Optoacoustic characterization of breast conserving surgery specimens – A pilot study

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ABSTRACT

In this pilot study, we tested an ultrasound-guided optoacoustic tomography (US-OT) two-dimensional (2D) array scanner to understand the optoacoustic patterns of excised breast conserving surgery (BCS) specimens. We imaged 14 BCS specimens containing malignant tumors at eight wavelengths spanning 700 – 1100 nm. Spectral unmixing across multiple wavelengths allowed for visualizing major intrinsic chromophores in the breast tissue including hemoglobin and lipid up to a depth of 7 mm. We identified less/no lipid signals within the tumor and intense deoxy-hemoglobin (Hb) signals on the rim of the tumor as unique characteristics of malignant tumors in comparison to no tumor region. We also observed continuous broad lipid signals as features of negative margins and compromised lipid signals interrupted by vasculature as features of positive margins. These differentiating patterns can form the basis of US-OT to be explored as an alternate, fast and efficient intraoperative method for evaluation of tumor resection margins.

1. Introduction

In spite of the increasing awareness, yearly mammogram screening programs, and advanced treatment regimens, breast cancer remains the most commonly occurring cancer in women with over 2 million new cases worldwide in 2018 [1]. It is also the leading cause of death in women in over 100 countries [1]. Essentially, early stage breast cancers (stage I and II) are managed using breast conserving surgery (BCS) followed by radiation therapy. In recent times, BCS is increasingly preferred worldwide over total mastectomy as the former offers improved aesthetic benefits with similar treatment outcomes as the latter. Nevertheless, there are at least 20 % chances that these tumors are not completely excised in BCS [2] due to the lack of a rapid and accurate margin assessment tool.

Histopathology analysis has remained the gold standard to date for resection margin assessment in clinics. The technique is targeted at cellular and molecular level analysis that involves up to 48 h of specimen fixation followed by several days of sectioning, staining and microscopic imaging to assess the involvement of margins. While intraoperative frozen section analysis (FSA) of BCS specimen has been demonstrated to be useful in preventing reoperation rates to some extent [3,4], it is not a standard procedure in many oncologic centers due to its non-availability, low sensitivity (65–78 %) and extended surgical procedure duration [5,6]. Intraoperative specimen X-ray is also routinely used in clinics to assess the complete excision of non-palpable BCS lesions [7,8]. This technique is targeted at providing two-dimensional structural information at any depth in a few minutes. However, owing to poor contrast differences between tumors and fibroglandular tissue (FGT), the technique sometimes results in sensitivity as low as 40 % [9], thus, questioning its reliability. Intraoperative high-frequency ultrasound imaging is becoming increasingly popular for margin assessment as it is not affected by breast density and offers a cheaper and quicker alternative to specimen X-ray imaging [10]. However, the technique assesses the margins based on structural information and the inability to resolve functional chromophores renders it losing edge over upcoming optical imaging techniques including diffuse reflectance
imaging [11,12], optical coherence tomography [13] and Raman spectroscopy [14,15] which are impeded by the depth of penetration and limited field-of-view (FOV) for clinical translation. Therefore, new imaging techniques that can provide functional and molecular contrasts are needed for improving the specificity of breast cancer specimen margins assessment. 

