Investigating the feasibility of a hand-held photoacoustic imaging probe for margin assessment during breast conserving surgery

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ABSTRACT

Approximately 19% of breast cancer patients undergoing breast conserving surgery (BCS) must return for a secondary surgery due to incomplete tumour removal. We propose a single sensor, low-frequency hand-held photoacoustic imaging (PAI) probe for detection of residual cancer tissue during BCS within the surgical cavity and on the excised specimen based on lipid content differences.

The probe incorporated a single polyvinylidene fluoride acoustic sensor, a 1-to-4 optical fibre bundle and a polycarbonate axicon lens for light delivery. A phantom consisting of nylon strings was imaged to find an optimal scanning geometry and resolution of the probe. The effect of limited angular coverage was evaluated by comparing the PAI results of a phantom mimicking an ex-vivo breast cancer specimen obtained with the hand-held probe and near-full view PAI system.

Translation of the probe with 4 mm steps and rotation over 6° steps resulted in lateral and axial resolution of 1.8 mm and 1 mm, respectively. Experiments with the prototype hand-held PAI probe at 930 nm resulted in excellent image contrast exclusively from lipids. Lipid-free gaps mimicking positive margins were clearly visible in the images. Compared to images from the near full-view PAI system, the hand-held PAI probe had a higher signal-to-noise ratio but suffered from more negativity image artefacts.

Taken together, the results show that PAI with the hand-held probe has the potential for detection of residual breast cancer tissue during BCS.

Keywords: Photoacoustic imaging, Optoacoustic imaging, hand-held probe, breast conserving surgery, lumpectomy, limited view angle, limited frequency bandwidth

1. INTRODUCTION

Approximately 19% of breast cancer patients undergoing breast conserving surgery (BCS) must return for a secondary surgery due to incomplete tumour removal reported by pathology [1]. During BCS tumour tissue is excised along with a margin of healthy tissue. Pathology is then used to assess the margin. Current guidelines for invasive breast cancer recommend that no tumour cells be detected on the surface of excised tissue, while for ductal carcinoma in situ (DCIS), the criterion is a minimum 2 mm margin of healthy tissue at the surface [2]–[4]. However, since pathology takes place post-surgery, there is no intraoperative feedback about the margin status, and it is often difficult to ensure the margin criteria are met.

Various technologies have been proposed for real-time feedback during the surgery, such as imprint cytology, frozen-section analysis, ultrasound, X-ray imaging, and Raman spectroscopy [5]–[9]. However, these techniques have not yet become a standard of care, mainly due to increased procedure time or lack of sensitivity. Additionally, most of these techniques are performed on the excised specimen rather than inside the surgical cavity, making it challenging for the surgeon to relate a position on the specimen to its associated position inside the cavity. Only a few devices are currently under investigation for intracavity use, such as ClearEdge (LSBioPath), MarginProbe® (Dilon Technologies® Inc.) and the intelligent knife (iKnife) (Waters Corporation). The main common drawbacks of these devices are sparse tissue sampling and their inability to assess the extent of the detected anomaly.

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1. INTRODUCTION

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We propose the use of a hand-held photoacoustic imaging (PAI) probe for intraoperative margin assessment during BSC. Imaging techniques can overcome sparse tissue sampling and fully visualise the extent of the disease. In recent years, PAI has shown excellent results in differentiating cancerous and healthy tissue [10], [11]. Several groups have evaluated tomographic PAI for breast cancer margin assessment on excised specimens and have shown sensitivity and specificity comparable to other devices [12]–[14].

In PAI studies by Kosik et al. (2019, 2020) and Li et al. (2015), lipid optical absorption was used to differentiate tumour tissue from healthy tissue [12], [15], [16]. Breast tumour tissue contains significantly less lipids compared to healthy tissue, resulting in a lack of contrast (hypointense contrast) in the PA images. However, both techniques were applied to the specimen and as such prolonged the procedure time due to the time needed to prepare the sample and perform imaging. A hand-held tool applied inside the cavity alleviates the need to prepare the sample and allows for examination only of the regions of interest.

PAI has not yet been tested in a real-time intracavity scenario during BCS. One of the main challenges is that imaging inside a surgical cavity limits the angular coverage, resulting in incomplete data collection, which can cause image artefacts such as blurring, streaking, and incomplete visualisation of objects [17]–[19]. The main objective of this work was to determine the feasibility of a compact, hand-held PAI probe specifically designed for breast cancer margin imaging based on lipid content differences. This study (i) reports the design and (ii) characterisation of a prototype hand-held PAI probe and (iii) demonstrates preliminary imaging results of a simulated ex-vivo breast cancer specimen with a positive margin. The study has been since published, and more information can be found elsewhere [20].

