Use of adjunct wide-field optical coherence tomography to visualize margins during breast conserving surgery for ductal carcinoma in situ: a case series

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ABSTRACT

Background: We recently adopted the use of wide-field optical coherence tomography (WF-OCT)—an imaging modality that enables high-resolution visualization of tissue organization and architecture near the surface of excised tissue samples—into our breast surgical oncology practice. Herein we describe adjunct, intraoperative use of WF-OCT to image the margins of lumpectomy specimens during breast-conserving surgery (BCS).

Case presentation: Three adult women (ages 75, 64, and 76) with biopsy-proven ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC) underwent BCS according to institutional standard of care, except that immediately following specimen radiography and prior to inking for permanent histopathology, resected specimens were scanned using WF-OCT imaging. In each case, the surgeon reviewed the images intraoperatively and, based on visualization of tissue microarchitecture suspicious for malignancy, removed additional tissue prior to conclusion of BCS. Permanent histopathology confirmed residual and occult DCIS or IDC, involving one or more margins, in all primary specimens and also confirmed that all final margins were negative for residual disease. None of these 3 patients were called back for re-excision.

Conclusions: The intraoperative decisions made by the surgeon after review of the WF-OCT images improved confidence in the completeness of resection, while sparing these 3 patients—2 of whom faced social obstacles to follow-up care—from the need for reoperation.

Key words: Breast-conserving surgery; intraoperative margin analysis; optical coherence tomography; social determinants of health.

Abbreviations: ASBrS – American Society of Breast Surgeons; ASCO – American Society of Clinical Oncology; ASTRO – American Society for Radiation Oncology; BCS – Breast-conserving surgery; DCIS – Ductal carcinoma in situ; ER – Estrogen receptor; IDC – Invasive ductal carcinoma; LCIS – Lobular carcinoma in situ; OCT – Optical coherence tomography; PR – Progesterone receptor; SSO – Society of Surgical Oncology.

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In the United States, the overall rate of reoperation to remove additional tissue and achieve negative margins after breast-conserving surgery (BCS) has been estimated at 23.2% of cases,[1] and under some circumstances may be as much as double that figure.[2,3]

Reoperation for positive margins is associated with tens of thousands of dollars in additional health care costs, a 47.6% higher likelihood of postoperative complications compared to the primary surgery, delays in initiation of adjuvant treatment, detrimental effects on cosmetic outcomes, and emotional trauma to the patient.[1,4–7]

In order to better guide clinical decision-making regarding the need for re-excision surgery, the Society of Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO) have issued consensus guidelines calling for a 2 mm negative surgical margin for ductal carcinoma in situ (DCIS), and "no ink on tumor" for invasive breast cancer, when BCS is followed by adjunct breast irradiation.[7,8]

Together with a toolbox of evidence-based recommendations, issued by the American Society of Breast Surgeons (ASBrS) for reducing lumpectomy reoperations,[2,3] the SSO/ASTRO guidelines have improved reoperation rates;[9-11] however, room for improvement remains.

Among the 10 recommendations in the ASBrS toolbox, one with strong scientific support is the use of intraoperative pathology assessment, although the authors of the toolbox have added qualifiers that such assessments are highly resource intensive and should be performed "when feasible." These caveats reflect the known limitations of current methods for intraoperative margin assessment. Available techniques —such as specimen radiography, ultrasound, touch -prep cytology, and frozen-section analysis—each come with a specific set of limitations that represent areas for improvement, including requirements for specialized pathology staff, poor sensitivity or visual resolution, sampling bias, delays that extend overall procedure time, and prohibitive costs. While routine shave margins have recently been recommended by ASBrS, they are not without potential drawbacks including unnecessary removal of healthy tissue, negative effects on cosmesis, and increased pathology costs.

Optical coherence tomography (OCT) is an imaging modality that exploits the light-reflecting, transmitting, and backscattering properties of biological tissues to produce images in a manner analogous to the use of sound waves in ultrasound imaging.[12-17] Recent advances in OCT imaging include the use of a flatbed scanner capable of producing wide-field (WF-OCT) images with improved power and resolution compared to handheld, swept-source OCT probes.[12,13] As a rapid, simple, high-resolution, and non-destructive modality, WF-OCT is a promising potential adjunct imaging tool to help surgeons evaluate specimen margins in the operating room.

