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Portable Real-Time Optical Coherence Tomography System for Intraoperative Imaging and Staging of Breast Cancer

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ABSTRACT

Breast cancer continues to be one of the most widely diagnosed forms of cancer amongst women and the second leading type of cancer deaths amongst women. The recurrence rate of breast cancer is highly dependent on several factors including the complete removal of the primary tumor and the presence of cancer cells in involved lymph nodes. The metastatic spread and staging of breast cancer is also evaluated through the nodal assessment of the regional lymphatic system. A portable real-time spectral domain optical coherence tomography system is being presented as a clinical diagnostic tool in the intraoperative delineation of tumor margins as well as for real time lymph node assessment. The system employs a super luminescent diode centered at 1310 nm with a bandwidth of 92 nm. Using a spectral domain detection system, the data is acquired at a rate of 5 KHz / axial scan. The sample arm is a galvanometer scanning telecentric probe with an objective lens (f = 60 mm, confocal parameter = 1.5 mm) yielding an axial resolution of 8.3 μm and a transverse resolution of 35.0 μm. Images of tumor margins are acquired in the operating room *ex vivo* on freshly excised human tissue specimen. This data shows the potential of the use of OCT in defining the structural tumor margins in breast cancer. Images taken from ex-vivo samples on the bench system clearly delineate the differences between clusters of tumor cells and nearby adipose cells. In addition, the data shows the potential for OCT as a diagnostic tool in the staging of cancer metastasis through locoregional lymph node assessment.

Keywords: Optical Coherence Tomography, Breast Cancer, Metastasis, Clinical Imaging, Lymph Node, Biomedical Optics, Image Guided Surgery.

1. INTRODUCTION

1.1 Breast Cancer

Breast cancer continues to be one of the most frequently diagnosed cancers among women and the second leading source of cancer deaths in women. According to the 2006 American Cancer Society statistics, approximately 212,920 new cases (or 31% of all new cancer cases amongst women) of invasive breast cancer and 61,980 new cases of *in situ* breast cancer were expected to be reported in the U.S. in 2006 [1]. The number of U.S. deaths attributed to breast cancer this year is estimated at 40,970, second only to lung cancer [1]. Over the years, the decrease in the number of breast cancer deaths has largely been attributed to increased awareness, earlier detection, and improved treatment.

As of January of 2002, the National Cancer Institute estimated that 2.3 million women have had a history of breast cancer which points to the importance in monitoring the recurrence of breast cancer. Being able to detect smaller foci of cancer cells as well as detecting other progressive changes in not only the tissue morphology but also the molecular makeup of the tissue will provide further insights into how to not only better diagnose but also better treat earlier stages of breast cancer. There is a continued emphasis on the early diagnosis of breast cancer in order to provide better managed care. The ability to detect and remove a tumor prior to metastases is essential to lowering the breast cancer mortality rate. The survival rate for U.S. breast cancer patients when the disease is detected at a localized stage is

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currently 97.9% [2]. However, according to the American Cancer Society statistics, approximately 36.3% of the newly reported breast cancer cases in the U.S. are diagnosed at later stages when the tumor is no longer localized [2].

The staging of breast cancer is currently based on three main criteria: the size of the primary tumor, the infiltration of lymph nodes by cancer cells, and the subsequent metastasis of cancer cells to other sites. Table 1 delineates the current criteria used by physicians to stage the progression of breast cancer in patients. Two of the main factors are the size of the primary tumors and the infiltration of the cancer into the lymph nodes [3]. The status of lymph node involvement has long been used by the medical community for determining the metastatic state of the cancer. The ability to identify the migration of cancer cells away from the primary tumor using OCT is currently under investigation.

The feasibility of using OCT to image tumor margins for breast cancer was first demonstrated in an NMU-carcinogen induced rat mammary model [4]. There are reported studies that have been examined the spectral information from single line scans. Using newly developed computational algorithms, one can analyze the spatial frequency content of the axial scan to distinguish between normal tissue and invasive ductal carcinoma lesions with high sensitivity [5]. Due to the location of the breast lesions, the use of needle-based imaging probes may be needed to place the breast lesion within the working distance of the OCT beam.

