device components include a console and a sterile, disposable hand-piece, which are connected by cables. Measurement is performed by applying the probe tip to a point on the resected lumpectomy specimen (Figure 1). At each point measured, radiofrequency signals are transmitted from the probe to the tissue, reflected back, and collected by the console. The reflected signals are algorithmically analyzed and the device readings are displayed as "positive" or

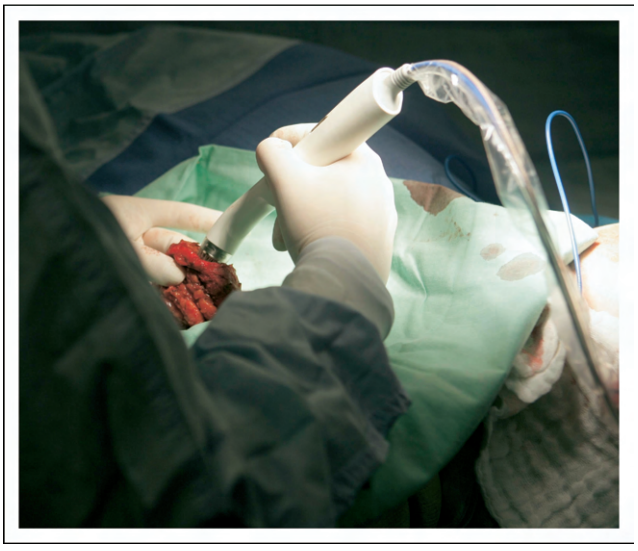

Figure 1 Intraoperative application of device to breast lumpectomy specimen.

"negative." The probe has a footprint diameter of 16 mm, an effective measurement area diameter of 7 mm, and a detection depth of about 1 mm. Each measurement is completed in 1.5 seconds, allowing for sampling of multiple points over the specimen surface in a short period of time.

Intraoperative procedure

Lumpectomy was performed in the standard fashion. Only once the excision and suture orientation of the main lumpectomy specimen were completed, the patient was randomized to 1 of 2 study arms: "device" or "control." In patients randomized to the "device" arm, the device was applied by the surgeon to the main lumpectomy specimen, as follows: each of 6 margins (medial, lateral, superior, inferior, deep and anterior) was sampled by the probe at 5–8 points. Output was displayed on the screen, and results were grouped and labeled by margin (Figure 2). A short blue bar indicated a negative reading, while a long red bar indicated a positive reading. A margin was considered positive if 1 or more readings were indicated as positive by the device. In both study arms the surgeons used standard intraoperative margin assessment at their discretion, and performed re-excision of cavity margins as deemed necessary. In addition to palpation, the intraoperative modalities used included specimen imaging and intraoperative pathological assessment (gross and microscopic). Both specimen imaging and any intraoperative pathological evaluation, if used, were performed after device application away from the operating room, by a professional blinded to the patient's randomization arm. Results of these assessments were reported back to the surgeon. Following sampling of all margins on the lumpectomy specimen, the surgeon re-excised tissue from the lumpectomy cavity in the margins indicated as positive by the device (in the "device" arm), as well as any margins indicated by standard intraoperative methods in both arms. The device was only applied to the main lumpectomy specimen. Applying the device to intraoperatively re-excised margin specimens was precluded by protocol. Likewise, the device was not used in reoperations.

