Research article

Assessment of prostate cancer progression using a translational needle photoacoustic sensing probe: Preliminary study with intact human prostates ex-vivo

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A B S T R A C T

In our previous studies, we demonstrated the ability of an interstitial all-optical needle photoacoustic (PA) sensing probe and PA spectral analysis (PASA) to assess the aggressiveness of prostate cancer. In this clinical translation investigation, we integrated the optical components of the needle PA sensing probe into a 18G steel needle. The translational needle PA sensing probe was evaluated using intact human prostates in a simulated translation investigation, we integrated the optical components of the needle PA sensing probe into a 18G steel needle. The translational needle PA sensing probe was evaluated using intact human prostates in a simulated ultrasound-guided transperineal prostate biopsy. PA signals were acquired at 1220 nm, 1370 nm, 800 nm and 266 nm at each interstitial measurement location and quantified by PASA within the frequency range of 8–28 MHz. The measurement locations were stained for establishing spatial correlations between the quantitative measurements and the histological diagnosing. Most of the quantitative PA assessments reveal statistically significant differences between the benign and cancerous regions. Multivariate analysis combining the PASA quantifications shows an accuracy close to 90% in differentiating the benign and cancerous regions in the prostates.

1. Introduction

The standard diagnosis approach of prostate cancer (PCa) is needle-based core biopsy guided by transrectal ultrasound (TRUS). Histopathologic processing of the extracted tissue visualizes the microscopic architecture of the tissue, which reflects the aggressiveness of the PCa [1]. TRUS guided prostate biopsy has a poor core yield and a high false negative rate owing to TRUS’s limited sensitivity to PCa and the small volume of the biopsy core [2]. Magnetic resonance imaging (MRI) TRUS fusion biopsy has recently been introduced as a method to improve the identification of the clinically significant PCa in patients with initial negative biopsies [3–5]. Nonetheless, the procedure requires the fusion of MRI and Ultrasound (US) imaging that is subject to registration and targeting error.

Photoacoustic (PA) imaging and sensing, taking advantage of the unique optical absorption profiles of tissue components, is able to acquire microscopic tissue architecture at US resolution [6]. Our previous studies validated that the frequency domain analysis of the photoacoustic signal power distribution, namely PA spectral analysis (PASA), can statistically quantify the content and microarchitectural distribution of tissue components inside the tissue-volume-of-interest [7]. Recent studies using human and animal prostates, including those by our [8,9] and other groups [10,11] have demonstrated that PASA can differentiate between benign and cancerous prostate tissues, and assess the
aggressiveness of PCa. Therefore, PASA technology holds the promise to provide a diagnosis of PCa in situ without the need for tissue extraction, and may reduce the amount of biopsy core extractions and post-core-biopsy complications [12].

Encoding fine microarchitecture information comparable to histology, high frequency PA signal components attenuate fast through the biological tissue [13]. Aimed at capturing these high frequency signal components, we recently developed an interstitial PA measurement approach [8]. The interstitial measurement instrumentation includes a fiber optic diffuser for illumination and a needle hydrophone for signal detection. When joined together, the two components possess a slim profile for insertion into the prostate and allow for broadband PA signal acquisition from the surrounding tissue. The approach has been validated in detecting the progressive PCa in prostate tissue blocks [14] and intact prostates from human subjects ex vivo [8] and animals in vivo [9]. Our latest work further miniaturized the interstitial needle PA sensing probe with an all-optical design that consists of a fiber optic diffuser and a fiber optic hydrophone [14].

In this study, we integrated the all-optical components into the inner lumen of a steel needle with the dimension close to a core-biopsy needle with the purpose of clinical translation. The mechanical reliability of the needles was examined by a certified medical device testing company (DDL, Inc., Eden Prairie, MN). The performance of the translatable needle PA sensing probe was examined in a simulated TRUS guided transperineal biopsy procedure using intact human prostates procured through radical prostatectomies. When inserted into the prostate, the needle PA sensing probe collected PA signals at multiple wavelengths targeting a series of tissue components. The measurement locations were stained by dye injection so that the histopathology results from the same locations can be compared to the PASA quantifications.