Prior to most of the breast cancer related procedures such as breast biopsy procedures, lumpectomy procedures, or mastectomy procedures, the use of guides for the biopsy needle have experienced sampling difficulties using ultrasound or X-ray imaging techniques to guide the needle. The incorporation of a fiber based OCT sample arm into the biopsy needle would provide real-time information guiding the needle to the appropriate location of the breast lesion for biopsies or for the placement of wire localization [6-8]. Studies have shown that there are diagnostically significant information within the backscattering information and the refractive index information that can be used to differentiate between various tissue types found in breast lesions [6-8].

Table 1. Staging of breast cancer [3].

Staging Breast Cancer			
Stage	Tumor Size	Lymph Node Involvement	Metastasis
I	< 2cm	No	No
II	2-5 cm	No/Ipsilateral	No
III	> 5cm	Yes/Ipsilateral	No
IV	N/A	N/A	Yes

Table 2. Based upon the pre-defined stages of breast cancer, the 5-year survival rates are presented reinforcing the need for earlier detection and diagnosis (American cancer Society).

Survival Rates	
Stage	5-Year Survival Rate
0	100%
I	100%
IIA	92%
IIB	81%
IIIA	67%
IIIB	54%
IV	20%

1.2 Cancer metastasis

The metastatic spread of cancer from the primary tumor to a secondary site is one of the criteria used to stage breast cancer. This process is primarily preceded by the migration of tumor cells via the lymphatic system. The tumor cells that have detached themselves from the primary tumor must invade through the basement membrane through the vasculature to reach the lymph vessels. Once in the lymphatic system, free tumor cells are shuttled through the lymph vessels to the lymph nodes to be recognized, processed, and destroyed by the immune system.

As has been previously demonstrated, OCT can be used to visualize the microstructure of lymph nodes such as the capsule, and the follicles and sinuses located within the cortex of the lymph nodes [9]. These preliminary experiments indicate that OCT could potentially be used to do intraoperative in-vivo nodal assessment. By providing real time assessment of the lymph nodes, surgeons would be able to reduce the amount of non-diagnostic tissue removed during surgery. In addition, reducing the number of nodes during surgery will decrease the chances of developing lymphedema. Currently 10% - 20% of patients who have had their lymph nodes removed develop lymphedema. Lymphedema is the accumulation of lymph in the interstitial spaces due to the disruption of the lymphatic system by the removal of lymph nodes. Risk factors of lymphedema include nodal dissection of the axillary lymph nodes, radiation therapy in the treatment of breast cancer, and the presence of cancer cells in the resected lymph nodes. For example, in the patients enrolled in this study, the pathology reports indicated the vast majority of the lymph nodes removed did not contain any tumor cell deposits within the lymph nodes (< 5%). This small number in lymph node involvement is more likely due to the advancements for the early breast cancer screening and diagnosis allowing physicians and surgeons to treat the patient at earlier stage leading to a higher survival rate from breast cancer.

2. METHODOLOGY

2.1 Instrumentation (hardware)

The clinical OCT system developed for this investigation is a spectral domain OCT (SD-OCT) system which uses light from a super luminescent diode (BWTek–SLD1C) centered at 1310 nm with a bandwidth of 92 nm. The source is coupled into a low loss optical circulator (Gould Fiber Optics – CIRC-3-31-P-BB-10-6: 3 port) which helps maintain the power of the signal coming back from the fiber coupler to the detector. From the circulator, the light source is passed into a 95/5 fiber optic splitter (Gould Fiber Optics, Inc.) which splits the incident light respectively into the sample and reference arm. The sample arm currently uses a 60 mm achromatic lens focusing approximately 4.75 mW of light onto a 35.0 μm spot size (transverse resolution). The broad bandwidth of the laser source yields an axial resolution of approximately 8.3 μm in free space or 11.0 μm in tissue. The objective lens in the sample arm was chosen to roughly match its confocal parameter (1.47 mm) to the penetration depth (2 mm) observed in imaging human breast cancer samples. The light reflected back from the gold mirror in the reference arm and the tissue specimen in the sample arm are re-coupled through the two arms of fiber optic splitter and a set of polarizer controllers (Fiber Control: FPC-2). Through the fiber coupler, a commonly-used Michelson-type interferometer couples the beams of light from the two arms, the reference and sample arms. The resulting OCT signal is subsequently passed through the optical circulator and into the detector arm. Spatial scanning in the X-Y plane currently employs a set of galvanometers with a telecentric probe to scan the beam across the sample surface. Data acquisition is currently achieved via a spectrometer setup which collimates (20 mm) the OCT beam onto a plane ruled reflectance grating (Richardson Gratings, Newport Corporation, 53004BK01-148R). The diffraction grating with 1000 grooves/mm and blazed for 1310 nm is used to disperse the light which is focused by a 150 mm singlet lens onto an InGaAs line scan camera (Sensors Unlimited SU1024LE-1.7T1-0500) with 1024 pixels. The data acquisition is accomplished through a National Instruments NI-DAQ card (#PCI-6111E) in a dual Xeon processor (3.20 GHz) computer with 1 GB RAM. With exposure times ranging from 24.4 μs to 408.4 μs, the measured SNR ranges from 96 dB to 116 dB respectively The SNR values were measured by placing a perfect reflector in the sample arm at the focus of the beam. Using neutral calibrated density filters, the SNR was calculated using the following formula

