Original Investigation

Optical Coherence Tomography: A Novel Imaging Method for Post-lumpectomy Breast Margin Assessment—A Multi-reader Study

Richard Ha, MD, Lauren C. Friedlander, MD, Hanina Hibshoosh, MD, Christine Hendon, PhD, Sheldon Feldman, MD, Soojin Ahn, MD, Hank Schmidt, MD, PhD, Margaret K. Akens, PhD, MaryAnn Fitzmaurice, MD, PhD, Brian C. Wilson, PhD, Victoria L. Mango, MD

Rationale and Objectives: This study aimed to assess whether different breast cancer subspecialty physicians can be trained to distinguish non-suspicious from suspicious areas of post-lumpectomy specimen margin in patients with breast cancer using optical coherence tomography (OCT) images (a near-infrared based imaging technique) with final histology as the reference standard.

Materials and Methods: This institutional review board-exempt, Health Insurance Portability and Accountability Act-compliant study was performed on 63 surgically excised breast specimens from 35 female patients, creating a 90-case atlas containing both non-suspicious and suspicious areas for cancer. OCT images of the specimens were performed, providing 6.5–15 μm resolution with tissue visualization 1–2 mm subsurface. From the 90-case atlas, 40 cases were chosen for training and 40 were randomly selected for reader assessment. Three breast imaging radiologists, two pathologists, two breast surgeons, and one non-clinical reader were trained and assessed for ability to distinguish non-suspicious from suspicious findings blinded to clinical data and corresponding histology slides. Duration of training and assessment, sensitivity, specificity, positive predictive value, negative predictive value, and the area under the curve for each reader were calculated as well as averages by subspecialty.

Results: The average training time was 3.4 hours (standard deviation, 1.2). The average assessment time was 1.9 hours (standard deviation, 0.7). The overall average reader sensitivity, specificity, and accuracy for detecting suspicious findings with histologic confirmation of cancer at the surgical margin for all eight readers were 80%, 87%, and 87%, respectively. Radiologists demonstrated the highest average among the disciplines, 85%, 93%, and 94%, followed by pathologists, 79%, 90%, and 84%, and surgeons, 76%, 84%, and 82% respectively.

Conclusions: With relatively short training (3.4 hours), readers from different medical specialties were able to distinguish suspicious from non-suspicious OCT imaging findings in ex vivo breast tissue as confirmed by histology. These results support the potential of OCT as a real-time intraoperative tool for post-lumpectomy specimen margin assessment.

INTRODUCTION

Wide local excision (WLE) is a surgical technique intended to achieve complete removal of malignant neoplasms with negative margins. WLE procedures are performed as part of the preferred surgical management of solid tumors including melanomas (1), cancers of colon or rectum (2), prostate (3), and breast (4,5). In the context of breast cancer, WLE is also known as breast-conserving surgery (BCS) (6). The success of BCS has been linked with the adequacy of disease-free (negative) margin widths on the primary resected specimen (7–10). Failure to achieve negative margins during the primary surgery necessitates a re-excision surgery to remove any residual disease, so increasing health-care costs and surgery-associated physical or psychological morbidity (11–13). Currently, the average re-excision rate among the patients who undergo BCS is about 20% (14,15), with re-excision rates as high as 60% reported in the literature (10,16–18). The high degree of variation in re-excision rates could be reduced with a reliable real-time intraoperative tissue assessment tool for margin involvement of the tumor (18–21).

Current intraoperative breast lumpectomy assessment tools are either histopathology based (such as touch preparation

Acad Radiol 2017; ■:■■–■■

From the Columbia University Medical Center, New York, New York (R.H., L.C.F., H.H., C.H.); Montefiore M-E Center for Cancer Care, Bronx (S.F.); Mount Sinai, New Icahn School of Medicine, New York, New York (S.A., H.S.); Princess Margaret Cancer Centre/University Health Network, Toronto, ON, Canada (M.K.A., B.C.W.); Case Western Reserve University School of Medicine, Cleveland, OH (MA.F.); Memorial Sloan Kettering Cancer Center, New York, New York (V.L.M.). Received June 7, 2017; revised September 12, 2017; accepted September 18, 2017. **Address correspondence to:** R.H. e-mail: rh2616@cumc.columbia.edu

https://doi.org/10.1016/j.acra.2017.09.018

TABLE 1. Requirements for an Ideal Clinically Useful Intraoperative Ex Vivo Breast Tissue Assessment Tool

