WHITE PAPER

Adjunct intraoperative optical coherence tomography imaging and reoperation rate after breast-conserving surgery

Amelia A. Gunter, M.D.

The Center for Cancer and Blood Disorders, Weatherford, TX

ABSTRACT

Background: Breast-conserving surgery (BCS) has become standard of care for treating early-stage breast cancers, including both invasive carcinomas and ductal carcinoma in situ (DCIS). However, when negative surgical margins are not achieved during the primary BCS procedure, re-excision may be necessary. In the U.S., optical coherence tomography (OCT) is available as an imaging modality with a general indication for use as an imaging tool in the evaluation of excised human-tissue microstructure. In October 2022, our institution adopted use of the Perimeter S-Series OCT (Perimeter Medical Imaging AI, Inc., Dallas, Texas) for obtaining adjunct imaging data from all specimens excised during BCS procedures. The purpose of the present study was to perform a retrospective, quantitative assessment of reoperation rates among patients in our practice who underwent OCT imaging during BCS in order to gain insight into the potential benefits and limitations of OCT for patient outcomes.

Methods: This was a retrospective, single-center, observational cohort study using existing data from all eligible BCS procedures that were performed in our practice in the era after adjunct, intraoperative OCT imaging was adopted into our routine practice. Patients were adults (≥ 18 years of age) who underwent primary BCS for a biopsy-proven breast malignancy, with adjunctive OCT imaging for intraoperative margin assessment, between 11 OCT 2022 and 21 NOV 2023. Patients who had undergone prior BCS in the same breast, or whose procedure was performed outside of the study date range, were excluded. During each operation, the surgeon decided whether to excise additional margin shaves based on their clinical judgment and the interpreted results of both OCT and any standard-of-care intraoperative assessments. Postoperative decisions to excise remaining residual solid tumor were made by the surgeon based on the results of standard-of-care final histopathology, performed by a pathologist. The primary endpoint was the rate of reoperation for close or positive margins among patients in our practice compared to the most recent published national average range of 14.9% - 21.1%.[1,2]

Results: Out of 95 records assessed for eligibility, 72 patients (66.2 ± 9.96 years of age, 100% female) met eligibility criteria and were included in the analysis (Tables 1 and 2). Two patients underwent bilateral BCS at the time of index procedure, for a total of 74 surgical procedures. Reoperation for close or positive margins, as determined by final pathology, was performed in 4/72 patients for a patient-level reoperation rate of 5.6% (4/74 individual breasts, 5.4%). Final pathology for the four reoperations confirmed DCIS in three patients and DCIS/IDC/mucinous carcinoma in one patient.

Conclusions: In the era after OCT was adopted into our practice, the reoperation rate after BCS (5.6%) was lower than the most recent published national average (14.9%-21.1%).[1, 2] Our results provide insight into the potential use of intraoperative OCT imaging as an adjunctive margin assessment tool to achieve negative margins during primary BCS. Further research is warranted to ascertain how our results may be generalized to help address the current BCS reoperation epidemic.

KEY WORDS

Breast-conserving surgery; intraoperative margin analysis; optical coherence tomography; reoperation; re-excision

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

HER2 – Human epidermal growth factor receptor-2

IDC – Invasive ductal carcinoma

ILC – Invasive lobular carcinoma

LCIS – Lobular carcinoma in situ

OCT – Optical coherence tomography

PR – Progesterone receptor

SSO – Society of Surgical Oncology

INTRODUCTION

Breast-conserving surgery (BCS) has become standard of care for treating early-stage breast cancers, including both invasive disease and ductal carcinoma in situ (DCIS), with an estimated 60 to 70% of those patients undergoing BCS.[2]

The achievement of negative resected margins during BCS is essential to minimizing the risk of local recurrence. Therefore, a postoperative finding of positive or close margins—defined in Society of Surgical Oncology-American Society for Radiation Oncology (SSO-ASTRO) and American Society of Breast Surgeons (ASBrS) guidelines as "ink on tumor" for invasive disease (IDC with or without DCIS) and 2 mm or less for isolated DCIS[3-5]—generally results in the patient returning for a second BCS, undergoing additional treatments, or having to undergo a total mastectomy. Additional surgeries due to close or positive margins have been reported to occur at an average rate of approximately 20%, although rates vary widely and range from less than 10% to 40% or higher.[6] While they are necessary to reduce the risks of local recurrence, the trade-off is that reoperations increase the risk of treatment delays, surgical complications, adverse outcomes, and additional healthcare costs.[1, 6-8]