Optoacoustic imaging is a hybrid imaging modality that captures the optical absorbers in the tissue like hemoglobin, melanin, lipid, water, etc using acoustic detectors to achieve optical contrast and resolution at acoustic depths. Its capacity to offer functional information up to a few centimeters depths [16,17], particularly without using ionizing radiations has garnered humungous interest among many research groups to further the research on developing it as an alternative in vivo breast imaging tool (reviewed in [18]). However, it’s applications for ex vivo imaging of tissues with a realistic clinical intraoperative translation has not been investigated until recently. Rui Li et al. used a customized single wavelength (in the second optical window) photoacoustic tomography system guided by ultrasound for intraoperative breast tumor margin assessment in fresh lumpectomy specimens [19]. Though the usage of a single wavelength lying in the second overtone absorption peak of lipid for imaging fat-rich BCS specimens is a clever time saving strategy, increasing the number of wavelengths has shown marked improvements in spectral unmixing accuracy and sensitivity [20,21] which in turn will enhance the accuracy of resection margin assessment. Therefore, in this study, we have used an ultrasound-guided optoacoustic tomography (US-OT) handheld probe with eight different wavelengths spanning 700–1100 nm to image 14 fresh lumpectomy specimens containing malignant tumors and resolved them for the distribution of intrinsic chromophores including hemoglobin and lipid in tumors and normal breast tissue surrounding the tumor. The fundamental aim of this pilot study was to understand the optoacoustic features of BCS specimens and investigate the differences in optoacoustic characteristics of specimens with negative and positive margins using intrinsic optical absorption contrast from hemoglobin and lipid.

2. Materials & methods

2.1. Study population and patient characteristics

Freshly excised lumpectomy specimens (n = 14) with malignant lesions comprising Invasive Ductal Carcinoma (IDC), Invasive Lobular Carcinoma (ILC); Ductal Carcinoma In-Situ (DCIS) (Table 1) collected at the National University Hospital, Singapore were imaged by the ultrasound-guided optoacoustic scanner. All tumors were collected from patients above 18 years of age with the mean age being 52.5 ± 12.5 years (24–83 years) after obtaining written informed consent. Malignant lesions/tumors that were sonographically occult (e.g. Ductal Carcinoma In-situ (DCIS) with mammogram micro-calcifications only) were excluded from the study. All specimens had an average volume of 200 cm³. All experimental protocols in this study were approved by the Institutional Review Board and carried out in accordance with the relevant guidelines and regulations.

2.2. Handheld MSOT probe and imaging chamber

The customized handheld 2D optoacoustic scanner has been described previously [22,23]. Precisely, illumination was provided by a wavelength-tunable optical parametric oscillator (OPO) laser in the working range of 660–1300 nm with 10 ns duration and 10 Hz repetition rate with per pulse energy of 35 mJ at 760 nm through fiber bundles connecting the scanner to the MSOT inVision 512-ECHO system (iThera Medical GmbH, Munich, Germany) as shown in Fig. 1A. The scanner consisted of an arc-shaped (125 degree angular coverage) curvilinear array of 256 detector elements arranged on a spherical surface (radius 40 mm) with a center frequency of 5 MHz (Fig. 1B). The transducer was enclosed in an optoacoustically transparent low-density polyethylene membrane with the cavity between the arc elements and the specimen filled with heavy water for optimal acoustic coupling. The scanner was fixed to a computer-controlled stage and moved across the sample placed on a silicone bed in an imaging chamber through heavy water to provide optimal acoustic coupling. The scanner provided cross-sectional 2D optoacoustic images with an in-plane spatial resolution of 150 µm and an effective FOV of 25 mm. A real-time image preview window generated based on the backprojection algorithm was available during data acquisition. OT images were acquired at multiple wavelengths –710, 730, 760, 800, 850, 930, 1050, 1100 nm – 5 frames were averaged per wavelength.

2.3. Imaging protocol

After BCS, all samples were oriented with silk sutures by surgeons (Fig. 1C) and washed briefly with saline to remove the excess blood and clots on the surface. The specimen was placed on a custom designed grid sheet within the imaging chamber. An optoacoustically transparent bag of heavy water was placed on the specimen and allowed to surround it to cover the entire top surface. The US-OT probe was lowered into the heavy water to touch the thickest portion of the specimen and