$$\text{SNR (dB)} = 10 \log \left(V_{peak}^2/(\text{noise variance})^2\right) + \text{Total OD}$$

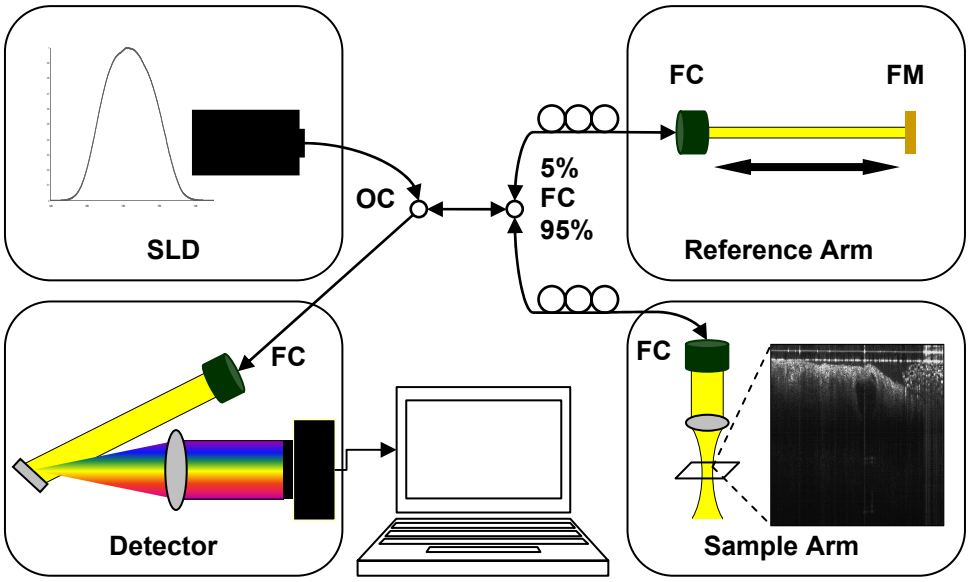


Fig. 1. A schematic diagram of the clinical spectral-domain optical coherence tomography system. OC – Optical Circulator, FC – Fiber Collimator, FC1 – 5/95 Fiber Coupler, RM – Reference Mirror

2.2 Instrumentation (software)

The OCT instrument is controlled by a custom LabVIEW software package which interacts directly with the galvanometers and the line scan camera. It also interacts with a data processing sequence written in Matlab/C++. The raw signal received from the line scan camera is first up-sampled through zero-padding in the time domain. Due to the non-linearity response in the grating, line scan camera, and other optics in the system, a cubic spline interpolation was implemented to compensate for these aberrations. The spline interpolation parameters are calculated using collected data from a perfect reflector placed at the focus of the sample arm while the reference arm is moved moving the corresponding signal throughout different depths of the OCT image. The collected data is compiled to yield a Modulation Transfer Function (MTF). The spline interpolation parameters are optimized to give the flattest MTF possible. These parameters are determined each time the detector arm of the system is realigned. The up-sampled data is re-indexed in the frequency domain using the spline interpolation. Lastly, a Fourier Transform is taken to bring the data from the spectral domain back to the time domain producing the traditional OCT image.