Despite improvements in national reoperation rates following the release of the SSO-ASTRO and ASBrS guidelines for lumpectomy margins, the rates remain stubbornly high and have been described by ASBrS as an 'epidemic' in breast cancer care.[1, 6, 9] Unfortunately, technologies to help surgeons assess specimen margins intraoperatively and understand the extent of disease before concluding a BCS procedure are limited. Most surgeons must wait for a week or more for the results of final pathology before deciding whether or not a second surgery is necessary. New tools for intraoperative tissue imaging and margin assessment are needed to help surgeons achieve negative resection margins during the primary BCS procedure.[9, 10]

One emerging approach to address the reoperation issue is the application of wide-field optical coherence tomography (OCT) for intraoperative imaging of excised tissue. WF-OCT is a nondestructive imaging modality that uses the principle of near-infrared interferometry to produce high-resolution, cross-sectional, and volumetric images of tissue regions of interest, in a manner analogous to the use of sound waves for ultrasonographic imaging.[11, 12]

In October 2022, our practice adopted use of the Perimeter S-Series OCT (Perimeter Medical Imaging AI, Inc., Dallas, Texas) to obtain adjunct imaging data from all specimens excised during BCS procedures. The S-Series OCT has U.S. FDA 510(k) clearance under a general indication for use as an imaging tool in the evaluation of excised human tissue microstructure, by providing two-dimensional, cross-sectional, real-time depth visualization, with image review manipulation software for identifying and annotating regions of interest. The S-Series OCT has not been evaluated by the FDA specifically for use in breast tissue, breast cancer, other types of cancer, margin evaluation, or in reducing reoperation rates, although this specific use has been an area of research since 2018.[13-16]

The following study is an analysis of our first year of clinical experience with the S-Series OCT. Our goal was to provide a retrospective, quantitative assessment of reoperation rates among patients that had OCT imaging compared to the national average reoperation rate (without OCT imaging), in order to gain insight into the potential benefits and limitations of OCT for patient outcomes.

METHODS

Study overview and ethics

This was a retrospective, single-center, observational cohort study using de-identified data from patient charts. The protocol was reviewed by WCG IRB (Princeton, New Jersey, USA) and determined to be exempt from informed consent requirements. The objective of the retrospective study was to determine the rate of reoperation for close or positive margins after primary BCS for biopsy-proven malignancy when adjunct, intraoperative OCT imaging was used as a tool to aid the surgeon in evaluating lumpectomy specimen

margins, as compared to the most recent published national average range of 14.9% - 21.1%.[1, 17]

Test article description

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.[11, 12, 14, 15, 18, 19] 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.[14, 15] 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.[9, 11-16]

The first system for flatbed, WF-OCT imaging of surgical specimens (Perimeter S-Series OCT; Perimeter Medical Imaging AI Inc., Dallas, Texas) was cleared by the United States Food and Drug Administration for commercial 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.[14, 15] 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.[14, 15]

The Perimeter S Series OCT system in use at the study site was installed in October of 2022. The system components include 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. An on-board library of pathologist-curated OCT and histopathology images on multiple tissue types were used for training and reference for OCT interpretation.

Training on the interpretation of WF-OCT images was conducted 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 his or her own clinical judgment.

Patient selection

The study population consisted of all consecutive adult patients (≥ 18 years of age) who underwent primary BCS at our practice, with adjunctive OCT imaging for intraoperative margin assessment, for a biopsy-proven breast malignancy between 11 OCT 2022 and 21 NOV 2023. Patients who underwent a prior BCS on the same breast, or whose index procedure was performed outside of the study date, were excluded.

Study procedures

During the BCS procedures, in addition to standard-of-care intraoperative assessment, intraoperative OCT imaging of the surgical specimen was also performed. The decision to excise additional margin shaves was based on clinical judgment and consideration of all information available from the intraoperative assessment methods used. When margin shaves were excised, the additional tissue was also imaged using OCT.

Following surgery, the primary specimen and additional margin shaves were sent for final pathology assessment. Decisions to bring patients back for reoperation were made by the surgeon based on the results of final pathology, in accordance with the ASBrS Consensus Guideline on Breast Cancer Lumpectomy Margins.[5]

Endpoints and measures

The primary outcome measure was reoperation due to close or positive margins as determined by the study-site pathology department's standard of care.

