Quantitative Comparison of Surgical Margin Histology Following Excision With Traditional Electrosurgery and a Low-Thermal-Injury Dissection Device

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Background: This study is the first to examine in vivo the effect of thermal injury in breast conservation pathology in a direct comparison of traditional electrosurgery and an alternative low-thermal-injury device.

Methods: A prospective study of 20 consecutive subjects with biopsy-proven invasive ductal carcinoma (IDC) tumors 1 cm was conducted. Following excision, incisions were made into the tumor with the two devices. Thermal injury depth, margin distance, tissue type, and histological effect were compared on the same breast tissue cut with each excision instrument. A probability evaluation of close and positive margin cases for the true tumor margins was conducted.

Results: Compared to traditional electrosurgery, the low-thermal-injury instrument reduced collagen denaturation depth from 435 to 102 μm (77%), fused tissue depth from 262 to 87 μm (67%), and distortion depth from 1,132 to 774 μm (30%).

Conclusions: Based on analysis of the close subset of the true margins, using the traditional electrosurgical device in place of the low-thermal-injury device would have resulted in 48% of the close margin samples being negatively converted to false-positive, and in 11% converting from close to false-negative. The methodology of this work may be readily applied to larger, more definitive studies.


INTRODUCTION

Breast conservation therapy (BCT) is the standard surgical treatment for breast cancer [1,2]. The goal of BCT is total excision of the malignant lesion while simultaneously preserving the cosmetic appearance and functionality of the breast. The completeness of resection and the potential for residual disease are determined by post-operative histopathologic analysis of permanent tumor sections. A second surgery is indicated when at least one of the following criteria are met: (a) malignant cells are identified at the tissue margin (ink on cancer cells) or (b) malignant cells are identified adjacent to the boundary that separates readable tissue from tissue that is unreadable due to thermal damage (e.g., fused cells, loss of specific staining within nuclei, etc.). Despite advances in surgical technique and pathologic analysis, approximately 20–50% of malignant breast lump excision margins are diagnosed “positive,” and yet, on re-operation, residual disease is found to be present in only 40–70% of these cases [1,3]. False-positive margins can be created by (a) post-operative shrinkage of tissue, (b) the inking process, (c) electrosurgical damage to the margin during excision, and/or (d) appropriately conservative practices with respect to assigning indeterminate specimens. Therefore, reducing thermal injury may reduce a percentage of false-positive margins.

False-negative margin calls also present a serious issue, as they may result in under-staging and under-treatment, especially if the patient does not receive post-surgical radiation. For example, invasive breast cancers may have small, malignant foci near the margin which, when rendered unreadable secondary to thermal damage, can create the illusion of total excision when, in fact, residual cancer is present. The use of a low-thermal-injury technology in this setting, as well, could potentially decrease the number of erroneous negative evaluations.

Abbreviations: Coag, coagulation; ES, traditional electrosurgery; H&E, hematoxylin and eosin; PB, PEAK PlasmaBlade; RF, radiofrequency; SC, scalpel; SD, standard deviation of the mean; SOC, standard of care (scalpel and traditional electrosurgery)

Grant sponsor: PEAK Surgical, Inc.

Disclosures: Manuel E. Ruidiaz, Maria J. Cortes-Mateos, Sergio Sandoval, David T. Martin, Jessica Wang-Rodriguez, Farnaz Hasteh, Anne Wallace, Andrew C. Kummel, and Sarah L. Blair have no relevant disclosures; Joshua G. Vose is an employee of PEAK Surgical, Inc.

Clinical Trial Registry Information—Registry Name: Clinicaltrials.gov, a service of the U.S. National Institutes of Health; Registration ID Number: NCT00972010; Registry URL: http://clinicaltrials.gov/ct2/show/NCT00972010.

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Received 3 February 2011; Accepted 8 June 2011