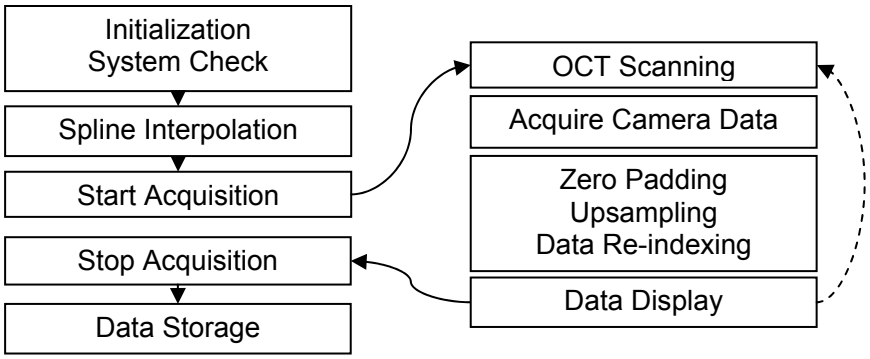


Fig. 2. Flow diagram for LabVIEW software package indicating the major components and processes.

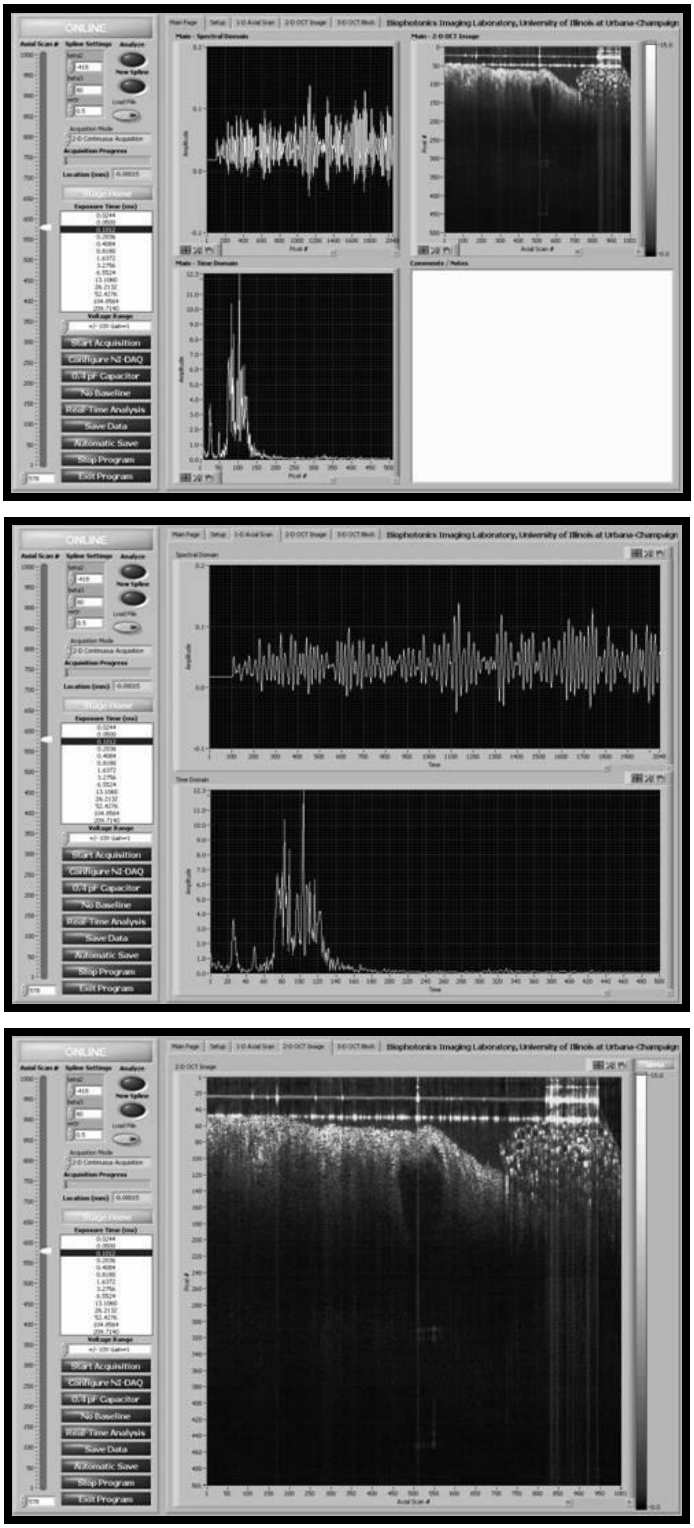


Fig. 3. LabVIEW Graphical User Interface with main overview screen (top), detailed screen view (middle), OCT image screen view (bottom).