Data analysis

This study was a retrospective chart review with no control cohort. Statistics were descriptive only, with no formal inferential analysis, hypothesis testing, or regression/correlation analysis.

RESULTS

Baseline demographics and clinical characteristics

Between 11 OCT 2022 and 21 NOV 2023, 95 patients in our practice underwent primary BCS. A total of 72 patients met eligibility criteria (Figure 1). Of those, two underwent bilateral BCS procedures and therefore a total of 74 BCS procedures were performed.

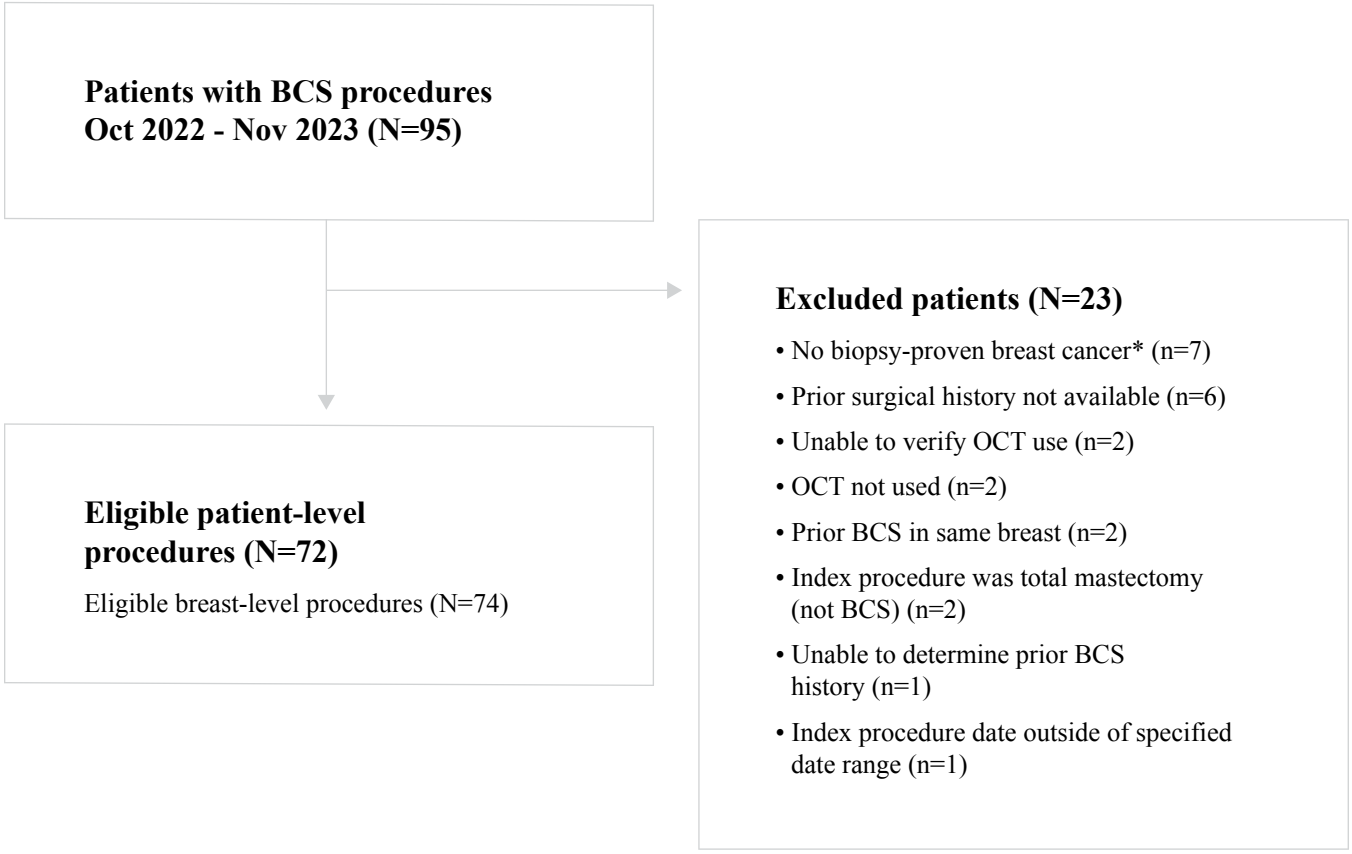

Figure 1. Patient Disposition.

*Preoperative diagnoses for excluded patients included atypical ductal hyperplasia (n=2), complex sclerosing lesion (n=1), atypia (n=1), apocrine metaplasia (n=1), atypical papillary neoplasm (n=1), and abnormal mammogram with history of LCIS and focal LCIS (n=1).