The first system for flatbed, WF-OCT imaging of surgical specimens (Perimeter S-Series OCT; Perimeter Medical Imaging AI, Inc., Toronto, Ontario, Canada) was cleared by the United States Food and Drug Administration for clinical use in 2021. This system captures highly detailed optical tissue sections at a resolution of 6 to 15 µm and at a depth of up to 2 mm.[12,13] These images are of sufficient detail to allow visualization of lobules and ducts, glands, blood vessels, cysts, adipose tissue, fibrous tissue, calcifications, and the overall cellular organization within the tissue layers of a specimen.[12,13]

We recently adopted this WF-OCT system into our practice and are evaluating it as an adjunct method for intraoperative margin assessment during BCS. In this paper, we describe the outcomes from 3 cases in which WF-OCT image review revealed residual margin microstructure that was not evaluable with preoperative diagnostic imaging or with intraoperative specimen radiography. Using all of the clinical and laboratory information along with the supplemental data from WF-OCT images, the surgeon decided to remove additional tissue, ultimately sparing these patients from re-operation.

PATIENTS AND METHODS

Ethics approval and consent to participate

This was a retrospective review of prospectively collected data from patients undergoing BCS at our hospital. IRB review was waived for this small retrospective case series. All patients gave written informed consent for their data to be published as part of this case series.

WF-OCT imaging system

The WF-OCT imaging system in use at our institution is the Perimeter S-Series OCT System (Perimeter Medical Imaging AI, Inc., Toronto, Ontario, Canada). The components of the system are a cart-mounted, flatbed scanner, a control console with touch-screen user interface, and single-use lidded trays for specimen handling and immobilization. The user interface controls the device settings and contains all software necessary for viewing, analyzing, and annotating 2D images and 3D, volumetric reconstructions, as well as an onboard library of pathologist-curated OCT and histopathology images on multiple tissue types for training and reference.

The surgeon was trained to interpret WF-OCT images using a protocol and materials developed by the device manufacturer. The protocol included training in the image acquisition and interpretation process; skills practice; and a summative evaluation using a curated set. The device itself does not identify regions of interest, such as those suspicious for malignancy. Images provided by the device are reviewed by the surgeon, who evaluates tissue microstructures according to their own clinical judgement.

Patients and procedures

Patients were adult women diagnosed after routine surveillance and/or diagnostic mammography with either biopsy-proven DCIS or IDC, who subsequently underwent BCS. Procedures were conducted according to institutional standard of care, except that after intraoperative specimen radiography and just before inking, all margins of the primary lesions were scanned using the WF-OCT imaging device.

After radiographic location of biopsy clips, wireless localization devices, and calcifications, each specimen was placed in a tissue-handling tray and the anterior, posterior, medial, lateral, superior, and inferior

specimen margins were scanned under gentle vacuum pressure, according to the device operating manual. The surgeon reviewed images to evaluate tissue microstructures and identify regions of interest. Using all clinical and laboratory information available during the procedure, along with the supplemental data from WF-OCT images, the surgeon decided whether or not to remove additional tissue. Following intraoperative clinical assessments, the primary and additional tissue samples were inked according to standard techniques, fixed in neutral buffered formalin, and submitted to pathology to be processed for standard, permanent histopathology.

Patient 1

Patient 1 (Fig. 1) was a 75-year-old woman who had a past medical history of hypertension and hypothyroidism, and who was being followed for a benign, chronic meningioma. A routine surveillance mammogram in May 2021 revealed new, clustered, suspicious calcifications central to the nipple middle depth that were indeterminate (BI-RADS 0). Subsequent diagnostic mammography in October 2021 revealed a 1.6 cm area of clustered, heterogeneous calcifications suspicious for malignancy (BI-RADS 4B) in the right breast.

A right stereotactic core needle biopsy (CNB) identified DCIS, positive for estrogen and progesterone receptors (ER and PR, respectively). Notably, the diagnosis and biopsy were delayed due to COVID-19 concerns, causing the patient generalized anxiety about her appointments and necessitating prescription anxiolytics.