2. MATERIALS AND METHODS

2.1. Hand-held PAI probe design, characterisation, and imaging experiments

The probe consists of a single polyvinylidene fluoride (PVDF) acoustic sensor, a 1-to-4 optical fibre bundle, and a polycarbonate axicon lens for light delivery (Fig.1a). Figure 1b shows the complete imaging set-up. The optical fibre from the probe was coupled, using a lens, to an optical parametric oscillator (OPO) (Phocus™, Opotek Inc.) and a 10 Hz Nd: YAG laser (Brilliant, Quantel). This study used a wavelength of 930 nm with approximately 10 mJ at the axicon lens output (unless otherwise stated). Photodiode (PD) was positioned adjacent to the laser path to capture and compensate for laser energy fluctuations. The software saved the digitised data acquired by the data acquisition system (DAQ) and stored it in computer (PC) memory. Experiments were conducted in a water tank, and the location of the probe was controlled using a 6-axis robot (C3-A601S-UL, Epsom) (Fig. 1c).

The illumination profile of the probe was estimated by performing measurements on breast tissue-mimicking phantoms (TMP). To make the TMP, a suspension of PDMS (184 Sylgard Elastomer, Ellsworth Adhesives Canada Corp.), glycerol (Sigma-Aldrich) and a curing agent (184 Sylgard Elastomer, Ellsworth Adhesives Canada Corp.) was mixed 10:2:1, respectively. The phantom was placed within a transparent water tank and illuminated with the hand-held PAI probe. The illumination pattern exiting the underside of the phantom was captured with a CMOS camera (STCMBCM40143V, Omron Sentech Co., Ltd.). The distance between the probe and TMP was adjusted in increments of 5 mm (range: 0-25 mm) using the beforehand mentioned robot. The mean pixel value from a circular ROI, corresponding to the area directly in front of the acoustic sensor, was extracted from each recorded imaging.

The frequency response of the sensor was measured using a method adapted from that described by A. Rosenthal et al. in 2011[4]. In brief, a highly absorbing phantom was used as a broadband planar point source. The phantom comprised of water, 2% w/v agarose (VWR Life Science Agarose RA™) and 50% v/v India ink (Speedball), resulting in a μs of approximately 181 mm−1 and a transport mean free path of 5.5 µm. The phantom was positioned in a water tank beneath the acoustic sensor. Photoacoustic waves were generated at the phantom surface by illuminating the phantom with 700-nm laser pulses. The fast Fourier transform was applied directly to the raw PA signal to obtain the frequency response of the acoustic sensor.

The image quality in PAI depends on the characteristics of the acoustic sensor and scan geometry used for imaging. Imaging of a string phantom was performed to estimate the optimal scanning geometry with the hand-held PAI probe realistic to repeat inside the surgical cavity. A string phantom consisting of six Ø400 µm nylon strings with different spacing was constructed. The phantom was imaged using several different scan types. Imaging in this study was done only in 2D due to constraints placed by the robot motion range. The first set of imaging experiments was done by translating the probe over the phantom with a step size ranging from 0.5 to 8 mm. In the next set, the number of angular views was increased by rotating the probe around each translational position, as shown in Figure 1d. The probe was translated in the x-direction in B-mm increments (blue circles, Fig.1d), ranging from 0.5 mm to 8 mm and rotated around each translational step in θ over 84° of A° increments (red circles, Fig.1d), ranging from 0.5° to 8°. Considering the restriction posed by the surgical cavity, the assumption was made that the probe could be tilted by ±42°. The image quality was then visually
compared between the scans and by measuring the FWHM of the cross-sectional intensity profiles of each sting in lateral and axial directions.

An open-source PAI reconstruction software package was used for image reconstruction [21]. The images were reconstructed with a delay and sum algorithm [22], including directivity weighting [23]. Unless otherwise stated, forced zeroing was applied as the only post-processing step [17].

Figure 1: (a) Photograph of the prototype hand-held PAI probe attached to a robot head. The acoustic sensor casing, light guide and optical fibres were held together with two optical rods and two 3D-printed mounts to align the sensor, optical fibres, and lens. (b) block diagram of the complete imaging set-up (robot not included). (c) Illustration of the prototype hand-held PAI probe mounted on a robot with a coordinate system and direction of rotation indications. (d) Illustration explaining scan geometry carried out with the probe attached to the robot end effector. The probe is positioned a set distance from the imaging surface (Radius), typically 15-25 mm. The red circles in the illustration are examples of sensor face location during angular steps (A), while the blue circles indicate the translational steps (B). Each translational step becomes a centre of rotation.