2.3 Human subjects protocol (inclusion/exclusion criteria, consent)

The recruitment and enrolled of patients was performed by the clinical collaborators from the Carle Foundation Hospital and Carle Clinic Association who identified potential human subjects based on patients undergoing lumpectomy procedures for the removal of primary tumors or of ductal carcinoma in situ (DCIS) of the breast. The patients were included in this study if their tumors were considered suspicious and in need of surgical resection, as determined by the physician based on medical histology, previous radiological films, and/or other relevant diagnostic results. All recruitment and research protocols were approved by the Institutional Review Boards of the University of Illinois at Urbana-Champaign and the Carle Foundation Hospital. Potential subjects were informed about the study, the procedures, and the potential benefits and risks, and were consented to the study prior to the surgery in accordance with the approved IRB protocols.

2.4 Imaging protocols

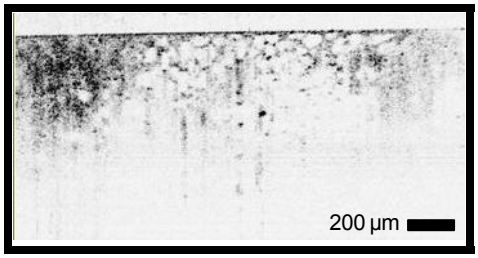
The clinical OCT system was initially tested using the same human breast cancer specimen imaged under the Clinical SD-OCT system (1310 nm CW, 92 nm BW, 116 dB SNR, 5000 lines / sec acquisition rate), a titanium:sapphire-based Time Domain OCT (TD-OCT) system (800 nm CW, 120 nm BW, 106 dB SNR, 10 lines / sec acquisition rate), and a titanium:sapphire-based SD-OCT system (800 nm CW, 120 nm BW, 96 dB SNR, 29000 lines / sec acquisition rate). The 800 nm OCT systems were used in current ongoing human cancer specimens received from Carle Foundation Hospital. These specimens were excess tissue specimen discarded by the pathology department during examination / diagnosis of the tissue received from lumpectomy or mastectomy procedures. The specimens were transported to the Beckman Institute for Advanced Science and Technology where 3-D OCT images were taken along the tumor margins and the tissues were fixed and stained with haematoxylin and eosin (H&E).

At Carle Foundation Hospital, the clinical SD-OCT system was placed inside the operating room during lumpectomy procedures. After the tissue was removed from the patient but prior to being sent to the pathologist for gross examination, the tissue specimen was imaged using the clinical OCT system. The OCT beam was scanned over a 1.0 cm x 1.0 cm region over areas that initially appear suspicious under visual examination or along the metal guide wire, if available, which was previously inserted to guide the surgeon to the location of the tumor. After the imaging was completed, the tissue was inked to mark the location of the OCT scanning. The tissue was transported to the pathology department for gross examination of margins, and subsequently for sectioning and staining to help provide correlation histology to the OCT images taken. A subset of the patients also had their lymph nodes removed to assess the extent of the cancer metastasis. To date 16 patients were enrolled in the study where the tissue was imaged at the Beckman Institute during the preliminary studies evaluating the potential of OCT to study breast cancer. Approximately 20 patients have been enrolled in the second study with the real-time imaging in the operating room using the clinical OCT system.

3. DATA

3.1 System validation

To initially evaluate OCT for the study of tumor margins, discarded excised tissue of a specimen with a tumor margin was imaged under the three OCT systems described in section 2.4. These images show that despite system differences, there are still observable similarities along with reasonable penetration depths for breast tissue.

