In vivo transrectal imaging of canine prostate with a sensitive and compact handheld transrectal array photoacoustic probe for early diagnosis of prostate cancer

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Abstract: In this study, we built a novel handheld array photoacoustic probe by integrating multiple optical components with a transrectal ultrasound (TRUS) transducer array. The optical components deliver laser energy and TRUS is used for photoacoustic signal detection. Compared to the previously reported probe, the new photoacoustic probe utilizes an optimized light illumination scheme to enhance the utilization-efficiency of the laser energy, thus improving the imaging sensitivity of the probe. In addition, the new probe is compact and easy to handle for clinicians. We validated the use of this photoacoustic probe for prostate cancer imaging through both phantom studies and in vivo canine model study, which mimics the prostate cancer conditions. The results showed that the probe is suitable for clinical use and can be used in the clinics for several potential clinical applications, including early diagnosis of prostate cancer, targeted image-guided biopsy, and image-guided intra-operative procedure.

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1. Introduction

Prostate cancer is one of the most common malignancy affecting men worldwide [1]. Early diagnosis of prostate cancer is of vital importance for better treatment and prognosis of this cancer. Due to the lack of symptoms at the early stage and shortage of effective screening methods, prostate cancer is mostly diagnosed at an advanced stage, when the cancer is progressed and has metastasized to other organs, such as bone. Therefore, the mortality rate due to the prostate cancer remains at high level [2–4]. The transrectal ultrasound (TRUS) guided needle biopsy is currently the gold standard for detecting the prostate cancer. Due to the low contrast and low specificity that exists between the malignant areas and the normal tissues in the ultrasound image, non-targeted 12 sites systematic biopsies covering the whole prostate is typically performed to detect cancer. This procedure is excessive and invasive, causing unnecessary pain to the patient. In addition, more importantly, since the detection rate
using this technique is very low, repetitive biopsies are often performed increasing the cost as well as pain to the patient [5,6]. Therefore, it is of great importance to develop a novel imaging method to improve the sensitivity and specificity of prostate cancer screening at an early stage of the cancer. The new imaging method would also benefit in image guided biopsy, image guided therapy, improved prognosis prediction, and monitoring of therapy.

Tumor angiogenesis is regarded as a distinct hallmark in most cancer cases including prostate cancer [7]. Extensive new blood vessels are generated in the tumor area to provide increased nutrition and oxygen demanded by the proliferation of maniac tumor cells. Compared to the normal tissue, the vascular structure in the tumor tissue is generally more chaotic, resulting in low oxygen transfer efficiency and hence hypoxia in the tumor blood vessels. Imaging the vasculature would potentially provide vital information to differentiate tumors from benign tissues while screening for prostate cancer. The photoacoustic imaging is considered as an ideal tool for vascular imaging compared to the currently available mainstream imaging modalities such as CT, MRI and PET [8–10] because it is non-ionizing, easy to use, real-time, and is available at relatively low cost. The photoacoustic imaging is label-free and is more sensitive to small blood vessels compared to contrast-enhanced ultrasound imaging and color Doppler imaging [11–13]. Besides vascular structural information, photoacoustic imaging is also capable of displaying functional information such as blood oxygen saturation (i.e., to detect tumor hypoxia) and oxygen metabolic rate when multiple wavelengths are used at the absorbance peaks of oxy- and deoxy- hemoglobin (i.e., using photoacoustic spectroscopy). Photoacoustic imaging has high specificity to the signature absorption of different kinds of molecules and thus, is inherently suitable for acquiring molecular information. By labeling prostate tumor cells with exogenous molecular probes, the sensitivity and specificity of photoacoustic imaging to detect prostate cancer can be further enhanced. Finally, the photoacoustic-imaging platform can be conveniently integrated into the clinical ultrasound-imaging platform providing both an ultrasound image and photoacoustic image on the same modality. The combination of photoacoustic imaging and ultrasound imaging provides complementary structural, functional and molecular information of the biological tissues providing the benefits of both modalities.

Several studies have been reported in the literature using photoacoustic imaging to detect prostate cancer. Wang et al. [14,15] were the first to establish the proof of concept of using photoacoustic imaging for prostate cancer. They applied a phased array probe based photoacoustic computed tomography system for ex vivo and in vivo imaging of a canine prostate with the cancer lesions simulated via injection of blood to the prostate organ. Bell et al. investigated the potential use of photoacoustic imaging for guiding brachytherapy seeds placement during the prostate cancer therapy [16,17]. They used a single fiber to deliver the laser energy for photoacoustic signal excitation through the urethra after a small incision was made at the skin surface, making it an invasive procedure. More recently, Horiguchi et al. developed a handheld transrectal photoacoustic-imaging probe by integrating the TRUS transducer with an optical fiber bundle [18,19]. This was the first transrectal photoacoustic-imaging probe, making the imaging procedure least invasive and more convenient. The photoacoustic imaging procedure using this probe was similar to clinical TRUS examination, making the probe highly suitable for clinical application and translation. The probe was applied for human prostate cancer imaging and intra-operative navigation.