Required Feature	Description and Rationale
Adjunctive information	Assessment tool output can be combined with the clinician's judgment (based on the current standard of care) and all patient-specific clinical factors
Provides subsurface context	Allows clinicians to review, measure, and differentiate near-surface tissue microstructures, including distinctive features and different breast tissue types, specifically: adipose tissue, fibrous stroma, breast lobules and ducts, as well as in situ and invasive carcinomas
High spatial resolution	Able to discern the subsurface features with 6.5–15 μm resolution (close-to-histology)
Automated acquisition	Standardizes data collection of the whole specimen to eliminate sampling errors, ideally with no increased operator workload (ie, from manipulating an imaging probe) or even minimizing or eliminating the need for an operator
Non-destructive	Preserves entire tissue sample for postoperative pathology. Does not require special subsectioning, staining, or other preparation of the tissue specimen
Rapid intraoperative results	Does not substantially extend the time required for the surgical procedure
Useable by diverse clinicians	Enables use of tool by surgeons, radiologists, or pathologists, as appropriate per institution-specific workflow needs
High accuracy	Provides improved quantitative clinical outcomes (ie, sensitivity, specificity, PPV, NPV, and accuracy) compared to the current standard of care

NPV, negative predictive value; PPV, positive predictive value.

cytology (22,23) and frozen section (23,24)) or non-destructive imaging based (including ultrasound (25,26) and specimen radiography (27,28)). Although histopathology-based methods provide high-resolution representation of the tissue and have shown high sensitivity or specificity in detecting invasive carcinoma (22,25,27,29), they are associated with a number of limitations, including being time-intensive, destructive, prone to sampling error, lacking subsurface information, low sensitivity or specificity in detecting ductal carcinoma in situ (DCIS), and requiring the presence of a pathologist in proximity to the operating room (22–25,27,30). The imaging-based margin assessment techniques have the advantage of being faster compared to the histopathology-based tools; however, it has been shown that imaging has a much lower sensitivity than histopathology in detecting breast cancer within the margin (27). Both imaging techniques (ie, ultrasound and specimen radiography) perform poorly in detecting DCIS without microcalcifications (26,31).

Optical coherence tomography (OCT) is a label-free, non-destructive near-infrared–based imaging technique capable of providing three-dimensional (3D) 6.5- to 15-μm resolution images of resected BCS specimens rapidly without the need for prior gross sectioning (Table 1). OCT is referred to as the optical counterpart of ultrasound because of the similarity of the acquired grayscale images, but uses light instead of sound to extract higher resolution subsurface information to a depth of ~1–2 mm. The source of contrast is differences in absorption or scattering properties of tissue types. OCT is successfully used clinically for ophthalmic (32), intravascular (33,34), and breast (35–40) applications. The sensitivity and specificity of the interpretation will likely improve, dependent on achieving higher resolution with OCT.

The aim of the current study was to assess whether different breast cancer subspecialty physicians (surgeons, radiologists, and pathologists) can be trained to distinguish non-suspicious from suspicious areas of post-lumpectomy specimen margin in patients with breast cancer using OCT images (a near-infrared–based imaging technique), with final histology as the reference standard.

MATERIALS AND METHODS

This study was performed in multiple stages (Fig 1).

Breast Specimen Collection and Imaging

Breast specimens were acquired and imaged at two different sites using two OCT systems with slightly different specifications, as described below. Tissue was obtained through (1) Pathologists Diagnostic Services, NC and (2) Columbia University Medical Center (CUMC), NY. Both instruments used a near-infrared light source centered at 1325 nm. They both provided depth-resolved two-dimensional cross-sectional grayscale images (B-scans) to a depth of about 1–2 mm beneath the tissue surface of excised breast tissue. Dynamic 3D images of the tissue were acquired through continuously acquiring B-scans while laterally scanning the specimen. There is a slight technical difference in axial resolution 12 μm and 6.5 μm and a slight difference in lateral resolution 20 μm and 15 μm for the two systems, respectively, which does not significantly change the quality of the image and is unlikely to impact reader performance. In collaboration with Pathologists Diagnostic Services, de-identified human breast tissue samples that were not being processed as part of standard of care were obtained from lumpectomy or mastectomy specimens in 16 patients. Imaging was performed in the pathology preparation area typically within 1 hour following the surgery. All tissue samples were imaged ex vivo using an OCT system with axial and lateral resolutions of 12 and 20 μm in air, respectively. The acquired 3D images were $14 \times 14 \times 3$ mm^3 in volume. The system took