(a) 

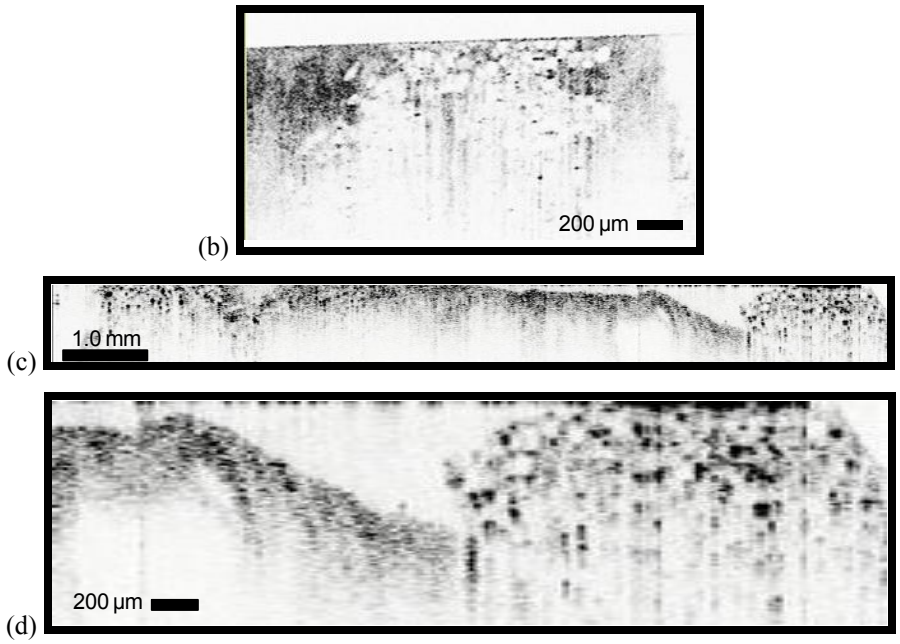


Fig. 4. OCT images taken with three different systems on the same tissue specimen. On visual examination, the left portions of the images (a) and (b) are of a tumor and the middle areas are adipose cells. Image (a) was taken with the TD-OCT system at 800 nm, and the image (b) was taken with the SD-OCT system at 800 nm. These images are both 2.0 x 1.0 mm. Image (c) was of the same tissue in a plane parallel to those of the images taken above where a portion is enlarged in image (d). General morphology is still observed with the tumor and adipose margin. Image (d) was taken with the clinical SD-OCT at 1300 nm with an image size of 10.0 x 1.0 mm.

3.2 Representative surgical margin data collected in the operation room

Evaluation of the surgical margins is investigated in these studies. The surgical margin is defined to be the margin of the tissue that makes up the outer surface of the excised tissue. For an invasive primary tumor, the current standard of care calls for having at least a 1.0 cm margin of tissue around the primary tumor. Upon resection, the assessment made by the surgeon and the pathologist is made grossly to determine whether there is at least 1 cm of tissue surrounding the primary tumor. The surgical margin is defined to be the outermost section of tissue compared to the tumor margin which is being defined as the margin separating the normal tissue from the primary tumor. However, even at this point, there is no current method for the surgeon to define the microscopic margins in real-time during the surgery. Pathologists will often perform a consult by doing a frozen section of the tissue in order to determine the microscopic margin status at the time of surgery. However, these are always followed by traditional methods of tissue fixation, sectioning of the paraffin embedded tissue, and subsequent staining. The microscopic margin is synonymous to the surgical margin and is used interchangeably depending on whether one is examining the tissue through gross examination or through histology slides. A positive surgical margin is currently being defined as one where cancer cells are found along the surgical margin.

Presented below are a series of OCT images taken of the surgical margins which range from normal adipose tissue (Figure 5) to those with small pockets of non-adipose cells (Figure 6) to those with larger areas of more highly scattering tissue (Figure 7).

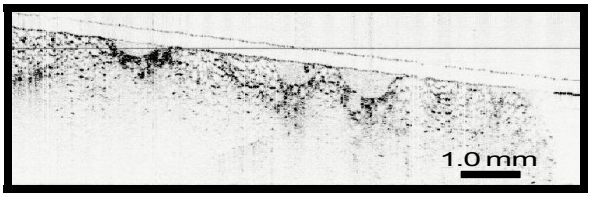


Fig. 5. OCT image taken of the surgical margin of an excised tissue using the clinical SD-OCT at 1300 nm. The OCT image size is 10.00 x 3.0 mm. This image is mostly composed of adipose tissue.