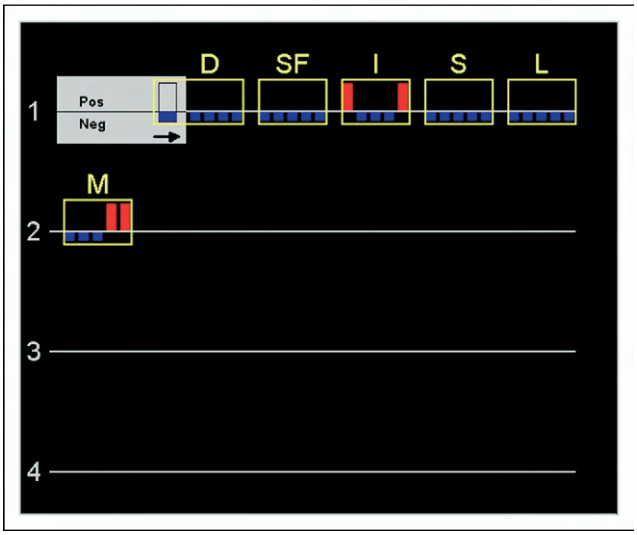

Figure 2 Device output display for a typical patient. Data accumulate on the screen from left to right and from top to bottom. Most recent measurement is highlighted at the top left. Blue and red bars are negative and positive readings, respectively. Yellow frames and labels mark the margins from which readings were obtained.

Pathology

All specimens were suture-oriented in the operating room and sent for permanent pathological analysis. Specimens were inked, sectioned, and embedded in paraffin as per each institution's standard procedure. Slides were stained with hematoxylin and eosin and evaluated for the presence of carcinoma at or near the margins.

Repeat surgical procedures

Postoperative patient management was not dictated by the protocol. Surgeons recommended and performed reoperations according to institutional treatment paradigms and patient preferences. For example, various institutions apply different criteria for insufficient margin width requiring additional surgery. Furthermore, reoperation is sometimes avoided despite insufficient margin width, eg, when all breast tissue has already been excised in the relevant aspects. Performance of additional breast-conserving surgeries, as well as conversions to mastectomy, were followed and documented within 6 months of primary surgery.

Data analysis

Effectiveness in both study arms was determined according to final histology data. The ability to correctly and intraoperatively identify *all* of the involved margins on the main specimen, and re-excise them was defined as correct intraoperative surgical reaction (ISR). Correctness or incorrectness of ISR was defined based on permanent histology data. ISR was defined as correct only when *all* main specimen margins detected as positive by histology were re-excised intraoperatively. A margin was considered positive (for the purpose of ISR calculation) if tumor was present within 1 mm of the inked surface. Study arms were compared for correct ISR, reoperation rates (including and excluding mastectomy), long-term cosmetic outcome, and total volume of tissue excised. Figure 3 describes the calculation of correct or incorrect ISR. Thus all of the histologically positive margins had to have corresponding re-excised specimens (as documented in the histology report) in order for the case to be considered one with correct ISR. Total tissue volume was calculated from the specimen dimensions as recorded in the histology report by applying the spheroid volume formula (including main specimen and all additional intraoperatively re-excised specimens). Sub-