The patient underwent a right, wireless localized, partial mastectomy. The primary excised specimen measured 4.0 x 3.6 x 3.2 cm. All margins appeared satisfactory by intraoperative specimen radiography and the previous biopsy clip was centered within the specimen; however, the surgeon's review of WF-OCT images collected intraoperatively showed features, including 3 annular intraductal lesions, at the inferior margin, which the surgeon interpreted as likely representing DCIS. A short video shows this in more detail. https://oct.perimetermed.com/tower-case-study

Additional inferior margin tissue measuring 3.1 x 2.5 x 0.8 cm. was excised as a precaution and submitted to pathology with the primary specimen. On evaluation of tissue microstructures within the final intraoperative margin, the surgeon did not identify any additional regions of interest.

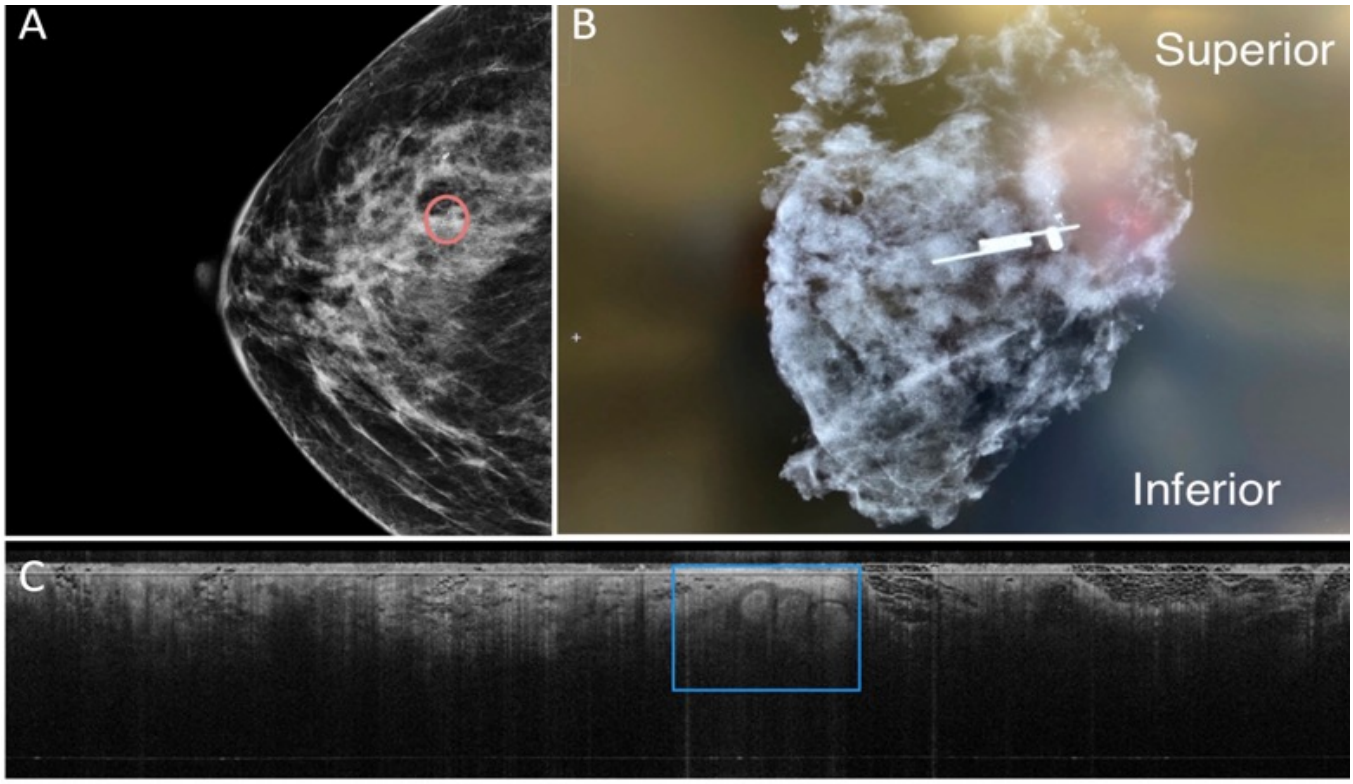

***Fig. 1**: Imaging results from Patient 1. A) mammogram showing clustered, heterogeneous calcifications evaluated by a radiologist to be suspicious for malignancy (red circle). B) Specimen radiograph with biopsy clip, localization device, and calcifications present. C) WF-OCT section (b-scan) of the region of interest showing 3 dilated intraductal annular lesions approaching the margin (blue box), which pathology confirmed to be extensive DCIS.*