| Patient | Age  | Tumor Type            | Grade | Observations                  | US-OT                  |
|---------|------|-----------------------|-------|--------------------------------|------------------------|
| 1       | 59   | IDC                   | 3     | Clear margins                  | Continuous lipid layer |
| 2       | 83   | DCIS                  | 1     | Clear margins                  | Continuous lipid layer |
| 3       | 45   | IDC + DCIS            | 1     | Clear margins                  | Continuous lipid layer |
| 4       | 55   | IDC + DCIS            | 3     | Involved margin                | Continuous lipid layer |
| 5       | 63   | IDC + DCIS            | 2     | Clear margins (FGT on the inferior margin) | Continuous lipid layer (Remarkable intensity variations noted on inferior margin) |
| 6       | 62   | IDC                   | 2     | Clear margins                  | Continuous lipid layer |
| 7       | 56   | ILC + DCIS            | 2     | Clear margins (Close inferior margin, 0.3 cm) | Interrupted lipid layer |
| 8       | 45   | IDC                   | 3     | Clear margins                  | Continuous lipid layer |
| 9       | 53   | IDC                   | 2     | Clear margins                  | Continuous lipid layer |
| 10      | 47   | ILC                   | 2     | Clear margins                  | Continuous lipid layer |
| 11      | 34   | Intraductal Papilloma | 1     | Involved margin                | Interrupted lipid layer |
| 12      | 54   | IDC + DCIS            | 2     | Clear margins                  | Continuous lipid layer |
| 13      | 39   | IDC                   | 3     | Clear margins                  | Continuous lipid layer |
| 14      | 40   | IDC + DCIS            | 2     | Involved margin                | Interrupted lipid layer |

IDC - Invasive Ductal Carcinoma; ILC – Invasive Lobular Carcinoma; DCIS – Ductal Carcinoma In-Situ.
from thereon moved top to bottom and right to left and flipped to cover the entire specimen. After scanning, the specimen was placed in formalin and sent to the histopathology laboratory for further analysis. Pathologists reviewed the specimens via standard hematoxylin-eosin (H&E) stained tissue sections. Stitched photomicrographs and US-OT images were reviewed together by imaging scientists, radiologist and pathologist to confirm correlations between imaging and pathology.

2.4. Data analysis and image representation

Data were processed using ViewMSOT Version 3.8. Images obtained at different wavelengths were bandpass filtered with cut-off frequencies 50 kHz and 6.5 Mhz and reconstructed using a model-based (MB) algorithm [24]. The implemented MB reconstruction is based on modeling the forward problem using a semi-analytical solution to the acoustic propagation equation. This method is based on finite-element approach to solving integral equations in time domain and the solution is exact when OA image is a piecewise linear function. Under this condition, the measured acoustic fields can be represented as a linear combination of the values of the OA image on the grid that covers the image FOV. Therefore, OA image is recovered by minimizing the error between the measured acoustic signal and the signals theoretically predicted by the model by means of LSQR algorithm.

Subsequently, the reconstructed images were linearly unmixed using the absorption spectra of three main endogenous contrast agents – lipid, deoxy- (Hb) and oxy-hemoglobin (HbO2) to generate three separate images. Different color look-up tables (LUT) were used to represent the distribution of the three absorbers: Lipid- green; deoxy-hemoglobin-red and oxyhemoglobin – cyan (Fig. 1D). Image processing was performed on ImageJ.

3. Results

3.1. US-OT imaging of excised breast tissue without tumor

Fig. 2 shows a representative US-OT image of a section of excised breast tissue of size 4.5 × 5.7 × 3.0 cm in a no-tumor region. Images acquired at different wavelengths spanning 700–1100 nm showed various structures in the sample up to 7 mm depth. Images at lower wavelengths that were more sensitive to hemoglobin (700 – 850 nm)
showed high resolution vascular structures in the excised tissue. Particularly, optoacoustic signals at 760 nm (Fig. 2A) where the absorption of Hb is higher, was more intense than that at 850 nm (Fig. 2B) where the absorption of HbO₂ is higher. As the specimen imaged was an excised tissue, it is expected that the intensity at 760 nm is higher than that at 850 nm. Images at higher wavelengths (Fig. 2C & D) that are less sensitive to hemoglobin (900−1100 nm) showed broad patterns depicting the widely distributed lipids that are strongly absorbing at those higher wavelengths.