DOI 10.1002/jso.22012

Published online in Wiley Online Library (wileyonlinelibrary.com).
Attempts to avoid unnecessary re-operation by developing an effective, reliable intraoperative analysis of surgical margins have met with limited success. For example, imprint cytology (i.e., Touch Prep) [4] has been tried in the past, but is not used routinely because an experienced cytopathologist may not always be available to correctly interpret the slides and, as with permanent sections, the reliability of test results are strongly affected by electrosurgical artifact at the sample margin [5]. At the University of California, San Diego, (UCSD), margins of breast malignancies are sub-classified. All measured distances to cancer cells are referenced to the inked surface since that is the most definitive reference point. However, classification of margins as “close” or “positive” is based on the distance between the cancer cells closest to the line dividing the histologically readable tissue (low-thermal damage) and the histologically unreadable tissue (high-thermal damage). Therefore, the three categories of margins at UCSD are: (1) “negative” when margins have greater than 1 mm of normal tissue from cancerous cells to the boundary between readable/unreadable tissue due to thermal injury (other institutions may use 2 mm), (2) “close” when there is less than 1 mm of normal tissue between cancerous cells and the readable/unreadable boundary, and (3) “positive” when cancerous cells are in contact with the readable/unreadable boundary or are at the inked surface. Traditional electrosurgery, even when completely submerged in a liquid medium, introduces thermal injury artifact to a depth of 1–2 mm from the surface, potentially destroying nuclear grading information and degrading fine tissue architecture throughout the critical margin depth [6–12].

At UCSD, a novel, low-thermal-injury technology has recently been evaluated for surgical soft-tissue dissection. The PEAK PlasmaBlade® (PEAK Surgical, Inc., Palo Alto, CA), uses brief (40 μsec), high-frequency pulses of radiofrequency (RF) energy to induce the formation of electrical plasma along the edge of a very thin (12.5 μm wide), flat, 99.5%-insulated electrode [13,14]. With a burst rate less than 1 kHz, a typical duty cycle (percentage of time that energy is transferred to the patient when the device is activated) that does not exceed 5% and a very small exposed electrode surface area, the operating temperature of the PlasmaBlade remains between 40 and 100 °C [14]. This technology, which received FDA 501(k) clearance in 2008 for general surgery applications, has been shown to effectively dissect ophthalmological tissues [14–21] and skin [22] as precisely as a scalpel with the hemostatic control of traditional electrosurgery, even when completely submerged in a liquid medium. In this report, a model is developed to quantify the effect of thermal injury on different breast tissue types and to predict the effect on margin status and final pathology. This model was created to address the absence of a standardized method for quantifying thermal injury, and may be adapted to reflect variation in parameters among individual institutions.

METHODS

Study Design

The protocol for this prospective, controlled clinical study was approved by the Institutional Review Board of UCSD and was conducted in accordance with all accepted standards for human clinical research. All patients gave written informed consent prior to study enrollment. The study tested the hypothesis that reduced thermal injury during resection would result in superior diagnostic quality of tumor specimens, including increased effective distance from the visualized malignant tissue to the excision margin, compared to traditional electrosurgery. The primary quantification was depth of thermal injury artifact, by instrument, as evaluated by permanent histologic analysis. Secondary quantifications were the false-positive and false-negative margin call rates.
paraffin embedding. During the embedding process, the tissue was oriented such that the inked surface (scalpel side) was placed on one side and the electrosurgically incised surface on the other side, thereby allowing slices to show the relationship of the tissue transitioning from unaffected histology to tissue with thermal injury. Ten histological levels were sampled from each paraffin block; five levels (each 5 \( \mu \text{m} \) thick with 30 \( \mu \text{m} \) spacing between levels) from each end of the tissue block. Sectioned levels were stained with hematoxylin and eosin (H&E), coverslipped, and digitally scanned at 20 \( \times \) (0.50 \( \mu \text{m} \) per pixel) magnification on a ScanScope XT (Aperio Technologies, Inc., Vista, CA) slide scanner followed by manual histopathological analysis of thermal injury.

Thermal injury model

There is currently no standardized technique for the evaluation or quantification of thermal injury on tissue sections. Therefore, several quantifiers for thermal injury were created in this study to account for cellular and fibrocollagenous tissues. In our de novo thermal injury model, two zones of fibrocollagenous thermal injury (FTI) and four zones of cellular thermal injury (CTI) were defined by successive levels of heat-exposure-induced stress, which provide discernible visual characteristics on tissue sections. The interplay between CTI and FTI is intermixed and variable across samples. The FTI zones (collagen-denaturized vs. undisturbed tissue) were delineated by the observed thermally induced smoothing of the collagen fibers and darkening of the tissue (Fig. 2, top) [23]. The CTI zones were defined as: (I) complete charring with no cellular structure; (II) fused tissue with severe tissue denaturation, few identifiable structures, indistinguishable nuclei, and tissue breakdown; (III) distressed cellular architecture with a wispy appearance, irregular elongated and spindled nuclei, smudged chromatin, visible distorted fibroblast nuclei, no clear cellular outlines, and cells visible but not clear whether they are epithelial or stromal; and (IV) undisturbed tissue with no signs of thermal injury, fibroblasts identifiable, clear distinction between epithelial and stromal cells, nuclear ultrastructures and chromatin identifiable. The differences are apparent in changes in staining property and tissue structure at low magnification, and changes in cell structures at high magnification (Fig. 2, bottom).