Permanent histology confirmed extensive DCIS in the primary specimen, with involvement at the primary inferior margin. At the new inferior margin, histology showed additional DCIS measuring 0.1 cm. All final margins were negative. The total inferior surgical margin was 1.1 cm. No invasive carcinoma was identified in any specimen. The patient recovered from surgery with no complications and completed adjunct radiotherapy. She continues a recommended 5-year course of antiestrogen therapy.

Patient 2

Patient 2 (Fig. 2) was a 64-year-old woman who underwent routine surveillance mammography in September 2021 that revealed the presence of bi-lateral breast abnormalities (BI-RADS 0). Further diagnostics suggested a benign cyst of the right breast (BI-RADS 3), and suspicious calcifications in the left breast (BI-RADS 4). A subsequent stereotactic CNB confirmed high nuclear-grade ER/PR-positive DCIS with comedo-necrosis.

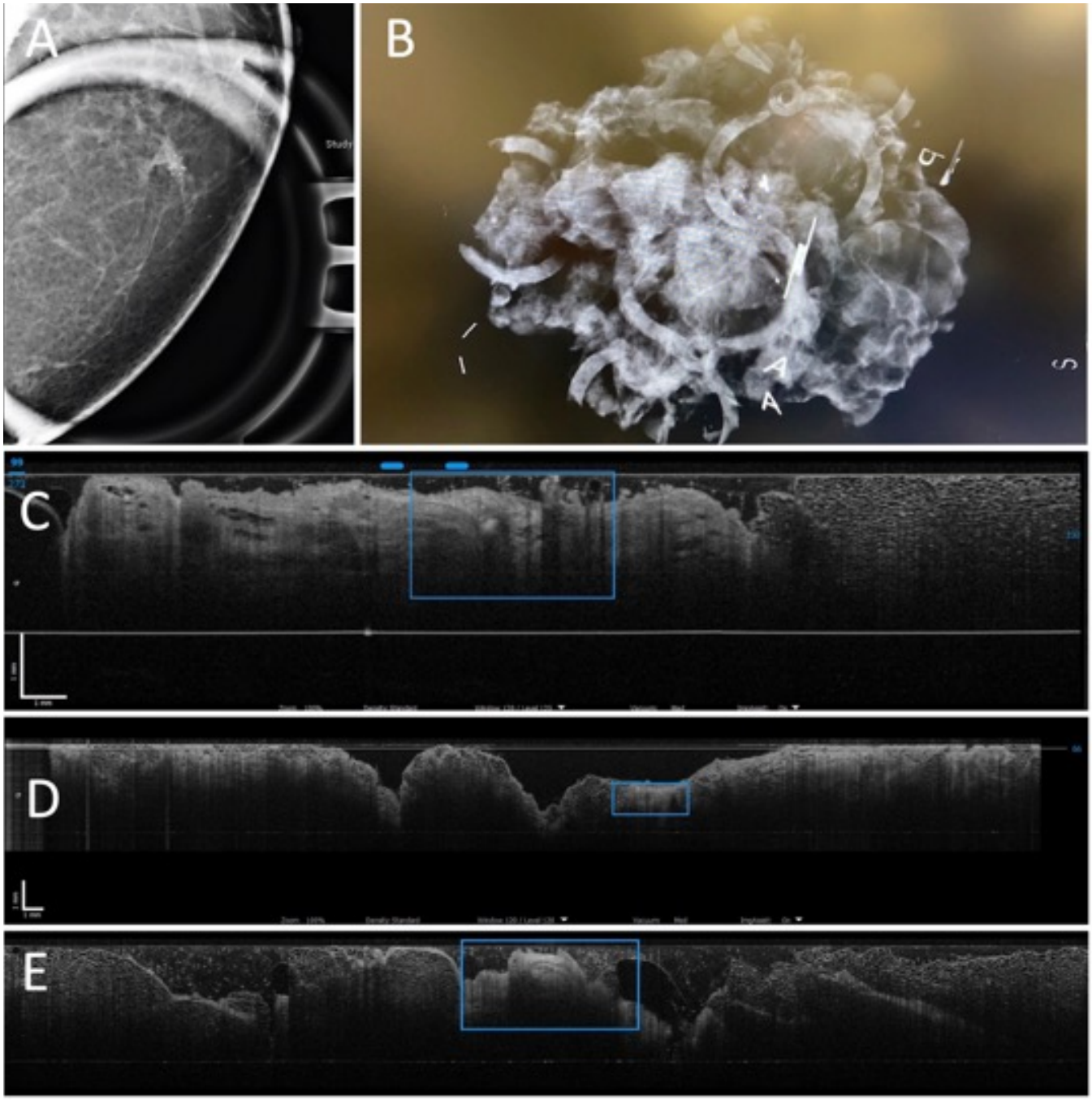

***Fig. 2**: Imaging results from patient 2. A) mammogram showing suspicious clustered calcifications. B) Specimen radiograph showing the biopsy clip, localization device, and calcifications. C) WF-OCT image from the inferior margin showing a dilated duct with an intraductal annual lesion and associated calcifications (blue box; confirmed as DCIS by pathology). D) and E) WF-OCT image from the posterior margin showing annular lesion within a dilated duct (blue boxes), which pathology confirmed to be pleomorphic LCIS.*

The patient's medical history was significant for essential hypertension and a myocardial infarction with stent placement 3 years prior. Her social history was significant in that she resided in a rural community 2 hours away from the surgical center and faced significant financial and logistical barriers to travel.

