A device for intraoperative detection of positive resection margins in breast conservation surgery.

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Background

The primary objective of breast conservation surgery is to achieve local control by removal of the tumor with a rim of healthy tissue. Postoperatively, the gold standard for margin assessment is permanent section histology. Since margin status is a prognostic factor for local recurrence and survival, positive margins trigger a second surgical procedure. Had the knowledge of unsatisfactory margin status been available intraoperatively, corrective measures such as additional tissue removal could have been taken by the surgeon, possibly preventing the need for a second, corrective, re-excision procedure. Methods available today (such as frozen section, ultrasound, specimen radiography) do not fully provide intraoperative margin assessment. A margin assessment device, designed to be intraoperatively used by surgeons was developed by Dune Medical Devices (Caesarea, Israel). The device is based on Radio Frequency (RF) spectroscopy, includes a console and a sterile disposable probe, and is sensitive to the presence of malignant tissue at the resected specimen surface, up to a depth of 1 mm. This study was designed to assess the potential of the device for intraoperative detection of positive margins and the subsequent minimization of postoperative positive margins.

Methods

Patients pre-diagnosed with carcinoma of the breast were enrolled. The device was applied to freshly excised partial mastectomy specimens in the operating room. Surgeons were blinded to device output, which was logged in the system but not displayed in real-time.
As breast surgeons usually orient partial mastectomy specimens relative to the body by margins (lateral, medial, superior, inferior, superficial, and deep), and pathologists, likewise, report margin status by this same convention, the study was designed to comply with this convention. The specimens were oriented by the surgeon and placed in a transparent, thin, frame apparatus (Figure 1), uniquely defining the boundaries of up to six margins. Each margin was sampled by the probe in multiple dime-like points, yielding a positive or negative output for each point. Each measurement output was logged in the system with its margin orientation, thus yielding a specific data set per margin. At the pathology lab, the specimen was inked in 6 colors (one for each margin) according to the frame apparatus (Figure 2), followed by removal of the frames. This procedure insured a well-defined correlation between the margin contour measured by the device and the histological assessment of the same margin contour, which was identified by the color visible on the slide. Gross handling and sectioning of the specimen were performed according to the centers' routine methods.

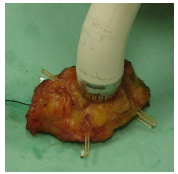

Figure 1

Figure 2

Data analysis was based on comparison of device output per margin, as compiled from all points oriented in that margin, to pathological margin data per each margin, as identified by its color. A margin was labeled positive by the device if 22% or more points on that margin gave a positive outcome. A margin was considered positive by histology if tumor cells were seen 1 mm or less from the inked surface.
To yield the final patient level output a two-step data analysis was performed: compilation of individual point data to obtain per-margin positivity status, and compilation of all margin data per patient.

Results

68 patients were enrolled in two medical centers from February 2005 through December 2005. Data from 57 patients was analyzed, while 11 patients did not meet the exclusion/inclusion criteria. Data was analyzed per patient and per margin.

Per patient: 31 out of 57 patients were positive after the initial excision. 9 of them were suspected as such by the surgeon and were re-shaved intraoperatively. The remaining 22 were positive in permanent pathology, thus the positive outcome rate in this set was 39%. In order to assess patient outcome, surgical reaction had to be assumed. Accordingly, it was assumed that any margin detected as positive would have been reshaved and if three or more positive margins were detected, the surgeon would have reshaved all margins. Thus, assuming the above reaction, the device enabled intraoperative correction of margin status in 19 out of 22 positive patients, yielding a potential reduced positive outcome rate of only 5%. Figure 3 presents a flowchart of patient outcome without vs. with device utilization.
Thus, re-excision reduction potential was found to be: 19/22=86%. Four out of twenty six (15%) pathology negative patients would have had excess tissue removed in margins which were falsely detected as positive.

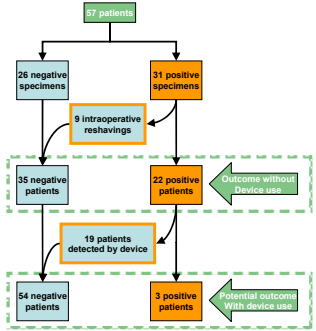

Figure 3 : Patient outcome as observed without device use vs. potential outcome with device use

Per-margin agreement with pathology : 314 margins were evaluated from 57 patients, with overall ~3600 measurement points. The average number of points which were sampled per margin is 11.5±8. Overall margin classification performance (Table 1) is : Sensitivity = 0.71 (95% CI: 0.55 - 0.84) and specificity = 0.68 (95% CI: 0.61 - 0.73). Confidence interval (CI) is 0.95.

		Device		
		Positive	Negative	
Histology	Positive	30	12	42
	Negative	88	184	272
		118	196	314

Table 1 : Per-margin results for all patients

Stratification of patients by margin status yields a per-margin specificity of 0.54(95% CI: 0.445 - 0.63) for pathology positive patients (Table 2), and 0.79(95% CI: 0.71 - 0.85) for pathology negative patients (Table 3).

		Device		
		Positive	Negative	
Histology	Positive	30	12	42
	Negative	57	67	124
		87	79	166

Table 2 : Per-margin results for pathology-positive patients

		Device		
		Positive	Negative	
Histology	Positive	0	0	0
	Negative	31	117	148
		31	117	148

Table 3 : Per-margin results for pathology-negative patients

Number of patients	N=57
Postoperative positive outcome rate	39% (22/57)
Device positive patient detection	86% (19/22)
Postoperative potential positive outcome rate with device use	5% (3/57)

Table 4 : Summary of results

Conclusions

The intraoperative surgical device used in this study has potential for drastic reduction of postoperative positive margin rate in breast conservation surgery. The device is simple to use and allows, within a few minutes, ample sampling and margin assessment of the oriented specimen. Surgical reaction to device positive output will include additional shaving of the relevant margins.
Results indicate that while some additional margins will be unduly shaved due to false positive output, a significant majority of positive device readings will occur in positive specimens. These cases can be intraoperatively corrected and converted to the desired negative margin outcome. The device does not preclude use of any other intraoperative or postoperative modality.