The photoacoustic probe reported by Horiguchi et al. adopted an optical illumination scheme by accommodating laser excitation on both sides of the TRUS transducer. During the imaging process, both the ultrasound transducer and the laser firing fiber bundle were placed in close contact with the imaging region. The laser energy enters the sample from both sides of the ultrasound transducer in close proximity. A similar design has also been reported by Salehi et al. in the transvaginal photoacoustic probe for human ovarian cancer imaging [20,21]. While decent imaging results have been obtained with these probes, the laser energy delivered to the region of interest (i.e., the probing region of the ultrasound transducer in the
sample) remains less efficient due to the bilateral illumination, resulting in low imaging sensitivity. The imaging sensitivity can be enhanced when laser illumination is optimized to achieve efficient delivery of the laser energy to the ultrasound-probing region.

In this study, to improve the prostate cancer imaging sensitivity, we propose a novel design for a transrectal photoacoustic probe. In this design, the light delivery scheme is reconfigured and is placed directly underneath the ultrasound transducer to enable highly efficient delivery of laser energy into the sample. We performed a theoretical simulation to validate the enhanced laser-energy-utilization-efficiency with this design, which will result in improved imaging sensitivity of the photoacoustic probe. Based on this design, a transrectal ultrasound transducer was modified to incorporate a photoacoustic probe without significantly increasing its size. Imaging of phantom and in vivo canine prostate mimicking the prostate cancer condition was carried out to validate the feasibility of using the probe for prostate cancer detection. The compact size and easy-to-use design of the photoacoustic probe make it suitable for potential clinical use by clinicians.