Upon spectral unmixing for three components namely Hb, HbO₂ and lipid, their respective distribution maps in the specimen were obtained. It was observed that the contrast of Hb (Fig. 2E) was better than that of HbO₂ (Fig. 2F). Blood vessels could be visualized up to a depth of ~7 mm. When Hb was distributed well across the entire depth of the imageable region, HbO₂ was predominantly found on the surface of the specimen, possibly due to the oxidation of hemoglobin when exposed to air. The lipid was observed to be distributed as a pretty uniform and continuous broad-band in no tumor regions (Fig. 2G).

3.2. US-OT imaging of malignant tumor with a negative resection margin

Fig. 3 shows a representative US-OT image of a section of excised breast tissue of size 3.7 × 3.5 × 2.0 cm containing grade 2 invasive ductal carcinoma. As observed from H & E staining (Fig. 3A), the specimen had 1.6 cm tumor (stained purple) amidst fat (white/no stain region) with clear margins on all sides. In the tumor identified by US image obtained from US-OT probe (Fig. 3B), very little lipid signal was noted surrounded by continuous lipid signals (Fig. 3C). This could be possibly due to the replacement of fat by vasculature rich tumor. Intense Hb signals were noticed along the tumor boundary (Fig. 3D). However, less or no Hb signals were detected within the tumor. This could be due to one of the following reasons: 1) limited penetration
depth of light in the excised specimen or 2) vasoconstriction of finer vasculature following excision or presence of finer blood vessels that could not be resolved using the OT probe. An overlay of the lipid and Hb images shown in Fig. 3E & F demonstrates continuous lipid layer with no interfering blood vessels as possible features of negative margins. 10 malignant tumor specimens with negative margins exhibited these features (Table 1).

3.3. US-OT imaging of malignant tumors with a positive resection margin

Fig. 4 shows a representative US-OT image of a section of excised breast tissue of size 4.5 × 5.7 × 3.0 cm containing a grade 3 invasive carcinoma. The specimen was positive for tumor on the anterior and superior margins as seen on gross pathology and H & E staining (Fig. 4A & i, indicated by black arrow). In the tumor identified by US image obtained from US-OT probe (Fig. 4B), very little lipid signal was noted (Fig. 4C) surrounded by intense Hb signals on the boundary (Fib 4D). Surrounding the tumor was compromised lipid signals (Fig. 4C) interrupted by Hb signals (Fig. 4D) indicating blood vessels extending to the tumor. An overlay of the lipid and Hb images shown in Fig. 4E & F demonstrates discontinuous lipid layer with interfering blood vessels as possible features of positive margins. Four malignant tumors (three with positive margins and one with close margin, 0.3 cm) exhibited these features (#4, #7, #11, #14, Table 1).

3.4. US-OT imaging of lesions with fibroglandular tissue

Fig. 5 shows US-OT imaging of a section of excised breast tissue of size 2.8 × 3.2 × 3.0 cm containing grade 2 invasive ductal carcinoma. As observed from H & E staining (Fig. 5A & B), the specimen had 1.3 cm tumor (stained purple) amidst fat (white/no stain region) with clear margins on all sides and fibroglandular tissue (FGT) on the inferior margin (stained pink). In the tumor identified by US image obtained from US-OT probe (Fig. 5C), very little/no lipid signal was noted. However, on the inferior margin, where FGT was present, continuous but varying intensities of lipid signals were noted (Fig. 5D). Precisely, FGT was observed to have less intense lipid signals and more intense Hb signals compared to its fatty counterparts. This was in line with the observation by Brooksby et al. [25], where FGT contained more Hb and water signals than that in the adipose tissue. As water and collagen are major components of FGT, unmixing optoacoustic signals for these chromophores will help understand the difference between lipid interruption in case of positive margins and that due to the presence of FGT. One of the negative margins of a malignant specimen (#5, Table 1) exhibited this feature.