2.2. Simulated ex-vivo breast cancer specimen imaging study

A phantom mimicking a simulated ex-vivo breast cancer specimen with a positive margin was constructed by wrapping a chicken breast in porcine fat to test the feasibility of the concept. The chicken simulated cancerous tissue with lower lipid content compared to the pork belly fat layer that simulated healthy tissue. A gap in the pork belly layer exposed the chicken breast to simulate a positive margin. The phantom was placed in a Ziploc bag and affixed as described by I. Kosik et al. (2019) for breast cancer specimen imaging [16]. Multiple dots were placed on the bag using a permanent black marker as landmarks for image registration. The phantom was imaged with the hand-held probe and a custom near-full view photoacoustic tomography (PAT) system, reported elsewhere [24], to assess the effects posed by the limited angular covered achievable with the hand-held PAI probe.

The phantom with the hand-held PAI probe was imaged from two sides by flipping it by 180°. Images acquired from both sides were stitched together with the help of markers placed as landmarks. Registration of images obtained with the hand-held probe and near full-view system was performed in 3D Slicer using marker dots as landmarks [25].
3. RESULTS

3.1. Hand-held PAI probe characterisation

The prototype hand-held PAI probe illumination profiles through a 2-mm thick TMP are shown in Fig.2a. The figure depicts how the profile changes with the increasing separation distance between the probe and TMP. At close separation distances, the illumination profile consists of four distinct spots from each fibre bundle. As the distance increased, the four spots started to converge into a single spot.

The estimated frequency response of the acoustic sensor is presented in Fig. 2b. The bandwidth of the sensor at -3dB was 216 kHz to 476 kHz (81%), with a centre frequency of 322 kHz. This corresponded to objects in the range of 3.2 mm to 6.9 mm.

A phantom consisting of six Ø400 µm nylon threads (Fig. 2c) was imaged using the hand-held PAI probe to find the optimal scanning geometry. Scans with only translation resulted in very poor lateral resolution. The most densely sampled translational image acquired (step size of 0.5 mm) is shown in Fig. 2d. None of the individual threads were visualised in this case. The lateral resolution was significantly improved by adding rotations around the translational points (Fig. 2e, f, g). A horizontal line profile was extracted for each completed scan, and the FHWM was measured for each peak. The mean lateral resolution from all six peaks for all scans deviated only by ±0.25 mm. No trend between increased translation and angular step sizes was identified at the examined step sizes and higher lateral resolution. However, the number of streak artefacts increased as the angular step size decreased (compare Fig. 2e and f). For this study, translational step of 4 mm and angular step of 6° were chosen as it allowed for fast imaging (2 minutes for a 100 mm long object) and contained fewer streak artefacts compared to scans with longer translational and angular step sizes (Fig. 2e). Spatial sampling at smaller angular increments resulted in minor improvements in image quality (Fig. 2g). The scan in image Fig. 2f resulted in an axial resolution of 1.07 ± 0.04 mm and a lateral resolution of 1.84 ± 0.40 mm.

![Figure 2](image)

Figure 2. (a) The hand-held PAI probe illumination profiles from 0 mm to 25 mm in 5 mm increments (left to right). (b) The frequency response of the acoustic sensor. (c) Grid phantom composed of a plastic frame and six Ø400 µm nylon threads. (d) PA image of the phantom in (c) obtained with the hand-held PAI probe with translational steps of 0.5mm. (e-g) PA images with a translation of 4 mm and angular step sizes of 8°, 6°, and 4°, respectively.

3.2. Simulated ex-vivo breast cancer specimen imaging study

Photographs of the top and bottom of the ex-vivo breast cancer specimen phantom are shown in Fig. 3a and Fig. 3b, respectively. The simulated positive margin is indicated with a yellow arrow in Fig. 3a. Lipid-containing phantom regions produced strong photoacoustic signals (intensity line profile example is shown in Fig. 3c). However, the signal
peak was surrounded by a negative signal and followed by a secondary peak (see item 1 and 2 in Fig. 3c, respectively). While the negative signal was removed by utilising forced zeroing, the secondary peak is a ghost artefact due to the ringing of the sensor and cannot be easily removed.

PA images of both the top (Fig. 3d) and the bottom (Fig. 3e) of the phantom were acquired with the hand-held PAI probe. Image artefacts (Fig. 3d, red arrow), as described above, were noticeable. Superimposed image of the top and bottom images using fiducial markers on the specimen holder (Fig. 3d, c, green arrows) allowed visualisation of the entire cross-section of the phantom (Fig. 3f). Aside from the ringing artefacts, the signal in the image was confined to the lipid layer representing a layer of healthy breast tissue. The mimicked positive margin was clearly detected as a lack of signal in the middle portion and on the surface of the phantom (Fig. 3f, yellow arrow).