Thermal injury evaluation and categorization. Evaluation of digitized tissue levels was performed using the ImageScope Viewer (Aperio Technologies, Inc.) software. Margins exhibiting signs of thermal injury were identified by locating staining artifact at the margin interface, which appears as a darkening of the stain along with distortion of the cellular architecture. Measurements to quantify FTI and CTI were manually performed using the ImageScope Viewer’s measurement tool: (1) distance from the true margin to the end of the collagen denaturation (FTI), (2) distance from the true margin to the fused/distressed boundary (between CTI zones II/III), and (3) distance from the true margin to the distressed/undisturbed boundary (between CTI zones III/IV) (Fig. 2).

Close margin measurement. Based on routine pathology reports, the true close margins of each patient were identified and digitally scanned at 40 \( \times \) (0.23 \( \mu \text{m} \) per pixel) magnification on an iScan Coreo Au (BioImagene, Inc., Sunnyvale, CA) followed by exact measurement of margin distances on the BioImagene Image Viewer (BioImagene, Inc.). Two distances were measured: the distance from the true inked margin to the closest cancer cells of the closest cluster of malignant cells, and the distance from the true margin to the farthest cancer cell in the closest cluster of malignant cells. In addition, the slides were categorized as FTI or CTI.

Evaluation of possible conventional electrosurgery effects on the true margin. For a negative or close margin, there is no direct extension of the malignant tissue to the true margin or to the
Fig. 2. Histopathologic features of thermal injury. The effects of thermal injury are characterized differently in the two tissue types observed: fibrocollagenous tissue (FTI, above) and cellular tissue (CTI, below). **Top:** The fibrocollagenous tissue is characterized by a zone of collagen denaturation as demarcated by a darkening and smoothing of the collagen staining and a zone of undisturbed tissue. **Bottom:** The cellular tissue is composed of four zones. Zone I is characterized by extensive charring that is often lost during the tissue embedding processing. Zone II has few identifiable cellular structures and mainly consists of fused tissue. Zone III has distressed tissue architecture with a wispy appearance. Zone IV is undisturbed, with cells displaying no evidence of thermal artifact. Dominant characteristics are exemplified in the conceptual drawings below each zone categorization. **Fused tissue:** increased staining uptake, cells not identifiable. **Distressed tissue:** smudge nuclei, unclear cell outlines, distorted cellular arrangement. **Undisturbed tissue:** rounded nuclei, visible nuclear substructures, cell types are identifiable. **Note:** The illustration of the dominant characteristics for each zone categorization are conceptual ink drawings of typical cell types; they are not microscopy images.
Boundary line between the readable and unreadable tissue zones (i.e., the FTI collagen denaturation boundary and the CTI fused/distressed boundary (zone II/III boundary)) (Fig. 3, top). For a margin to be called positive, the malignant cells are either at the true margin surface (touching the ink) or in contact with the zone of unreadable tissue caused by thermal injury adjacent to the true margin surface (Fig. 3, bottom). In excision with traditional electrosurgery, a region of unreadable tissue secondary to thermal injury is imparted just beyond the true margin, which decreases the effective readable distance between the excised cancer cells and the true margin. Therefore, to improve the sensitivity of the interpretation and potentially eliminate false-negative reporting, a cluster of cancer cells that is associated with the unreadable portion of the true margin are called positive by default (Fig. 3, bottom).

The estimated probability of a thermal damage region extending beyond a location near to the true margin, if a traditional electrosurgical device was used in place of the low-thermal-injury device, was calculated by mathematical integration of the traditional electrosurgery thermal injury probability distribution (calculated from the calibrated margins). Each “close” low-thermal-injury true margin was evaluated as three possible binomial event categories, in the case that the FTI collagen denaturation boundary and the CTI fused/distressed boundary line between the readable and unreadable tissue zones (i.e., the FTI collagen denaturation boundary and the CTI fused/distressed boundary (zone II/III boundary)) (Fig. 3, top). For a margin to be called positive, the malignant cells are either at the true margin surface (touching the ink) or in contact with the zone of unreadable tissue caused by thermal injury adjacent to the true margin surface (Fig. 3, bottom). In excision with traditional electrosurgery, a region of unreadable tissue secondary to thermal injury is imparted just beyond the true margin, which decreases the effective readable distance between the excised cancer cells and the true margin. Therefore, to improve the sensitivity of the interpretation and potentially eliminate false-negative reporting, a cluster of cancer cells that is associated with the unreadable portion of the true margin are called positive by default (Fig. 3, bottom).