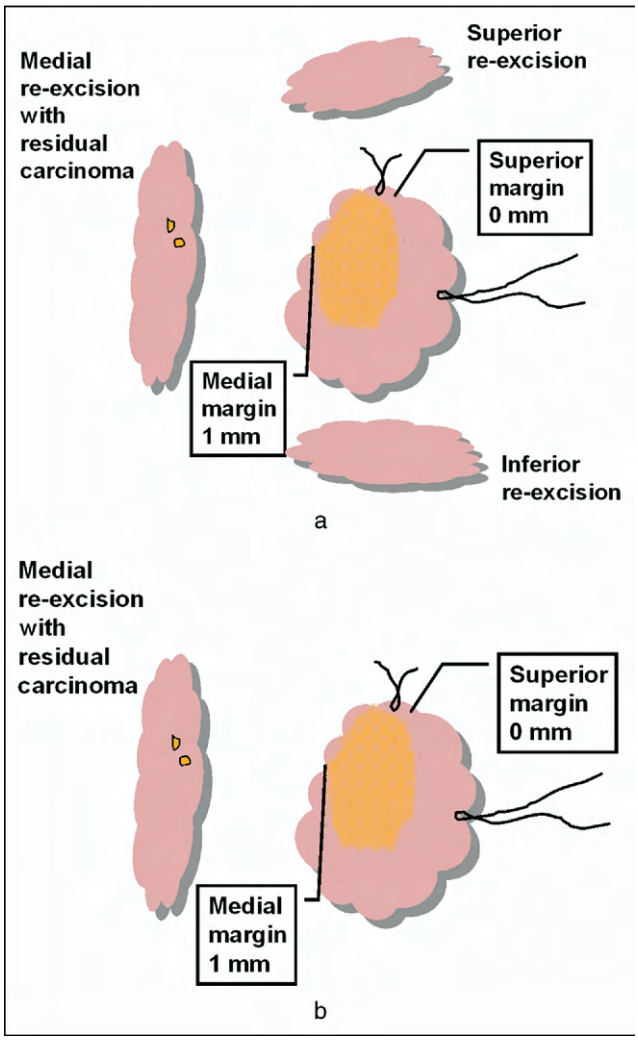

Figure 3 Description of intraoperative surgical reaction (ISR). A case is considered as: (a) correct ISR if *all* histologically positive specimen margins have corresponding re-excised specimens; or (b) incorrect ISR if at least 1 histologically positive specimen margin was not intraoperatively re-excised.

group analysis was performed for patients with nonpalpable lesions (NPL) who underwent preoperative image-guided localization. ISR and cosmetic outcome were compared between study arms using the Fisher exact test. Re-operation rates and excised tissue volume were compared using Poisson regression and Wilcoxon rank-sum test, respectively.

In order to assess the device's contribution to surgical decisions under varying surgical paradigms, ISR was recalculated for both study arms using a range of positive histological margin definitions of 1–5 mm.

Results

From November 2006 through November 2007, 300 patients were enrolled in the study, 149 and 151 in the "device" and "control" arms, respectively. Of these, 7 patients did not fit the inclusion/exclusion criteria for the study or had protocol violations and were excluded (1 received neoadjuvant therapy, 1 underwent a mastectomy as the primary procedure, 2 had prior surgery in the same quadrant, 1 was not preoperatively diagnosed with malignancy, and in 2 patients the device was not applied to all specimen margins). Analysis was performed on 293 patients, 143 and 150 in the "device" and "control" arms, respectively. For the NPL subgroup, 168 patients were analyzed, 82 in the "device" arm and 86 in the "control" arm. Demographic and tumor characteristics were well balanced between both arms for the entire cohort and for the NPL subgroup (Table 1). The 2 study arms were also balanced with regards to use and effect of intraoperative methods for margin assessment (Table 2).

Entire patient cohort

Randomization was performed following excision of the main lumpectomy specimen to ensure uniformity of the initial specimen excision in both study arms. Main lumpectomy specimen positivity rates, ie, tumor detected within 1 mm of a margin, were similar in both groups: 41% (58/143) in the "device" group and 41% (61/150) in the "control" group.

Correct ISR rate was significantly higher in the "device" arm than in the "control" arm, 60% (35/58) versus 41% (25/61), respectively ($P = .044$). Seventeen patients underwent 18 repeat operations (7 re-excisions and 10 mastectomies in a second operation, 1 re-excision in a third opera-

Table 1 Patient characteristics

	Entire cohort		NPL subgroup	
	"Device"	"Control"	"Device"	"Control"
n	143	150	82	86
Age (y)	59	60	60	62
Lesion size, mean (mm)	18.7	17.1	14.8	15.2
Histology (%)				
Invasive	37	38	36	37
Ductal carcinoma in situ (DCIS)	12	8	18	14
Invasive lobular	5	6	6	2
Mixed	46	48	40	47
Tumor grade (%)				
1	18	15	22	20
2	48	44	44	47
3	34	41	34	33
ER/PR status (%)				
Both positive	67	65	61	64
Both negative	19	19	18	15
One positive	14	17	21	21
Her2 neu status (%)				
Positive (2+, 3+)	24	32	28	24
Negative (0, 1+)	76	68	72	76

No statistical difference between arms.
ER = estrogen receptor; PR = progesterone receptor.