2. Method

2.1. Translational needle PA sensing probe

The needle PA sensing probe, as shown in Fig. 1, included an 800 μm-diameter fiber diffuser for light illumination, a 150 μm-diameter fiber optic hydrophone for US detection, and a 200 mm-long 18G medical needle (TruGuide, Bard Peripheral Vascular Inc, Tempe, AZ). The emission segment of the fiber optic diffuser has a length of 6 mm and a conical shape, as shown in Fig. 1(a). The detailed fabrication procedures of the fiber diffuser were described in [15] and our earlier study [14]. The fiber optic hydrophone with a plano-concave microlens-onator at the detection end [16] was driven by a commercial fiber optic hydrophone data acquisition system (Precision Acoustics, UK). The functional segments of both the fiber optic diffuser and the fiber optic hydrophone were exposed through a 12 mm-long side-view window at the end of the 18G medical needle, as shown in Fig. 1. The 12 mm length was chosen because the prostate biopsy core is 12 mm in length. The window cutout possessed introducing angles, as shown in Fig. 1(b), to prevent resistance during needle insertion and withdrawal. The inner surface of the side-view window was coated with gold for optimal illumination efficiency, as shown in Fig. 1(c).

2.2. Simulated TRUS guided transperineal needle PA sensing probe insertion procedure

This study simulated a TRUS guided transperineal biopsy procedure [17] using intact human prostates ex vivo. The protocol for procuring the prostate after prostatectomy procedures and using the prostates in our experiments was approved by the Institutional Review Board of the University of Michigan Medical School. All subjects provided written informed consents. Fig. 2 depicts the experiment setup, and the procedures are explained below.

In the simulated system in Fig. 2, the 2D imaging plane of an endocavity US array (E9-4, Zonare, Mountain View, CA) was aligned with a biopsy template with evenly distributed sampling holes for the needle PA sensing probe. Before the experiment, the sampling track in US imaging corresponding to each sampling hole were determined, as illustrated in Fig. 3. A silicone rubber mold (Ecoflex 00-30, Smooth-On Inc., Macungie, PA) imitating the skin and subcutaneous tissue in the perineal region was used to seal the human prostate. The rubber mold containing the prostate was secured underneath the positioning system. The US array was coupled to the surface of the rubber mold with US gel. By rotating the holder attached to the US array, the US field-of-view can cover the whole prostate volume. Most of the prostatectomy patients went through preprocedural MRI. The MRI reports provided the approximate locations of the benign and cancerous regions. Along with the prostate contour shown in the TRUS imaging, we can have samplings targeting either the benign or the cancerous region. Once a needle insertion location was determined through US imaging, an 14G introducer needle (PrecisionPoint, Perineologic, Cumberland, MD) used in regular biopsy procedure were inserted through the sampling template into the rubber mold and made a pathway for the needle PA sensing probe. The needle PA sensing probe was then inserted to the desired location inside the prostate guided by the needle position presented in the real-time US imaging, as illustrated by Fig. 3 and the supplemental video. During the operations, TRUS was only to identify the contour of the prostate and monitor the position of PA sensing probe during insertion.

The outputs of an optical parametric oscillator (OPO) pumped by the second harmonic of an Nd:YAG laser (Phocs Mobile, OPOTEK, Carlsbad, CA 690–950 nm and 1200–2400 nm, 5–7 ns pulse width, 10 Hz repetition rate) with pulse-to-pulse switching function and an Nd:YAG laser (using the fourth harmonic output, 266 nm, 5–8 ns pulse width, 10 Hz repetition rate, Surelite, Continuum, San Jose, CA) were integrated into the same light path and coupled into the fiber optic diffuser. This study employed illumination at 1220 nm, 1370 nm, 800 nm, and 266 nm to target lipids, collagen, total hemoglobin, and cell nuclei, respectively, in the prostates. 800 nm measurement is insensitive to the blood oxygenation and, therefore, was selected for imaging the total hemoglobin content in ex vivo prostate in this study. Since the samples were fresh and intact, and the experiment was started immediately after the operation, we believe there was hemoglobin content remained in the sample, although the hemoglobin may have been deoxygenated. 266 nm illumination targets the contrast of cell nuclei [18,19]. Since the tissue architecture described in the Gleason scoring system of PCa is formed by cancer cells, PASA at 266 nm is a direct measurement of the tissue architectures. We have successfully differentiated the PCa stages in mice prostates ex vivo and in vivo, as well as human prostate tissues ex vivo [9,14]. In this setup, the optical energy at the surface of the side-view window of the needle PA sensing probe was 3.3 mJ at 1220 nm, 1370 nm, 800 nm, and 0.9 mJ at 266 nm. According to our previous paper [14], the sampling volumes for each wavelength were carefully compensated by the emission energy at each wavelength. We estimated
Fig. 2. Experiment setup simulating transperineal TRUS guided biopsy. (a) Overview of the setup. (b) Detailed illustration of the experiment components in the red dashed box in (a). (c) The controlling diagram of the transperineal needle PA sensing probe system. L: Convex len. M: Mirror. FOH: Fiber optic hydrophonr. FOD: Fiber optic diffuser. NIR: Near-infrared.