The estimated probability of a thermal damage region extending beyond a location near to the true margin, if a traditional electrosurgical device was used in place of the low-thermal-injury device, was calculated by mathematical integration of the traditional electrosurgery thermal injury probability distribution (calculated from the calibrated margins). Each “close” low-thermal-injury true margin was evaluated as three possible binomial event categories, in the case that traditional electrosurgery was used instead: (1) there would be no change in switching to traditional electrosurgery (thermal injury did not extend sufficiently to the closest malignancy), (2) there would be a switch to a positive margin with traditional electrosurgery (the closest malignancy is partially unreadable due to thermal injury), or (3) there would be an obscured false-negative margin with traditional electrosurgery (unreadable thermal injury extending beyond the farthest cancer cell of the closest malignancy to the true margin). Each category has an independent probability dependent on the exact margin distances and each was modeled as a Poisson binomial distribution and calculated with a previously described recursive algorithm [24].

Statistics

The R statistical environment software, version 2.12.0 was used for statistical evaluation [25]. Quantifications were described by univariate summaries unless otherwise indicated. Statistical significance was defined as $P < 0.05$. Estimates of probability distributions were performed with the density function in the stats package.

RESULTS

Demographics

Patients were enrolled in the study from July 9, 2009 through July 20, 2010. All patients had core-biopsy proven diagnosis of IDC. Pre-operative patient characteristics are summarized in Table I.

Calibrated-Margin Thermal Injury Depth Metrics

Average, instrument-dependent depth of thermal injury to the calibrated-margin, measured from the cauterized surface to the respective boundary, is summarized in Table II. Compared to traditional electrosurgery, average depth of collagen denaturation (FTI) was reduced by 77% (ES: 435 μm, PB: 102 μm) in PlasmaBlade samples; fused/distressed boundary (between CTI zones II/III) by 67% (ES: 262 μm, PB: 87 μm); and distressed/undisturbed boundary (between CTI zones III/IV) by 30% (ES: 1,132 μm, PB: 774 μm) ($P < 0.001$ for all three measures). The distributions for FTI denaturation, CTI fused/distressed boundary and CTI distressed/undisturbed boundary are displayed in Figure 4.

Estimation of Thermal Injury Reduction With the Low-Thermal-Injury Device Over Traditional Electrosurgery

Based on the probability distributions of each measurement modality of the model, it is possible to determine the probability distribution of the expected change in thermal injury should traditional electrosurgery be replaced with the PlasmaBlade for the calibrated margins (Fig. 5). The average change for FTI collagen denaturation, CTI fused/distressed boundary, and CTI distressed/undisturbed boundary was $-333$, $-175$, and $-358$ μm, respectively. Should traditional electrosurgery be replaced with the PlasmaBlade, it is expected that a reduction in thermal injury would be observed 89%, 74%, and 66% of the time, respectively.

Close Margin Evaluation on the True Surgical Margins

From routine pathologic evaluation of the true surgical margins, 12 permanent sections from 7 cases were assigned pathologic diagnosis of “close” margins (cancer cells within approximately 1 mm of the inked margin surface). Average (SD) distances for all cases were 461 μm (471) and 1,494 μm (976) for the closest and farthest cells, respectively, of the closest cluster of malignant cells (Table III).

TABLE I. Pre-Operative Characteristics of Invasive Breast Carcinoma Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) $^a$</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (9.9)</td>
<td>34–79</td>
</tr>
<tr>
<td>Body-mass index (BMI) (kg/m$^2$)</td>
<td>31 (8.3)</td>
<td>17–49</td>
</tr>
<tr>
<td>Modified Bloom–Richardson score</td>
<td>7.2 (1.6)</td>
<td>5–9</td>
</tr>
<tr>
<td>Sample volume (cm$^3$)</td>
<td>97 (89)</td>
<td>29–414</td>
</tr>
<tr>
<td>Widest sample diameter (cm)</td>
<td>8.3 (1.95)</td>
<td>6.2–14.4</td>
</tr>
<tr>
<td>Tumor volume$^b$ (cm$^3$)</td>
<td>10.4 (15.6)</td>
<td>0.09–66</td>
</tr>
<tr>
<td>Widest tumor diameter$^b$ (cm)</td>
<td>3.4 (1.6)</td>
<td>0.82–7.2</td>
</tr>
</tbody>
</table>

$^a$Sample size (N) = 20.