Table 2 Use of intraoperative modalities for margin assessment in both study arms

	Entire cohort		NPL subgroup	
	"Device"	"Control"	"Device"	"Control"
n	143	150	82	86
Specimen imaging (%)	51	48	85	83
Intraoperative pathology (%)	22	26	10	20

tion) in the "device" arm, and 23 patients underwent 28 repeat operations (17 re-excisions and 6 mastectomies in a second operation, 2 re-excisions and 3 mastectomies in a third operation) in the "control" arm. Reoperation rate was lower in the "device" arm compared with the "control" arm, 12.6% (18/143) versus 18.6% (28/150) respectively; however, despite this 32.3% reduction in repeat operation rate, this difference did not achieve statistical significance (P = .098). When excluding patients who ultimately underwent mastectomy, re-excision rate was significantly lower in the "device" arm, 5.6% (8/143) compared with 12.7% (19/150) in the "control" arm (P = .0027), amounting to a significant 56% decrease in re-excision rates.

The average total tissue volumes excised during the first procedure were 107 cm^3 and 94 cm^3 (P = .066) for the "device" and "control" groups, respectively. The proportion of patients with long-term "excellent" or "good" cosmetic evaluation was similar in both arms (71% and 69% for "device" and "control," respectively, P = .71). Results are displayed in Table 3.

NPL patient subgroup

The proportion of patients with NPL undergoing preoperative image-guided localization was balanced between study arms (57% [82/143] and 57% [86/150] for "device" and "control," respectively). The main lumpectomy specimen positivity rate was similar in both groups: 35% (29/82) in the "device" arm and 38% (33/86) in the "control" arm.

Correct ISR rate was significantly higher in the "device" arm than in the "control" arm, 69% (20/29) versus 39% (13/33), respectively (P = .024). Eight patients underwent 8 reoperations in the "device" arm and in the "control" arm 13 patients underwent 18 reoperations. Thus, reoperation rates were significantly lower with device use compared to the control arm, at 9.8% (8/82) and 20.9% (18/86), respectively (P = .02), a 53% decrease. A similar significant 52% decrease in re-excision rates is observed when excluding mastectomy procedures.

The average tissue volumes excised during the first surgical procedure in the NPL group were 100 cm^3 and 96 cm^3 (P = .30) for "device" and "control," respectively. The proportion of patients with long-term "excellent" or "good" cosmetic evaluation was similar in both arms, 78% and 71% (P = .31) for "device" and "control," respectively. Results are displayed in Table 3.

Surgical reaction using device output

Device output should have led to removal of additional tissue in the aspects that were indicated as positive. This was not always feasible, eg, if tissue was excised down to the pectoralis major muscle or anteriorly up to the subdermal plane. In this study, 448 margins were indicated as positive by the device in 143 patients. Only 76% (342/448) and 78% (186/237) of these margins were intraoperatively re-excised by the surgeons in the entire cohort and NPL subgroup, respectively. Of the 106 margins in 65 patients that were not re-excised in the entire cohort, 57% (60/106) were in the anterior or deep aspect where no breast tissue remained to be resected. The surgeons could have re-excised the remaining 43% (46/106) of device-detected positive margins but elected not to do so. Had these latter margins been re-excised, correct ISR for the "device" arm would have increased to 67% (39/58). Similar proportions