Abbreviations: BCS, breast-conserving surgery; OCT, optical coherence tomography.

Baseline characteristics are summarized in Table 1. Data were not consistently available for race, menopause status, prior radiation treatment, prior chemotherapy treatment, and current medications for all patients. Therefore, those baseline characteristics were not included in the analysis.

Table 1. Baseline demographics and clinical characteristics*

Characteristic		Value
Age, y	Mean ± SD	66.2 ± 9.96
	Median (Min, Max)	65 (44,75)
Sex, F		72/72 (100%)
BMI		30.8 ± 6.4
Previous surgery, not breast related		44/64 (68.8%)
Smoker		
Current		5/69 (7.2%)
Former		19/69 (27.5%)
Never		45/69 (65.2%)
Alcohol use		33/67 (49.3%)
Family history of breast cancer		18/54 (33.3%)
Pre-operative biopsy diagnosis		
IDC		32/72 (44.4%)
DCIS		17/72 (23.6%)
DCIS + IDC		12/72 (16.7%)
ILC		8/72 (11.1%)
ILC + LCIS		2/72 (2.8%)
Mucinous carcinoma		1/72 (1.4%)
Hormone receptor status		
ER +		62/68 (91.2%)
PR +		55/68 (80.9%)
HER2 +		8/59 (13.6%)

*Data are patient-level and presented as mean ± SD or n/N (%), with N representing the number of evaluable patients for each characteristic.

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; PR, progesterone receptor.

IDC, DCIS, and combined diagnosis of IDC/DCIS were the most common types of pre-surgical diagnosis, representing 84.7% of patients in the study group. A large majority of patients had hormone-positive breast cancers.

Primary outcome

Out of 72 eligible patients, four were brought back for reoperation due to the presence of positive margins, presenting an overall reoperation rate of 5.6% (at the level of individual breasts, the reoperation rate was 4/74 or 5.4%). The reoperation rate among patients with any preoperative diagnosis of IDC was 0/44 (0.0%), whereas the reoperation rate among patients with any preoperative diagnosis of DCIS was 3/29 (10.3%). The single patient with a mucinous carcinoma preoperative diagnosis underwent reoperation due to the final-pathology finding of DCIS at multiple margins, and therefore the overall rate of reoperation due to DCIS at or near the margin was 4/30 (13.3%).

There were no reoperations for positive margins in patients with ILC and/or LCIS; however, one patient with preoperative pathology of ILC and LCIS and postoperative pathology showing IDC with all margin widths ≥ 0.3 mm, underwent elective bilateral mastectomy due to extensive LCIS at the specimen margins and in a biopsy of the contralateral breast. This case was not counted as a reoperation because isolated LCIS is not considered to be cancerous, and the mastectomy was performed electively even though the ASBrS "ink on tumor" criterion for reoperation was not met.[5]

DISCUSSION

This study found that, in this real-world patient population, the patient-level reoperation rate was 5.6% (4/72) after primary BCS procedures in which OCT imaging was used as part of the intraoperative assessment routine. The breast-level reoperation rate was 4/74 (5.4%).

Historically, published rates of reoperation after primary BCS have varied widely between institutions and surgeons, ranging from approximately 10% to 32% or even higher.[6] Following the publication of the SSO-ASTRO consensus "no ink on tumor" guidelines for margin management in 2014,[4] average reoperation rates after primary BCS decreased internationally, from 23.5% before the guidelines were published, to 19.3% in the years 2014 - 2016.[17]

The most recent estimate of BCS reoperation rates in the U.S. was published in February 2024 by Kim et al. The results of this retrospective cohort study using commercial claims and Medicare fee-for-service data found that, in the 3-year period from 2017-2020, 3,620 of 17,129 women (21.1%) in the commercial cohort and 1,039 of 6,977 women (14.9%) in the Medicare cohort underwent re-excision or conversion to mastectomy within one year of the primary BCS.[1]

Our finding that reoperation rates in patients with DCIS was higher than in those with invasive cancers (10.3% vs. 0.0%, respectively) is consistent with the findings from the Kim study, which reported reoperation rates of 30.8% among women with DCIS vs. 18.0% among women with invasive breast carcinomas ($p<0.001$) in the commercial cohort and 24.0% vs. 12.7%, respectively, in the Medicare cohort ($p<0.001$).[1]