$^b$One tumor sample was poorly demarcated and unable to be measured.
Thermal Injury Depth and Effect on Margin Evaluation

Traditional electrosurgery probability distribution estimates for each measurement modality were applied to the respective distances that were observed for the 12 “close” margin sections from our dataset, and this method was also used to derive expected changes in margin status (Fig. 6). FTI best described 10 margins while the CTI tissue type best described 2 margins (Table III). For the FTI tissue type, the margin malignancy is possibly affected in three ways; (1) no denaturation effects, (2) partial denaturation effects, or (3) fully affected by denaturation effects. For the FTI tissue of close margins (10 out of the 12 close margins), it is expected the following changes would occur: 47% to have no denaturation effects, 41% to have partial denaturation, and 12% to be fully consumed by denaturation. For the CTI tissue type, the malignancy at the margin could have been affected in four ways: (1) no thermal injury effects so cancer only in CTI zone IV, (2) cancer cells in the distressed CTI zone III, (3) cancer cells partially in the fused CTI zone II, or (4) cancer cells fully in the fused/charred tissue, CTI zones II and I. For the CTI tissue of close margins (2 out of the 12 close margins in CTI IV), if low-thermal-injury excision was replaced by traditional electrosurgery excision, it is expected the following changes would occur: 4% no change in classification, 46% of close margins re-classified as in CTI III, 50% close margins re-classified as partially in CTI II, and 0% of close margin cancer cells totally obscured in CTI I and/or II.

Using the following definitions in our analysis, (1) cells within the CTI charred zone I or fused zone II are unreadable by pathologist, (2) cells within the CTI distressed zone III are readable 50% of the time, and (3) cells within the FTI denatured zone are unreadable, it is expected that from our 12 margin dataset, 41% of the margins would have been judged negative, 48% of the margins would have been judged positive, and 11% of the margins would have been obscured and therefore erroneously judged negative.

Study Cohort Clinical Outcomes

Four patients underwent re-excision for multiple close margins and had whole-breast radiation. Of the re-excisions, one patient had residual classic lobular carcinoma in situ (LCIS), one patient had 1 mm residual IDC and two patients had no residual tumor. One patient refused re-excision and radiation, and her cancer recurred after 1 year.

DISCUSSION

Currently, it is estimated that approximately 20–50% of breast lumpectomies are classified as having positive or close excision margins [26,27]. As excessive thermal injury may confound this critical classification by creating false-positive (changing a close margin to a positive) or false-negative (thermal injury obscuring cancer at or
near the margin) evaluations, it also may critically affect downstream treatment decisions. Therefore, a reduced thermal-injury profile that improves the specificity of the margin determination may in turn improve post-surgical treatment outcomes. To our knowledge, there is currently no published research on the impact of electrosurgical thermal injury on oncologic margin status, or even a standard technique for the evaluation of thermal injury on tissue sections. Furthermore, there currently exists no standardized method to accurately quantify the various degrees of thermal injury imparted by surgical excision tools. Therefore, a novel model (Figs. 1 and 2) was developed to quantify the degree of thermal injury from electrosurgical instruments on true margins. This model exemplifies the traditional types of positive margins that are encountered during routine BCT. FTI is representative of normal tissue with small cancer foci while CTI, being a mostly cellular tissue type, better represents the thermal injury encountered with invasive malignancies. The results of probability distribution estimation (Fig. 4) of the thermal injury quantifications, as defined by our model, showed that, by three different metrics, calibrated margins created using traditional electrosurgery demonstrated a significantly greater depth of thermal injury (Table II). These distributions were used to (1) estimate the reduction in thermal injury when using the low-thermal-injury device over traditional electrosurgery and (2) to estimate the fraction of close margins, created with the low-thermal-injury device which would have altered the margin status had a traditional electrosurgical instrument been used.

**Re-Excision Indications Based on Close Margin Evaluation**

Two potential histopathological outcomes were evaluated. By creating more thermal damage the effective readable distance between the margin and the “close” malignancy can be decreased, thereby forming a smaller “close” margin or an apparent positive margin (a false-positive indication for re-excision). A second possible outcome is that the thermal injury can obscure a small malignancy near the margin (a false-negative indication for re-excision). To properly account for the large variability in thermal injury from both instruments, the full probability distributions (Fig. 4) of thermal injury were employed to calculate probabilities of both outcomes for the true margins.