Fig. 3. TRUS guided insertion of the needle PA sensing probe. (a) is the schematic of the US guide system for needle inserting procedures. The US images (b) and (c) were taken before and after the needle insertion, respectively. The needle was marked in the red circle in (c). The red dotted line in (a–c) represents the inserting direction.

Fig. 4. Histopathology of the intact prostates. (a) Gross pathology of the prostate by slicing the prostate into 4–5 mm thick samples. The blue spots are the spatial markers of the PA measurements by dye injection. The 2D contours of the cancerous regions were delineated in black. (b–c) represent the histology photos of the benign and the cancerous regions. 10× objective magnification.

Fig. 5. Example PA signals acquired at 1220 nm, 1370 nm, 800 nm and 266 nm wavelengths for insertions in the benign and cancer regions in an intact human prostate. The orange curves are the measurements in the cancerous region and the blue curves are the measurements in the benign region.

the illumination surface as half of the cylindrical surface of the needle, which was $OD \times \pi \times h/2 = 1.27 \times \pi \times 12/2 \, \text{mm}^2 = 23.9 \, \text{mm}^2$. Hence, the optical energy density was approximately 13.8 mJ/cm$^2$ at 1220 nm, 1370 nm, and 800 nm, and 3.8 mJ/cm$^2$ at 266 nm. These energy levels are lower than the safety limits of 100 mJ/cm$^2$ at wavelengths larger than 1000 nm, 31.7 mJ/cm$^2$ for 800 nm, and 4.9 mJ/cm$^2$ for 266 nm, as established by American National Standard Institute (ANSI). The PA signals captured by the fiber optic hydrophone were amplified by 20 dB (5072 Pulse/Receiver, 1 k–35 MHz, Olympus, Center Valley, PA) and averaged 56 times, then displayed on an oscilloscope and stored in a computer. The needle PA sensing probe was removed after the measurements.

The needle sensing probe track in the prostate was revisited with a syringe containing a 22G needle under the guidance of US imaging. A depth stop was used to ensure that the tip of the needle was positioned at the distal end of the measured range. 0.05 ml Evans blue dye (E2129, Sigma-Aldrich, St. Louis, MO) was injected. During the needle withdrawal, the dye filled the needle track and stained the whole needle insertion track. For each prostate, 3–5 locations were examined.
2.3. Histopathological examination

After the PA measurements, the intact prostates went through routine histological processing. Each prostate was dissected into 7 to 9 slices along the apex-base orientation. The malignant regions in each slice were identified and marked in the gross photo, as shown in Fig. 4(a). The needle insertions were intentionally oriented perpendicular to the sliced planes. The stained spots in Fig. 4(a) are the locations where needle track intersected with the sliced planes. Considering that the thickness of the slices is around 4–5 mm and the window exposing the optical components are 12 mm long, the histological gradings within the last three slices before the staining disappeared were utilized to compare to the interstitial PA measurements. To accurately differentiate the measurements acquired in the cancerous and benign regions, only the signals acquired more than 2 mm away from the cancer boundaries were included in the statistical analysis. Table 1 summarizes the diagnoses of all the samples included in the statistical analysis.