A slice from the 3D data volume obtained with the near full-view PAT system is presented in Fig. 3g. The images from the two systems displayed as a false colour overlay for comparison are shown in Fig. 3h. Similar to the images obtained with the hand-held PAI probe, the signal was confined to the lipid layer and fiducial markers on the specimen holder (Fig. 3g, green arrow). The mimicked positive margin was also detected (Fig. 3g, yellow arrow); however, it was not as distinct and blurred (compare Fig. 3f and Fig. 3g). Differences in the signal-to-noise levels between the hand-held PAI probe and the near-full view system can be also well visualised in Fig. 3c. Additionally, the images obtained with the hand-held probe had signal dropout on the left and right side of the phantom and suffered from a greater number of image artefacts. Another noticeable difference between the two images is the apparent thickness of the fat layer. The thickness of the fat layer in the images obtained with the hand-held probe is uniform, while in the image from the near full-view PAT system thickness varies.

Figure 3: Comparison of PA images of a lumpectomy phantom acquired with the hand-held PAI probe and a near full-view PAI system. (a) A photograph of the top and (b) bottom portion of the ex-vivo breast cancer specimen phantom. (c) Intensity line profile through the cross-section of the phantom. The signal peak corresponds to the signal from the lipid layer. It is preceded and followed by a negative signal (1.), the next peak following the highest peak (2.) is believed to originate from the ringing of the sensor. (d) PA image of the top and (e) bottom surface of the phantom acquired with the hand-held PAI probe with indications of fiducial markers (green arrow) and artefacts (red arrow). (f) Overlay of the PA images of the top and bottom surfaces of the phantom corresponding
to (d) and (e), respectively. (g) PA image of the phantom acquired with a near full-view PAT system. (h) Overlay of images shown in panels (f) and (g), with colour coding in pink and blue, respectively. The yellow arrows indicate the location of the mimicked positive margin.

4. DISCUSSION AND CONCLUSION

We have developed a prototype hand-held PAI probe intended for breast cancer margin assessment based on lipid content differences. In this work, we have reported the design and the characterisation of the probe and demonstrated preliminary imaging results of a simulated ex-vivo breast cancer specimen.

Experiments with the prototype hand-held PAI probe at 930 nm resulted in excellent image contrast exclusively from lipids (e.g., see Fig. 3). Lipid-free gaps mimicking positive margins were clearly visible in the images. A significant limitation of the hand-held PAI probe is the presence imaging artefacts. Two types of artefacts were identified. The first type was negativity artefacts caused by incomplete data collection due to limited bandwidth and angular coverage, as described elsewhere [17]. Detector bandwidth can potentially be improved with the use of different piezoelectric materials. Additionally, artefacts could be mitigated by deconvolution of the acquired data with the impulse response of the sensor. This could also improve the visibility and detectability of objects outside the -3dB bandwidth range, as the sensor frequency response extends from 100 kHz to 2 MHz. A comparison of imaging results from the hand-held PAI probe with the full-view PAI system revealed that negativity artefacts could also be reduced by having more angular views. It needs to be tested if more angular views can be collected in free-hand scanning with a smaller probe capable of fitting inside a surgical cavity. The negativity artefacts in this study were mitigated by post-processing the images with forced zeroing, as previously suggested by K. Shen et al. (2020). The second type of ringing artefact was caused by the solid sensor backing intended to stop the acoustic waves entering the sensor from propagating further into the circuit of the sensor. Although a solid backing degraded image resolution 2-fold due to the back-and-forth travel of acoustic waves through the sensor, it also increased detection sensitivity. However, the stiffness of the solid backing layer could not dampen all sensor oscillations. The sensor oscillations resulted in ringing that generated ghosting artefacts in the reconstructed images. Typically, US sensors have an acoustically matched backing layer that guides the incoming acoustic wave away from the sensor element and dampens reverberations. However, the sensitivity of a sensor with a matched backing layer is reduced compared to a sensor with a solid backing layer. Therefore, the trade-off between sensitivity and the presence of artefacts needs to be examined closer. While artefacts degrade the image quality, lower sensitivity affects image quality also.

Currently available hand-held breast cancer margin assessment tools generally provide a binary output (yes/no) and tend to sparsely sample tissue without the ability to discriminate depth. Depth discrimination is important for correlating results to pathology in some cases (e.g. 2 mm DCIS criteria) [2]. The hand-held PAI probe provides a continuum of image contrast at useful depths from the surface, although optimisation is needed for human tissue. Additionally, compared to mass spectrometry techniques, it is non-destructive to tissue.

Future work on the hand-held PAI probe involves miniaturising the probe to fit inside the surgical cavity. As well, free-hand imaging with the probe needs to be demonstrated. The addition of optical positional tracking will likely provide real-time data with the necessary accuracy and precision to generate PA images with free-hand scanning. This will allow the surgeon to advance the probe and build an image of the region of interest in real-time.

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