**Clinical Impact**

Downstream treatment decisions are principally determined by margin status. Based on the 12 margin dataset, the replacement of traditional electrosurgery with the low-thermal-injury device, on average, results in 7 more margins being judged close instead of positive or obscured (false-negative), a conversion of approximately 58%. Therefore, a reduced thermal-injury profile improves the specificity of the margin determination, which in turn may improve post-surgical treatment efficacy. It is expected that the analysis of fibro-collagenous and cellular tissue thermal injury along with its

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**TABLE III. Distances From the Inked True Margin to the Closest and Farthest Cells of the Closest Malignancy, in the “Close” Margin Cohort**

<table>
<thead>
<tr>
<th>Case</th>
<th>Tissue block</th>
<th>Distance from true margin to closest cells of closest malignancy (µm)</th>
<th>Distance from true margin to farthest cells of closest malignancy (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>B13</td>
<td>366</td>
<td>NA (farthest cells not visible)</td>
</tr>
<tr>
<td>3</td>
<td>C3</td>
<td>908</td>
<td>1,365</td>
</tr>
<tr>
<td>3</td>
<td>D4</td>
<td>980</td>
<td>1,429</td>
</tr>
<tr>
<td>7</td>
<td>D7</td>
<td>1,568</td>
<td>3,070</td>
</tr>
<tr>
<td>7</td>
<td>B2</td>
<td>167</td>
<td>1,072</td>
</tr>
<tr>
<td>7</td>
<td>B1</td>
<td>391</td>
<td>614</td>
</tr>
<tr>
<td>9</td>
<td>B6</td>
<td>148</td>
<td>318</td>
</tr>
<tr>
<td>9</td>
<td>B5</td>
<td>67</td>
<td>636</td>
</tr>
<tr>
<td>10</td>
<td>C5</td>
<td>416</td>
<td>878</td>
</tr>
<tr>
<td>10</td>
<td>C6</td>
<td>169</td>
<td>2,660</td>
</tr>
<tr>
<td>17</td>
<td>C4</td>
<td>120</td>
<td>2,861</td>
</tr>
<tr>
<td>20</td>
<td>B2</td>
<td>138</td>
<td>1,029</td>
</tr>
</tbody>
</table>

*Twelve permanent sections from 7 cases, out of 20 total study patients.

*aThese cases were designated as CTI due to the high degree of cellular tissue.

![Fig. 5. Determined thermal injury reduction (red) probability distribution that would be expected when replacing traditional electrosurgery with the PlasmaBlade. Top: Collagen denaturation reduction distribution profile. Middle: Fused/distressed boundary distance reduction distribution profile. Bottom: Distressed/undisturbed distance reduction distribution profile.](image_url)
relationship to oncologic margin status has broad applicability to other tissue types.

**Study Limitations**

Although this study presents FTI and CTI as two uniform entities consisting of mainly fibrocollagenous and cellular tissues, it is often the case that a combination of FTI and CTI within the same tissue type is observed. Furthermore, due to the small dimensions of the calibrated tissue margins, it is possible that the distances for the CTI distressed/undisturbed boundary are under-reported and possibly hiding a larger difference for this category when comparing traditional electrosurgery to the low-thermal-injury device.

In the false-positive margin evaluation, the derived number of close margins affected by thermal injury is dependent on the exact margin distance from the clinical samples obtained. Although these results are encouraging, the present false-positive margin evaluation is a case study for our specific 20-patient clinical study and additional work in larger populations should be undertaken.

**CONCLUSIONS**

This study is the first to quantify the effects of different sources of RF energy on the analysis and interpretation of surgical margins in cancer resection. Thermal-injury artifact has been shown to negatively affect margin status, which consequently affects treatment after surgery and perhaps probability of recurrence. This is a small pilot study of 20 patients, but the methodology has been demonstrated for quantifying the impact of thermal injury on final pathology for use in a larger, definitive study.

**ACKNOWLEDGMENTS**

The authors would like to thank Robbin Newlin, PhD, and Guillermina Garcia for assistance with the digital imaging of histological samples. We also thank Jeanne McAdara-Berkowitz, PhD, Dominique Y. Atmodjo, and Larissa K. Low for assistance with data gathering and manuscript preparation.

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