2.4. Quantitative analysis with PASA

Fig. 5 shows the representative PA signals acquired at 1220 nm, 1370 nm, 800 nm and 266 nm in a benign and a cancerous region, respectively. The analyzed signal lengths were approximately 8 μs in

| Groups | Sample number @ 1220 nm, 1370 nm, 800 nm | Sample number @ 266 nm |
|--------|----------------------------------------|------------------------|
| Benign | 28                                     | 22                     |
| Cancer | 21                                     | 15                     |

Table 1

Disease conditions of the sampled locations.
validation method used in our previous study was implemented, where overfitting while accounting for the high cost of penalty. A 5-fold cross-validation approach was used to ensure that the model generalizes well to unseen data. The measurements at 1220 nm, 1370 nm, and 800 nm were excluded because part of the samples do not have measurements at this wavelength. Fitcsvm, a built-in SVM function in MATLAB, was used to classify the samples into benign and cancerous categories. The null hypothesis is that the accuracy between the two groups is not statistically different. The testing accuracy was calculated as the average of all 5 testing cycles.

3. Result

3.1. PASA at individual wavelength

Fig. 7 shows the averaged PA signal power spectra and the linear fits for all the benign and the cancerous insertions at the wavelengths of 1220 nm, 1370 nm, 800 nm and 266 nm, respectively. Since the fiber optic hydrophone is less sensitivity to low frequency components compared to piezoelectric hydrophone, the PA signal spectra in this study contain less low frequency components compared to our previous study.

In Fig. 7, at approximately 18 MHz, the signal power spectra of the cancerous group at both 1220 nm and 1370 nm, targeting lipid and collagen contents in the prostate, respectively, intersect with that of the benign group. Larger high-frequency signal components in the cancerous group lead to the larger spectral slopes compared to the benign region, indicating the reduced dimensions of the microarchitectures formed by lipid and collagen. Furthermore, the midbandfits of the cancerous group are slightly lower than those of the benign group, although no significance is shown. The low midbandfit values reflect the decrease of lipid and collagen contents in the cancerous regions.

The measurements at 800 nm targeting the total hemoglobin content show larger spectral slopes and smaller midband-fits in the cancerous group. Larger spectral slope (smaller absolute values as most of the spectra show descending trend) was observed in PCs by our and other groups. The midbandfit at 800 nm is lower in the cancerous region. This agrees with a previous study reporting that blood flow decreases in prostate tumor.

At 266 nm, the broadband fiber optic hydrophone detected the high frequency signal components generated by the thin layer of epithelium cells in benign prostate tissues. The low midbandfit values reflect the decrease of lipid and collagen contents in the cancerous regions. Considering that the connective tissue in the prostate is rich in lipid and collagen contents, these observations are consistent with previous studies where the connective tissues and collagen contents intersect with that of the benign group. Larger high-frequency signal components in the cancerous group give rise to the larger spectral slopes compared to the benign region, indicating the reduced dimensions of the microarchitectures formed by lipid and collagen. Furthermore, the midbandfit of the cancerous group are slightly lower than those of the benign group, although no significance is shown. The low midbandfit values reflect the decrease of lipid and collagen contents in the cancerous regions.

3.2. Multivariate analysis using SVM

Since 266 nm measurements were not acquired in some of the samples, the multivariate analysis does not include the PASA quantifications at 266 nm. Fig. 9 shows the scattered plot of all PASA values at 1220 nm, 1370 nm and 800 nm. The data points show differentiable clustering patterns. The decision surfaces in Fig. 9 were calculated using all the 49 measurements at the three wavelengths. The accuracy of the decision surface in separating the benign and the cancerous regions is 92%. Table 2 lists the accuracy of SVM classification with the measurements at individual wavelength and combined wavelengths using the 5-fold cross-validation approach described in the method section. The highest classification accuracy was achieved by combining the PASA measurements at all the three wavelengths.
but with relatively low significance when compared to slope. The lipid content can also be observed using the midbandfit parameter, in cancerous regions, were resolved. The decrease in collagen and of epithelium cells in benign prostate glands and connective tissues correlated to high frequency signal components, such as the thin layer of epithelium. Fine microscopic tissue architectures of microns, which were covered by the frequency range of the fiber dimensions of the cancer cell clusters are in the range of 10 s to 100 s of microns, was always oriented perpendicular to the central line of the convex US array surface. In US imaging, this orientation guarantees a robust reflection signal, which helps the operator in accurately positioning the needle probe. Furthermore, there is a marker along the entire needle body indicating the orientation of the measurement window which helps in matching with histologic diagnosis.