The patient underwent a left, wireless localized, partial mastectomy. The excised primary specimen measured 4 x 3.5 x 3.5 cm. Intraoperative specimen radiography suggested satisfactory margins with the previous biopsy clip centered within the resection; however, surgeon review of intraoperative WF-OCT images identified a dilated duct with an intraductal annular lesion and associated calcifications, which can be associated with malignancy, at the inferior and posterior margins. Additional tissue was excised at each margin and the final intraoperative margin was scanned using WF-OCT to visualize any remaining features. The additional tissue was submitted with the primary specimen.

Permanent histology of the primary specimen confirmed focal DCIS within 1 mm of the inferior margin, and focal pleomorphic lobular carcinoma in situ (LCIS) present within microns of the posterior margin. Histology of the new inferior margin showed benign fibroglandular tissue with no atypia or malignancy. The new inferior margin total was 1 cm. Histology of the new posterior margin confirmed the presence of pleomorphic LCIS, with a negative final margin (total depth 8 mm) and no DCIS. No invasive carcinoma was identified in any specimen. The patient recovered from surgery with no complications, completed adjunct breast radiotherapy, and continues on antiestrogen therapy.

Patient 3

Patient 3 (Fig. 3) was a 76-year-old woman whose most recent prior mammogram was in 2007 and who self-palpated a right-breast mass in September 2021. Diagnostics revealed a 1.9 x 1.9 x 1.7 cm mass with internal calcifications noted at 12:00 (BI-RADS 5). Ultrasound-guided CNB confirmed grade-2 invasive ductal carcinoma (IDC) that was ER/PR positive and HER2 negative. The patient's medical history was significant for type 2 diabetes mellitus and hypertension.