4. Discussion

Herein, we performed a pilot clinical study using an ultrasound-guided optoacoustic tomography (US-OT) two-dimensional (2D) array scanner on 14 BCS specimens containing malignant tumor to understand their optoacoustic features. With the usage of multiple wavelengths, US-OT imaging was able to offer the biochemical information of the specimens including lipid, hemoglobin and water. On US-OT imaging, lipid was the major contrast provider in excised BCS specimen and not hemoglobin. This was in contrast to the findings of in vivo optoacoustic imaging, whereby primary contrast comes from different forms of hemoglobin with lipid playing a secondary role [16]. This suggests that lipid is not altered in the excised specimen, unlike hemoglobin. US-OT imaging divulged some of the recurring features of
the lumpectomy specimen like a continuous lipid layer in areas of healthy fatty breast tissue and less or absence of lipid signal in malignant tumors. In the limited number of specimens we imaged, the continuous lipid band was noted to surround the lipid-less, vasculature rich malignant tumors in the case of negative resection margins whereas discontinuous lipid band intercepted by blood vessels were found around tumors in the case of positive resection margins.

Hb signals on the boundaries of malignant tumors were intense
compared to the non-tumoral regions. This was indicative of angiogenesis, a hallmark of cancer [26]. However, with the limited penetration depth of the probe, it was difficult to comment if the blood vessels were limited to the rim only or extending throughout the tumor. Another interesting observation is the presence of intense Hb signals and less lipid signals in the areas of FGT which could potentially pose a challenge in identifying positive margins, especially when FGT extends from tumor to the margin. As a collagen rich tissue, by choosing the appropriate wavelengths for imaging and unmixing for collagen, FGT may be identified [27]. This may help with the assessment of margins involving FGT.

The US-OT probe used in this study has a curvilinear array that helps in coverage of 2.5 × 2.5 cm field of view with 150 μm resolution. By fixing the probe to an imaging stage that allows lateral movement, we were able to cover the entire specimen in an average time of 20 min. The usage of multiple wavelengths enabled us to analyze multiple components like lipid and Hb and will enable analysis of additional components like water and collagen, provided right wavelengths are chosen for data acquisition, thus offering accurate information on the specimens, particularly the margins. Despite the leads that the current set up offers in assessing the tumor margins, substantial improvements can be made to the imaging probe, the image acquisition and processing. For instance, with the fixed FOV of the imaging head, larger specimens had to be manually moved to cover the entire surface thus taking longer acquisition times. Automating stage movement and developing algorithms to stitch images would substantially reduce the data acquisition times. Another improvement would be to the penetration depth. Though Society of Surgical Oncology has set acceptable margins as having “no ink on tumor” for IDC (invasive ductal carcinoma) and a 2-mm negative margin for DCIS [28,29], it does not hold true across all ages and types of tumor and therapies given and remains highly controversial [30]. Currently, the probe could offer biochemical information to a depth that is less than a centimeter from one surface. By using a multi-segment handheld array with larger FOV and lower central frequency, improved depth can be achieved [31]. Alternatively, a full ring US transducer array [32] could be used to reveal a 360° view of the specimen in one sweep.

5. Conclusion

Overall, ultrasound-guided optoacoustic tomography performed with multiple wavelengths on BCS specimens provided the much needed biochemical information, particularly of the margins, up to a depth of 7 mm from all sides in an average time span of 20 min. Distribution of lipid and hemoglobin in the specimen margins showed distinct features in positive and negative resection margins opening the avenues of US-OT as a potential tool for intraoperative evaluation of resection margins. Extension of this clinical study to investigate more BCS specimens across several tumor types will establish the robustness of the technique.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

NCB and YQ are employees of iThera Medical, GmbH. A research collaboration agreement (RCA) free of financial interests was initiated between Singapore Bioimaging Consortium and iThera Medical, GmbH.

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