With dye injection following the PA measurements, we successfully correlated the PASA quantifications with the pathological diagnosis at each sampled location. The needle PA sensing probe is only capable of 1D measurements [14]. Measurements taken close to the cancer boundaries were excluded from the statistical analysis because these measurements may contain unresolvable spectral characteristics of both benign and cancerous tissues. In future studies, we plan to investigate uniform sampling and estimating the volume of a cancerous region by the distribution of the PASA quantifications. Considering the large sampling volume provided by the needle PA sensing probe, we may be able to cover the whole prostate volume with limited number of needle probe insertions.

Compared to the piezoelectric hydrophone in our previous studies [8,9], the broadband fiber optic hydrophone significantly extended the frequency range in PASA. As shown in a pilot study [26], describing the histopathological diagnosis of PCa, i.e. Gleason scoring system, the dimensions of the cancer cell clusters are in the range of 10 s to 100 s of microns, which were covered by the frequency range of the fiber optic hydrophone in this study. Fine microscopic tissue architectures correlated to high frequency signal components, such as the thin layer of epithelium cells in benign prostate glands and connective tissues in cancerous regions, were resolved. The decrease in collagen and lipid content can also be observed using the midbandfit parameter, but with relatively low significance when compared to slope. The histopathologic diagnose of PCa is based on tissue architecture rather than tissue content. Therefore, slope representing the tissue architecture is a more reliable parameter in this study compared to the midbandfit, which represents the content of a certain tissue component. These results agree with our predictions drawn from the results derived from piezoelectric hydrophones [9]. Since slope and midbandfit are two natural derivatives of PASA, we included both in this study. The fiber optic hydrophone with broad frequency range in this study improved the differentiability between the benign and cancerous regions. With limited sample number, we observed overlapping between the benign and cancerous group and we did not examine the correlation between the Gleason grades and the PASA quantifications as did in our previous studies [9,14]. Further studies with larger sample size will help us understand the performance of the interstitial all-optical needle PA sensing probe in a simulated TRUS guided transperineal biopsy procedure. PASA of the measurements acquired by this translational needle PA sensing probe successfully differentiated between the benign and the cancerous regions in human prostate. This study using intact human prostates ex vivo paved the road toward clinical testing of our interstitial all-optical needle PA sensing probe powered by PASA for detecting and assessing the aggressiveness of PCa.

4. Discussion

In the simulation setup, a forward looking endocavity US array was used, although a side-viewing endocavity US array is commonly used in transperineal prostate biopsy. To match the US imaging field-of-view to that in the actual biopsy procedure, a 90-degree probe holder was fabricated. The translational needle PA sensing probe, with a diameter tightly fit to the introducer needle, was always oriented perpendicular to the central line of the convex US array surface. In US imaging, this orientation guarantees a robust reflection signal, which helps the operator in accurately positioning the needle probe. Furthermore, there is a marker along the entire needle body indicating the orientation of the measurement window which helps in matching with histologic diagnosis.

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5. Conclusion

In this study, we examined the feasibility of integrating a miniaturized, all-optical needle PA sensing probe in a simulated TRUS guided transperineal biopsy procedure. PASA of the measurements acquired by this translational needle PA sensing probe successfully differentiated between the benign and the cancerous regions in human prostate. This study using intact human prostates ex vivo paved the road toward clinical testing of our interstitial all-optical needle PA sensing probe powered by PASA for detecting and assessing the aggressiveness of PCa.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Guan Xu reports the 14G introducer needle in Fig. 2 was provided by Perineologic, 183 N Centre Street, Cumberland, 21502, Md, USA. Guan Xu reports financial support was provided by National Cancer Institute. Guan Xu reports financial support was provided by National Institute of Diabetes and Digestive and Kidney Diseases.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.pacs.2022.100418. Transrectal ultrasound guided video of the needle insertion.

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