The patient underwent right partial mastectomy

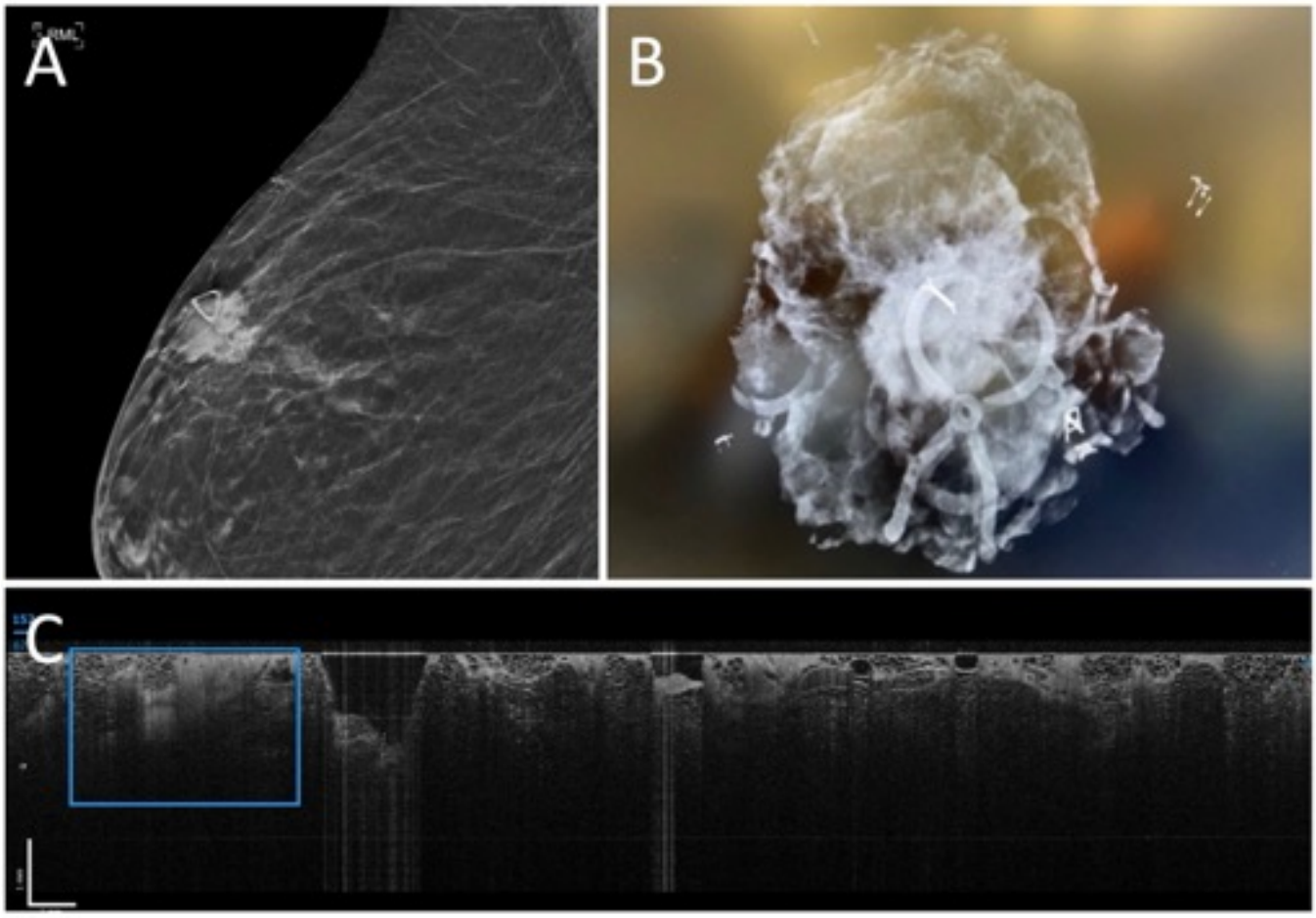

***Fig. 3**: Imaging results from patient 3. A) mammogram showing 1.9 cm mass with internal calcifications. B) specimen radiograph with biopsy clip. C) WF-OCT image of the lateral margin showing a dilated duct with annular lesion, which pathology confirmed to be extensive, occult DCIS <1 mm from the margin and located approximately 10 mm distant from the primary tumor.*

with a sentinel lymph node biopsy (2 nodes) for surgical management. The excised primary specimen was 6.5 x 5.3 x 4.2 cm. An intraoperative specimen radiograph suggested satisfactory margins with the biopsy clip centered within the specimen. On review of the intraoperative WF-OCT imaging, the surgeon noted a dilated duct with an annular lesion not observed in the biopsy specimen and decided to take additional tissue at the lateral margin. Once the surgeon was satisfied with the appearance of the additional margins, the additional tissue was submitted to pathology with the primary and lymph node specimens.

Final pathology of the primary specimen confirmed infiltrating ductal carcinoma of the right breast (grade 3; 2.4 cm) at 12 o'clock, with extensive DCIS (high-grade, solid type, with necrosis) extending up to 15 mm on a single slide, mostly outside the contours of the invasive component (approximately 20% of the tumor area). While all margins for the IDC component of the tumor were negative (>10 mm), DCIS foci were present less than 1 mm from the primary lateral margin. The additional excised margin tissue contained DCIS and was margin-negative (>5 mm from the final margin). The patient recovered from surgery with no complications and completed adjunct chemotherapy (recommended based on an Oncotype DX test result) and radiotherapy. The patient continues adjunct endocrine therapy.