With the potential to delay adjuvant treatment, cause emotional distress, and affect cosmetic outcomes, reoperations after primary BCS can have clinical, psychosocial, and economic consequences.[1, 7, 20, 21] They can also re-expose patients to the complications and risks associated with surgery. For example, Kim and colleagues reported that, in their claims database analysis, repeat BCS is associated with an increase in risk of complications between 66% and 82% compared to women who did not have a repeat BCS, after adjustment for covariates. Conversion to mastectomy is associated with an up to two-fold increase in risk.[1] Metcalfe and colleagues have reported that reoperation with conversion to mastectomy is associated with a 15.3% 2-year infection rate.[7]

Additionally, reoperations have a significant financial impact on patients, insurance companies, and healthcare providers. The study by Kim and colleagues found that reoperations were associated with 24% higher costs, which translated into as much as $21,607 in incremental costs per patient.[1]

Limitations

This was a retrospective study and subject to a number of associated limitations. For example, the data used in the analysis were originally collected for purposes other than research (e.g. to document patient care and inform clinical decision-making). Therefore, data were not always recorded in a standardized way, were not always complete, and some variables that could have been informative were not available for examination. The availability of patient records for query resolution was further limited due to a change in the Investigator's institutional affiliation during the data collection period; thus, it was not always possible to achieve clarity when complexity was encountered. Also for this reason, it was not possible to construct a control cohort to allow

a comparison of the surgeon's personal reoperation rate before and after OCT was introduced into practice. This is relevant because reoperation rates vary widely from surgeon to surgeon across the U.S. Further research from more rigorously designed, controlled studies are warranted before these findings can be generalized.

CONCLUSION

In the era after intraoperative OCT imaging was adopted into our practice, the reoperation rate after primary BCS (5.6%) was lower than the most recent published national average (14.9% - 21.1%).[1, 2] Secondarily, the analysis and results of this study provided valuable insights to inform the design of future studies that will include a control cohort, more rigorous data collection protocols, and more clearly defined outcomes. Our results provide insight into the potential use of intraoperative OCT imaging as an adjunctive margin assessment tool to achieve negative margins during primary BCS. Further research is warranted to ascertain how our results may be generalized to help address the current BCS reoperation epidemic.

REFERENCES

1. Kim Y, Ganduglia-Cazaban C, Tamirisa N, Lucci A, Krause TM. Contemporary Analysis of Reexcision and Conversion to Mastectomy Rates and Associated Healthcare Costs for Women Undergoing Breast-Conserving Surgery. *Ann Surg Oncol*. 2024; doi: 10.1245/s10434-024-14902-z

2. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide Trends in Mastectomy for Early-Stage Breast Cancer. *JAMA Surgery*. 2015; 150: 9. doi: 10.1001/jamasurg.2014.2895

3. Morrow M, Van Zee KJ, Solin LJ et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. Ann Surg Oncol. 2016; 23: 3801-3810. doi: 10.1245/s10434-016-5449-z 10.1245/s10434-016-5449-z

4. Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Ann Surg Oncol*. 2014; 21: 704-716. doi: 10.1245/s10434-014-3481-4

5. The American Society of Breast Surgeons. Consensus Guideline on Breast Cancer Lumpectomy Margins. Updated Dec 2017. Accessed May 29. https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Breast-Cancer-Lumpectomy-Margins.pdf

6. Landercasper J, Borgert AJ, Fayanju OM et al. Factors Associated with Reoperation in Breast-Conserving Surgery for Cancer: A Prospective Study of American Society of Breast Surgeon Members. *Annals of Surgical Oncology*. 2019; 26: 3321-3336. doi: 10.1245/s10434-019-07547-w

7. Metcalfe LN, Zysk AM, Yemul KS et al. Beyond the Margins-Economic Costs and Complications Associated With Repeated Breast-Conserving Surgeries. *JAMA Surg*. 2017; 152: 1084-1086. doi: 10.1001/jamasurg.2017.2661

8. Abe SE, Hill JS, Han Y et al. Margin re-excision and local recurrence in invasive breast cancer: A cost analysis using a decision tree model. *J Surg Oncol*. 2015; 112: 443-448. doi: 10.1002/jso.23990

9. McEvoy MP, Landercasper J, Naik HR, Feldman S. Update of the American Society of Breast Surgeons Toolbox to address the lumpectomy reoperation epidemic. *Gland Surg*. 2018; 7: 536-553. doi: 10.21037/gs.2018.11.03

10. Gray RJ, Pockaj BA, Garvey E, Blair S. Intraoperative Margin Management in Breast-Conserving Surgery: A Systematic Review of the Literature. *Ann Surg Oncol*. 2018; 25: 18-27. doi: 10.1245/s10434-016-5756-4

11. Wang J, Xu Y, Boppart SA. Review of optical coherence tomography in oncology. *J Biomed Opt*. 2017; 22: 1-23. doi: 10.1117/1.JBO.22.12.121711

12. *Optical Coherence Tomography: Technology and Applications*. Switzerland AG: Springer International Publishing; 2015.