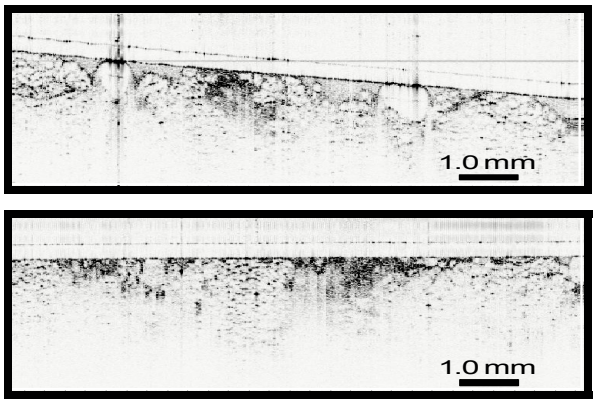


Fig. 6. OCT image taken of the surgical margin of an excised tissue using the clinical SD-OCT at 1300 nm. The OCT image size is 10.00 x 3.0 mm. This image is mostly composed of adipose tissue with smaller clusters of non-adipose cells embedded into the adipose tissue which is the major component of normal breast tissue.

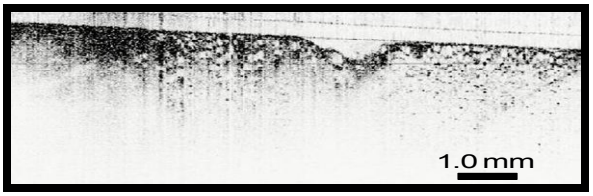


Fig. 7. OCT image taken of the surgical margin of an excised tissue using the clinical SD-OCT at 1300 nm. The OCT image size is 10.00 x 3.0 mm. This procedure was a re-excision procedure from a previous surgery. There is an observable higher scattering area on the left side of the image. The pathology report did not indicate the presence of any cancer cells on this tissue specimen. It is hypothesized that this may be cauterized tissue from the previous surgical procedure. These preliminary studies point to the need for further extensive studies to differentiate between the tumor tissue, stroma tissue, and cauterized tissue.

3.3 Representative lymph node data collected in the operation room

As previously mentioned, nodal assessment is a routine procedure that accompanies lumpectomies and mastectomies in order to stage the progression of the breast cancer. During some preliminary studies, the resected lymph nodes from patients undergoing removal of axillary lymph nodes were imaged under OCT. Representative OCT images of excised axillary lymph nodes are presented below.

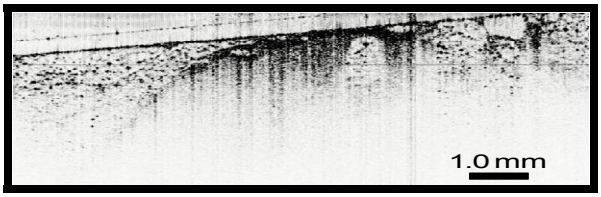


Fig. 8. OCT image taken of an axillary lymph node using the clinical SD-OCT at 1300 nm. The OCT image size is 10.00 x 3.0 mm. In this image, the lymph node can be seen in the middle of the image with a potential follicle and germinal center on the right side of the lymph node.

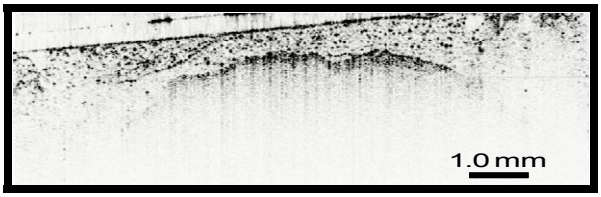


Fig. 9. OCT image taken of an axillary lymph node using the clinical SD-OCT at 1300 nm. The OCT image size is 10.00 x 3.0 mm. Here the lymph node can be seen with the capsule (dark layer) and the cortex (lighter layer with small sized scatterers).

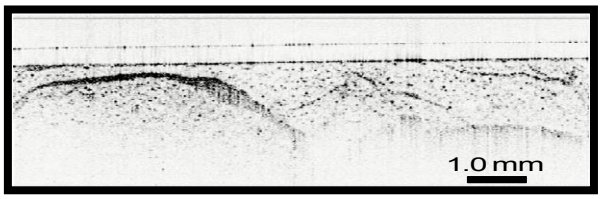


Fig. 10. OCT image taken of an axillary lymph node using the clinical SD-OCT at 1300 nm. The OCT image size is 10.00 x 3.0 mm. In this image the structures on the left side could potentially be a lymphoid follicle.