Table 3 Summary of results in entire patient cohort and NPL patient subgroup

	"Device"	"Control"	P value
Entire cohort			
n	143	150	
Correct ISR rate (%)	60 (35/58)	41 (25/61)	.044
Re-excision rate (%)	5.6 (8/143)	12.7 (19/150)	.0027
Reoperation rate (%) including mastectomy	12.6 (18/143)	18.6 (28/150)	.098
Excised tissue volume, mean (cm^3)	107	94	.066
Good or excellent long-term cosmetic outcome	71	69	1
NPL cohort			
n	82	86	
Correct ISR rate (%)	69 (20/29)	39 (13/33)	.024
Re-excision rate (%)	6.1 (5/82)	12.8 (11/86)	.039
Reoperation rate (%) including mastectomy	9.8 (8/82)	20.9 (18/86)	.020
Excised tissue volume, mean (cm^3)	100	96	.300
Good or excellent long-term cosmetic outcome	78	71	.311

were observed in the NPL subgroup with 51 margins indicated as being positive by the device in 31 patients not re-excised, 37% (19/51) of them which could have been re-excised, and correct ISR would have increased to 79% (23/29) had all these margins been re-excised.

Positive margin thresholds

Results of the benefit of device use presented above are for a positive margin defined as histologically detected cancer within 1 mm of the lumpectomy margin. However, in light of the variability in patient management paradigms, we decided to compare the study arms with other definitions of what constitutes a positive margin.

The positivity threshold was raised to 2, 3, and 5 mm and correct ISR was recalculated for both study arms. When positivity thresholds increase and become more conservative, correct ISR rates decrease in both arms, as can be expected; however, the benefit of "device" over "control" is maintained (Figure 4). Correct ISR rates for the "device" arm shifted from 60% when the margin was defined as 1 mm to 52% when the margin was defined as 5 mm. For the "control" arm, the correct ISR was 41% for a 1-mm margin and 33% for a 5-mm margin. A similar effect was noted when this analysis was performed for the NPL subgroup. Re-excision rates did not change since they were not dependent on the study definition of positive margins.

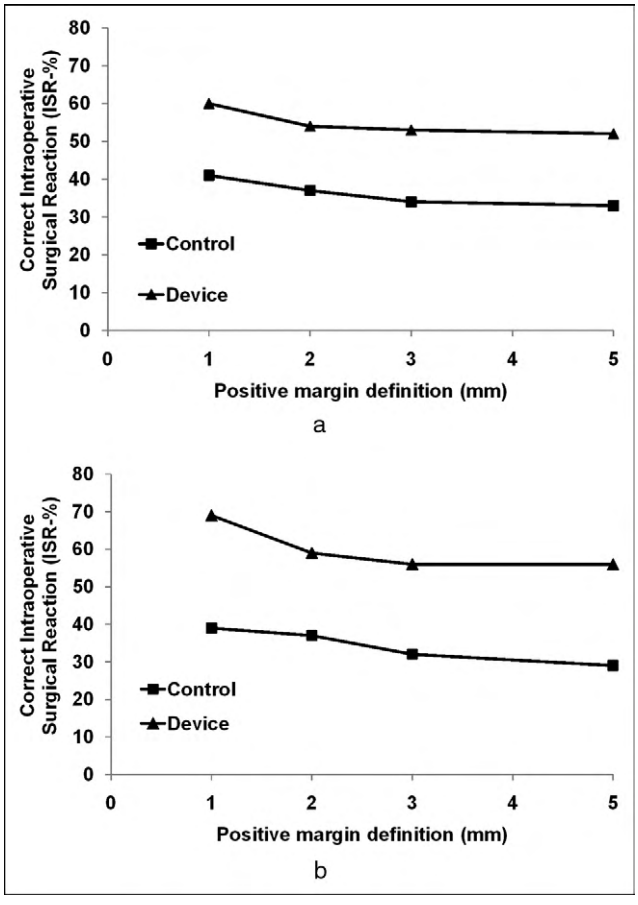

Figure 4 Comparison of "device" and "control" over a range of positive margin definitions in (a) entire patient cohort and (b) a subgroup of patients with nonpalpable lesions (NPL) who underwent preoperative image guided localization.

