Assessment of Lumpectomy Tissue Malignancy Status Using Radio Frequency (RF) Spectroscopy

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ABSTRACT

OBJECTIVE: Tissue assessment by RF spectroscopy is a novel intraoperative method for margin assessment. It is based on known dielectric differences between normal and malignant cell clusters, and corresponding changes in the reflection of electromagnetic waves. The technology was adapted for intraoperative use via a device that consists of a console connected to a hand held probe. The current work sets out to assess performance of this device, as compared to histology, when applied to freshly excised breast specimens.

METHODS: The device (Dune Medical Devices, Caesarea, Israel) was used to evaluate freshly excised, bread-loafed, lumpectomy specimens. The effective sensing volume is a dime shaped disk, 7 mm in diameter and 1 mm in depth, proximal to the probe's tip. In order to simulate intraoperative use, performance was evaluated only on tumor-peripheral sites, with malignant content of <30%. These contained IDC and DCIS. Device readings were compared to histopathological analysis.

RESULTS: Data from 282 measurement sites from 44 patients (46 specimens) was obtained. The rate of positive sites within the tested data set was 18.8%. Overall per-measurement site sensitivity, specificity, and agreement with pathology are 0.92 (95% CI: 0.82 - 0.98), 0.76 (95% CI: 0.70 - 0.82), and 0.79 (95% CI: 0.74 - 0.84) respectively. Positive predictive value and negative predictive value are 0.48 (95% CI: 0.38 - 0.58) and 0.98 (95% CI: 0.94 - 0.99) respectively. Device performance in invasive and in DCIS measurement sites was similar.

CONCLUSIONS: The performance sets the ground for further investigational use of the device by the surgeon as a tool for immediate assessment of margin status. The measurement process is fast. Intraoperative use of the device, followed by routine surgical reaction, has the potential to reduce post-lumpectomy positive margin rates. We believe the probe holds promise for future reduction of re-excision procedures.

INTRODUCTION

The goals of breast conserving surgery (BCS) are complete tumor removal, minimal local recurrence and favorable cosmesis. Lumpectomy margin status is generally associated with local control of the disease, and is one of the primary prognostic factors for its local recurrence. Re-excision rates are typically 20%-30% and contribute to increased health care costs, poorer cosmetic results and decreased patient satisfaction. Currently available methods for intraoperative margin assessment (e.g. gross examination, frozen section, touch prep, intraoperative imaging or ultrasound) have met with variable success and often present technical and practical limitations.

Tissue assessment by RF spectroscopy is an alternative intraoperative method. The technology was adapted for intraoperative use via a device that consists of a console, connected to a hand-held probe (figure 1). The probe can rapidly differentiate malignant and benign breast tissue intraoperatively. The effective sensing tissue volume per measurement site is a dime shaped disk, 7 mm in diameter and 1 mm in depth. In the current study we assessed device performance compared to permanent pathology.

METHODS

An ongoing, multicenter, IRB approved, prospective study included specimens from 44 patients undergoing BCS for invasive and non-invasive breast cancer. A probe that detects differences in electrical waveforms reflected from malignant and benign breast tissue was used to evaluate freshly excised specimens. Inclusion and exclusion criteria are listed in Table 1. Informed consent was obtained from all participating patients, who later underwent standard partial mastectomy, or mastectomy, procedures. At the pathology lab, following inking, freshly excised specimens were bread-loafed, in order to facilitate access to tumor peripheral tissue points (sites). Both cancerous and normal appearing sites were sampled. In order to ensure correct registration between probe measurement and pathological processing, numbered pins were placed in the specimen marking the sites at which the probe measurements were taken (Figure 2). For each pinned site the corresponding 7mm wide coin-shape tissue specimen was cut out with a 7mm circular blade. The specimens were further processed en-face in a routine manner, with histological sections covering the full surface area of each site, microscopically evaluated. Each site was recorded as positive or negative for malignancy. Both pathologists and surgeons were blinded to the device results, and surgical decisions were not affected by device data. Probe readings were analyzed, and compared to final histopathology data. The reflected waveforms were parameterized, and a sub-set of parameters which best characterize the probe's response was selected. Sensitivity and specificity were evaluated and optimized using a leave-one-out procedure.