DISCUSSION

In this case series of 3 adult women undergoing BCS for biopsy-proven breast carcinoma, intraoperative WF-OCT imaging provided the surgeon with beneficial adjunct information, within a timeframe that enabled clinical action at the time of surgery. WF-OCT images could be acquired, read, and interpreted in approximately 1 to 2 minutes per margin, or 10 to 15 minutes for a whole specimen, and did not interfere with the flow or overall duration of the surgical procedure. After scanning, the specimens could quickly be inked, fixed, and sent to pathology for full histopathologic analysis with no effect on their integrity or the pathology results.

In all 3 cases, the surgeon was able to use WF-OCT images to evaluate tissue microstructures to identify regions of interest that were not detected with intraoperative specimen radiography. Using this adjunct information in addition to all of the other clinical information available at the time, the surgeon made the decision to excise additional tissue from the tumor cavity. The high level of visual detail in the WF-OCT images was consistent with 2 previously published pilot studies.[12,13] The first showed that readers from different medical specialties could be trained to differentiate between suspicious and non-suspicious OCT imaging findings in ex vivo breast tissue, within a short (3.4 h) timeframe.[13] The second study demonstrated a high level of concordance between WF-OCT images and histopathology in ex vivo breast tissue samples.[12] While these were pilot studies that did not evaluate the utility of WF-OCT for intraoperative decision-making, in our patients, standard-of-care histopathology subsequently confirmed the findings at the primary margin(s) and helped the surgeon achieve negative margins following the excision of additional tissue.

Nationwide efforts to reduce the relatively high average rate of reoperation after BCS depend on a number of complementary strategies, which include improving surgeon acceptance and adherence to evidence-based guidelines for acceptable margins,[7,8,10] as well as encouraging the standardization and adoption of clinical practices that provide confidence that both the necessary and sufficient volume of tissue has been resected during the primary procedure.[2,3]

From the perspective of the patient, many of the clinical, economic, and psycho-emotional consequences of reoperation have been reported;[1,4-6,11] what is less easily measured, and therefore may be missed in such analyses is the impact of re-operation on the daily reality of patients' lives, especially considering the diversity of personal resources and barriers to health care access that comprise each patient's "social determinants of health." For example, the first patient reported here developed COVID—19 related anxiety that delayed her biopsy and resulted in reluctance to have procedures performed in the hospital setting. A call-back for reoperation could have precipitated additional anxiety, need for additional prescription medications, or even non-compliance for a re-excision. The second patient resided 112 miles away from the surgical center and required family coordination and extra finances for transportation to attend the surgical procedure—obstacles that would have become even greater with a reoperation.

On the other hand, while evidence suggests that intraoperative margin assessment can be an effective approach for reducing reoperation rates,[18-21] existing technologies have been criticized for poor accuracy; margin sampling errors; increased costs for additional pathology; disruptive effects on staffing, workflow, procedure time, and demand for operating room time; or some combination of these factors.[2,19,20,22-24] Such factors can be especially prohibitive at medical

centers serving small, dispersed, rural, or otherwise underserved populations. The ease of integrating WF-OCT into our surgical and pathology workflow and the high level of resolution and detail available in the images suggest that this technology may address some of the limitations of other tools and improve access to cutting-edge intraoperative margin visualization outside of regional academic centers.

Limitations

This is a small, descriptive case series presenting patients with similar outcomes, and therefore no generalizations can be made regarding the effect of WF-OCT use on clinical outcomes. However, our experiences to date with WF-OCT are encouraging and justify further, rigorous assessment of the technique in comparison to other methods for intraoperative margin evaluation.

CONCLUSION

Intraoperative imaging of primary lumpectomy specimen margins using WF-OCT during BCS provided the surgeon with useful adjunct information. The surgeon was able to make an intraoperative clinical decision to excise additional tissue during the primary surgery, sparing these 3 patients the need for a second surgery and relieving the associated burden on clinical, economic, and psychosocial resources.

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