Table 3. Summary of the number of enrolled patients in the OR imaging study: the table below indicates the current number of patients that were enrolled in these preliminary studies.

Real-Time Optical Coherence Tomography of Human Breast Tissue		
06/2006-12/2006	Patients Consented	Specimen Imaged
Breast	20	18

4. DISCUSSION

The initial system validation studies show that although the resolution of the 1300 nm clinical SD-OCT system is not as high as in the 800 nm systems, as expected, there is still remarkable corroboration between the three systems in identifying the margin between the primary tumor and the surrounding adipose tissue. Through these initial studies, the observed penetration depth for breast tissue is approximately ~1 mm at 800 nm. In comparison to the images presented in the representative data section taken in the operating room using 1300 nm light, the penetration depth appears to be approximately 2 mm.

Upon examination of the pathology reports for the patients whose excised tissue was imaged in the operating room, the average width of the margin uninvolved by invasive carcinoma (the distance between the outer surface of the tissue (surgical margin) and the primary tumor (tumor margin)) typically ranged from 10.00 – 20.00 mm. Compared to the penetration depth of OCT at 1300 nm in breast cancer, it is therefore expected that most of the OCT imaging would only be able to see normal tissue. The invasive tumor is usually much denser and easily palpable by the surgeon and therefore easier to assess if a large enough margin has been taken around the invasive tumor.

However, the scenario that is harder to assess in real time during surgery is the extent of the DCIS (ductal carcinoma in situ) beyond the invasive tumor. This is the case where the pathologist has to perform frozen sections to give the surgeons a preliminary assessment of the margin prior to closing up the patient. As can been seen from the images shown of the surgical margins taken with OCT, there are some cases where the tissue looks fairly homogeneous with adipose cells. In other cases, suspicious areas could be identified within the penetration depth of the OCT system. From the pathology reports, the margin uninvolved by DCIS was also reported in some cases when DCIS was present. These margin widths range from 0.1 – 10 mm which would be accessible by OCT.

As has been previously mentioned, the excision of an invasive tumor with a wide margin that is palpable by the surgeon has not been the main issue. The critical place where OCT could prove to be useful is in providing real-time information about the surgical margin such as the extent of the DCIS and whether the surgical margin is positive or negative. The current methodology is if one removes a large enough area around the tumor one would be able to remove any DCIS present. In the cases where there is not a palpable invasive tumor, wire localization is performed to help guide the surgeon to the location of the breast cancer lesion. The initial goal of this study was to determine whether OCT could identify potentially suspicious areas located in the surgical margin guiding pathologists to take frozen sections in those areas helping provide more accurate information to the surgeon about whether a margin was positive or negative.

In these preliminary promising studies, there were a few cases where areas of higher scattering tissue were observed which could be differentiated from adipose tissue. However, further studies need to be performed to investigate whether these areas of higher scattering are due to the presence of cancer cells, stroma tissue, cauterized tissue, or the presence of blood or other highly scattering particles. Thus far, most of the focus of the studies where tissue has been taken back to the research laboratory has been spent on defining the structural margin between the primary invasive tumor and the

adipose tissue. The intraoperative imaging studies have primarily been used to identify areas that appear to be suspicious or rather that are not made up of homogeneous adipose cells which would be more indicative of a negative margin.

The data from the lymph nodes also show promising results that need to be further investigated. From the images presented, one can observe distinct morphological differences between the various axillary lymph nodes that have been imaged. Some hypotheses were made as to the structures observed. The most promising results indicate that these morphological structures are all within penetration depth of the OCT imaging system.

5. CONCLUSIONS

Current studies have demonstrated the potential of OCT for imaging tumor margins, identifying suspicious areas along the surgical margin, as well as visualizing the lymph node morphology. Although penetration depth may be an issue, OCT should be able to image relevant structures as observed in the images presented. The implementation of needle based probes should allow further minimally-invasive probing of the tissue with OCT. Further studies need to be performed to further distinguish between the various breast tissue types from not only adipose cells which are easily distinguishable under OCT but also against other components such as cancer cells, stroma tissue, and cauterized tissue.

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