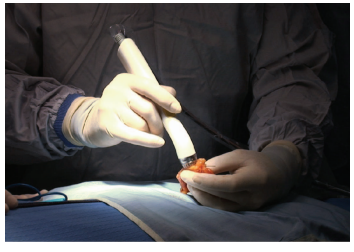

Figure 1:
Tissue characterization probe (Dune Medical Devices, Caesarea, Israel)

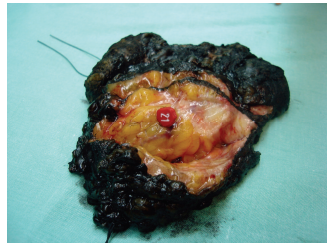

Figure 2:
Tissue data point (site) acquisition and registration process

Inclusion Criteria	Exclusion Criteria
Diagnosis of breast carcinoma (infiltrating or in situ) Undergoing breast conserving surgery Over 18 years of age Signed informed consent	Neoadjuvant chemotherapy Prior surgical procedure of the breast Implants in the operated breast Participating in any other study which may interfere with the protocol or device reading

Table 1:

RESULTS

The probe's performance was analyzed by evaluating 282 tissue measurement sites, from 46 lumpectomy specimens (44 patients), and comparing their histology to device readings. A total of 452 data points were collected. Of these, 143 were excluded due to signal integrity and pathological reporting related issues. There was a total of 76 (24.9%) positive sites within the valid data set. Of these, 23 (30.3%) sites were of malignant content of >30%, and were not used as part of the tested data set. Thus, 282 tested tissue measurement sites were used. Of these, 53 (18.8%) had a malignant tissue component. Out of the 53 positive measurement sites, 22 were DCIS sites, 20 were IDC sites, 6 were mixed invasive and in-situ sites, 3 were ILC, and 2 LCIS (Table 3).

Each probe measurement took only 1-2 seconds to acquire. The handheld probe was simple to use and yielded rapid, reproducible results. Per-measurement site sensitivity was 0.92 (95% CI: 0.82 - 0.98), specificity was 0.76 (95% CI: 0.70 - 0.82), and agreement with pathology was 0.79 (95% CI: 0.74 - 0.84) (Table 2). Positive predictive value and negative predictive value were 0.48 (95% CI: 0.38 - 0.58) and 0.98 (95% CI: 0.94 - 0.99), respectively. The device successfully detected 21 of the 22 DCIS sites, 17 of the 20 IDC sites, 6 of 6 mixed sites, 3 of 3 ILC, and 2 of 2 LCIS sites.

		Histology		
		Malignant	Non malignant	
Probe	Malignant	49	54	103
	Non malignant	4	175	179
		53	229	282

Table 2: ***Probe performance***

Type	Successfully detected by device	Total
DCIS	21	22
IDC	17	20
DCIS+IDC	6	6
ILC	3	3
LCIS	2	2

Table 3: ***Measurement sites composition***

CONCLUSIONS

The performance presented shows promise for use of the device by the surgeon as a tool for immediate assessment of margin status making it a potential attractive alternative to currently available methods of intraoperative margin assessment. The measurement process is fast. The use of the probe does not have any detectable permanent effect on tissue, and therefore will not hinder the routine histopathological assessment process, once used intraoperatively. The design of the probe enables direct use on the specimen as well as on less visible surfaces, possibly in the surgical cavity. The ability to detect DCIS is significant since today DCIS is considered a more challenging intraoperative tissue assessment target. Intraoperative use of the device holds promise for future reduction of re-excision procedures.

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