13. Faragalla H, Davoudi B, Nofech-Moses N, Yucel Y, Jakate K. The Use of Optical Coherence Tomography for Gross Examination and Sampling of Fixed Breast Specimens: A Pilot Study. *Diagnostics (Basel)*. 2022; 12: doi: 10.3390/diagnostics12092191

14. Schmidt H, Connolly C, Jaffer S et al. Evaluation of surgically excised breast tissue microstructure using wide-field optical coherence tomography. *Breast J*. 2020; 26: 917-923. doi: 10.1111/tbj.13663

15. Ha R, Friedlander LC, Hibshoosh H et al. Optical coherence tomography: a novel imaging method for post-lumpectomy breast margin assessment-a multi-reader study. *Acad Radiol*. 2018; 25: 279-287. doi: 10.1016/j.acra.2017.09.018

16. DuPree BB, Papez MJ, Pirruccello E, Hassenflug A. Potential Utility of Adjunct Imaging with Wide-Field Optical Coherence Tomography for Gross and Microscopic Evaluation of Breast Specimens in Real-Time in the Operating Suite. *Indian Journal of Surgery*. 2022; 84: 751-756. doi: 10.1007/s12262-021-03079-4

17. Tamirisa N, Lei X, Caudle AS, Giordano SH, Zhao H, Chavez-MacGregor M. Impact of SSO-ASTRO "No Ink on Tumor" Guidelines on Reexcision Rates among Older Breast Cancer Patients. *Ann Surg Oncol*. 2021; 28: 3703-3713. doi: 10.1245/s10434-020-09370-0

18. Vakoc BJ, Fukumura D, Jain RK, Bouma BE. Cancer imaging by optical coherence tomography: preclinical progress and clinical potential. *Nat Rev Cancer*. 2012; 12: 363-368. doi: 10.1038/nrc3235

19. Huang D, Swanson EA, Lin CP et al. Optical coherence tomography. *Science*. 1991; 254: 1178-1181. doi: 10.1126/science.1957169

20. Baliski C, Bakos B. Patient reported outcomes following breast conserving surgery are improved by minimizing re-excisions and excessive breast tissue removal. *Am J Surg*. 2022; doi: 10.1016/j.amjsurg.2022.03.008

21. Lamb LR, Mercaldo S, Oseni TO, Bahl M. Predictors of Reexcision following Breast-Conserving Surgery for Ductal Carcinoma In Situ. *Ann Surg Oncol*. 2021; 28: 1390-1397. doi: 10.1245/s10434-020-09101-5

INFORMATION ABOUT THIS WHITE PAPER

Perimeter Medical Imaging AI intends the sharing of this white paper for an investor audience and not for use by healthcare professionals. The data contained herein have not undergone peer review nor evaluation by FDA and should not be used to guide clinical practice.

The S-Series OCT has 510(k) clearance under a general indication and has not been evaluated by FDA specifically for use in breast tissue, breast cancer, other types of cancer, margin evaluation, and reducing re-excision rates. For more information, visit https://perimetermed.com/disclosures.

Perimeter Medical Imaging was involved in the study design, data collection, analysis & interpretation, and the writing of this paper. Additionally, Perimeter funded professional medical writing support.

INFORMATION ABOUT THE S-SERIES OCT DEVICE

Intended Use

The S-Series OCT is indicated for use as an imaging tool in the evaluation of excised human tissue microstructure by providing two-dimensional, cross-sectional, real-time depth visualization with image review manipulation software for identifying and annotating regions of interest.

Unapproved Uses

The S-Series OCT has 510(k) clearance under a general indication and has not been evaluated by FDA specifically for use in breast tissue, breast cancer, other types of cancer, margin evaluation, and reducing re-excision rates. The safety and effectiveness of these uses has not been established.

For full information on unapproved/off-label uses, visit https://perimetermed.com/disclosures or contact medicalaffairs@perimetermed.com.