Comments

This prospective, randomized, controlled study demonstrates the safety and effectiveness of a new device for real-time intraoperative margin assessment. After excision of the main lumpectomy specimen during BCS, the surgeon must decide whether additional tissue needs to be re-excised from the lumpectomy cavity, and if so, from which aspects. In this study, patients were randomized at this point of the procedure to 2 study arms, with or without device use. In both arms surgeons equally used other available intraoperative modalities for margin assessment, as deemed necessary. These included palpation, specimen imaging, and intraoperative gross and/or microscopic pathology assessment. We followed the surgical decisions to further remove tissue for every patient and judged them based on the final histological report. Results indicate that use of the device at this point in the procedure, in conjunction with other intraoperative modalities, will provide additional margin assessment data, and effectively improve the surgeon's ability to correctly react by further intraoperative re-excision. The ability to correctly re-excise all histologically positive margins was enhanced by nearly 50%, from 41% to 60% when device use was added to other intraoperative modalities. The need for reoperation was not defined or dictated by the study protocol. Every surgeon used his/her routine criteria for taking a patient back to the operating room. Sometimes patients with histological margins $\leq$1 mm were not taken back to the operating room for one of the following reasons: all breast tissue in the relevant aspect was already excised in the first procedure (eg, the deep margin was positive but had been excised down to the pectoral muscle); institutional criteria for margin positivity was different than the study defined 1 mm threshold; and patient preference. This accounts for the difference between incomplete ISR rates and reoperation rates in both arms. With all those real-life elements and considerations affecting results, actual re-excision rates decreased accordingly by 56%.

Device benefit is somewhat more pronounced in the subgroup of patients with NPL. Although it was initially presumed that surgeons may find these NPL more challenging to surgically locate and fully excise, results showed that correct intraoperative reaction and reoperation rates were maintained in the control arm at about 40% and 20%, respectively, in this subgroup. While the SOC modalities for margin assessment have similar performance in NPL compared to palpable lesions, device use improves and with it the benefit of the device relative to SOC. In nearly 70% of patients in the "device" arm the surgeon was able to intraoperatively re-excise all histologically positive margins,

compared to nearly 40% in the "control" arm, an increase of more than 75%. For this subgroup, over 50% fewer patients were taken back to the operating room for additional surgery when the device was used.

Device use does not lead to excision of significantly larger tissue volume for both the entire cohort and the NPL subgroup. Cosmetic outcome is maintained relative to SOC. Lacking a consensus on what constitutes a positive margin, surgeons use different criteria. Some consider a margin to be positive only if tumor cells are located at the specimen edge while others use more conservative paradigms requiring a clear margin of 1 mm, 2 mm or more. Initially, positive margins were defined in this study to be those with tumor detected within 1 mm from the margin, and correct ISR was judged accordingly. However, data from histopathology reports was also available for margin widths which were greater than 1 mm. Thus, device benefit over SOC was analyzed for positive margins that were more conservatively defined. Correct ISR was recalculated for a positive margin definition that was gradually reset at 1 mm to 5 mm. As the required clear margin width increases, more margins are rendered positive by definition, and it becomes more difficult to detect and re-excise all of them. It is thus not surprising that correct ISR in both study arms decreases when the wider margin definition is applied. However, it is noteworthy that the benefit of using the device in conjunction with other modalities is maintained throughout the range. This holds true for both the entire cohort and the subgroup of patients with image guided localization. In an earlier study performed with this same device, Karni et al[20] reported similar results. While in Karni et al's work device output was recorded but surgeons were blinded and did not respond to device output, data from the current work yield similar results in actual use of device output in intraoperative decision-making. The implication of these results is that whatever the preferred paradigm of clear margin width, patients are likely to benefit if surgeons add device use to their other available intraoperative modalities and re-excise all margins indicated by the device as positive.

The device is safe and effective in increasing the ability of the surgeon to detect positive margins and to react correctly during the primary procedure. The device thus contributes to a significant 56% reduction in reoperation rates for BCS.

In several cases in this study surgeons chose not to further excise when a positive margin was detected in a margin that was amenable to further excision (ie, not the anterior or deep margins). Future studies should seek to measure the effect of these decisions, and the optimal mode of use of this device.

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