2. Materials and methods

The detailed configuration of the transrectal photoacoustic probe design and the real photo of the probe are shown in Fig. 1(a) and 1(b), respectively. A bifurcated fiber bundle (FB) (Custom-designed, CeramOptec, Bonn, Germany) with an aperture size of $10 \times 1 \text{ mm}$ at the distal end was used to transmit the laser energy from the laser source to the photoacoustic probe. A custom manufactured naked one dimensional (1D) TRUS transducer array (128 elements, element size 0.152 mm, pitch 0.2 mm, 6.5 MHz central frequency, 60% Bandwidth, 30 mm elevational focus, Custom-designed by Sonoscape, Shenzhen, China) was used for photoacoustic signal detection. The ultrasound transducer includes a tip piece made of PZT piezoelectric ceramics and two flexible signal transmission belts (STB) connected to the back-end of the tip for electrical signal transmission. The transducer tip (TT) has a curved shape with 10 mm radius of curvature and 150° view angle. The fiber bundle was fixed to the side of the two STB. Unlike the previously reported photoacoustic probes, the laser energy coming out of the fiber bundle was not shed directly on the sample surface but deflected by two glass mirrors (GM) mounted on both sides of the ultrasound transducer tip. The two mirrors were fixed on a custom designed mechanical module (CDMM) as shown in Fig. 1(a). A probe cap (PC) made of plastic was placed to cover the tip of the photoacoustic probe to protect the mirrors. The PC also allows enough space for laser propagation and convergence on the sample surface. Due the existence of the PC, the ultrasound transducer tip is 11 mm away from the probe tip and this 11 mm of the transducer detection area is not used for photoacoustic imaging purpose. It should be noted that even though we did not use the shallow 11 mm of the transducer detection area, the photoacoustic imaging capability of our probe is not much compromised as the ultrasound transducer is more sensitive at larger depth. The higher sensitivity of the transducer at larger depth is mainly due to the following two reasons: (1) more elements of the transducer array can be included for image reconstruction at deeper region compared to the shallower depth due to the limited view angle of each element; (2) the elevational focus of the transducer array is fixed at 30 mm depth due to the physical focus of each element in the lateral direction. The fiber bundle, mechanical module, and ultrasound transducer were all sealed in a custom-designed 3D printed shell holder (SH) to provide mechanical support and protection. A rectangular aperture was cut at the center of the plastic cap to enable high optical and acoustic throughput (end view photo in Fig. 1(b)). A condom made of natural rubber material was used to wrap the cap during the experiment to retain deionized water inside the cap for acoustic signal transmission coupling. The transmission through the condom at 780 nm wavelength was measured to be 98.5%, implying the condom has minimal absorption at this wavelength. The photoacoustic probe remains compact (diameter < 25 mm) after all components were sealed within the 3D printed shell holder.
To compare the laser energy delivery of our probe design to the conventional design, Monte Carlo simulation of a photon propagating in semi-infinite scattering medium was performed using Tracepro software (Lambda Research Corporation, MA, USA). The light illumination schematics and beam patterns at the sample surface for the conventional design [18,19] and our design are shown in Fig. 2(a) and Fig. 2(b), respectively. The purple rectangular area in Fig. 2 indicates the ultrasound detection region at the sample surface. For the simulation, the optical beam size was set to 25 × 5 mm for the conventional design and the distance between the two beams was set to 10 mm. For our probe design, the optical beam size was set to 25 × 7 mm due to the oblique incidence of the laser. All the beam parameters were based on the true dimension of the photoacoustic probe. To make fair comparison between these two designs, the total laser energy was kept the same for these two illumination scenarios. The optical parameters used for the imaging sample approximates the real biological conditions of tissues, and were set as follows: 0.1 cm$^{-1}$ for optical absorption coefficient, 200 cm$^{-1}$ for optical scattering coefficient, 0.9 for anisotropic factor, and 1.37 for refractive index.
In this study, a custom-built photoacoustic imaging system, as shown in Fig. 3, was used for validating the performance of the transrectal photoacoustic probe. The system mainly consists of a nanosecond pulsed OPO laser source (Spitlight 600 OPO, Innolas, Germany) for photoacoustic signal excitation, and an open-platform ultrasound imaging system (Vantage 64 LE, Verasonics, Kirkland, WA, USA) for receiving and processing the signals acquired by the photoacoustic probe. The laser beam from the laser source was reshaped by an iris, attenuated by a neutral density filter, collimated by two identical convex lenses, and finally focused by another convex lens into the fiber bundle. The proximal end (i.e., the optical input end) of the fiber bundle was terminated into an SMA connector so that it is easily coupled with a standard fiber coupler for high-efficiency laser energy coupling. The mirrors deflect the laser beam coming out of both legs of the fiber bundle at the distal end and converge onto the sample surface to generate the photoacoustic signals. The generated photoacoustic signals were detected by the photoacoustic probe (specifically, the ultrasound transducer) and then transferred to a 128-channel data acquisition board inside the ultrasound platform for further post-processing and image reconstruction. The universal back-projection algorithm was applied to reconstruct all the photoacoustic images [22]. The current photoacoustic imaging speed is 20 frames per second and is limited by the pulse repetition rate of the laser source. It should be noted that integrating the photoacoustic imaging system into the ultrasound platform does not affect the inherent ultrasound imaging capability of the system since they are independent of each other. Following the acquisition of the photoacoustic signals, the system transmits the acoustic waves into the sample and detects the reflected echoes to obtain the ultrasound image. Therefore, co-registering photoacoustic and ultrasound dual-modality imaging was possible with this system.
For both phantom and in vivo canine experiments in this study, 780 nm laser wavelength was selected for photoacoustic imaging. Multiple black strings with a cross-section of 200 μm were placed in the water medium under the probe, and a cross-sectional B-scan photoacoustic image was obtained. The spatial resolution and field of view of the transrectal photoacoustic probe were then analyzed. To mimic molecular imaging of prostate cancer, a spherically shaped phantom made of the mixture of indocyanine (ICG) and agar solution was embedded in an egg-shaped agar phantom. The ICG and agar mixture mimics the contrast-enhanced cancer tissue while the egg-shaped agar phantom simulates the prostate. The ICG concentration in the phantom is 1mg/mL, whose absorption coefficient should be higher than the contrast-enhanced cancer tissues in most studies given the challenge of cancer tissue labeling and the low uptake efficiency of the contrast agent by the cancer tissue. For ultrasound visualization of the phantom, 10 mg/mL oral ultrasonic contrast agent was added to the phantom at 1:10 ratio. For the in vivo study, a healthy canine model was selected and surgery was performed to open the prostate site for implanting black sutures into the prostate to mimic the tumor angiogenesis. Photoacoustic and ultrasound imaging of the canine prostate were performed by applying the probe through the rectal site two days after the surgery. The dog was anesthetized using 2% isoflurane gas (Euthanex Corp., Palmer, PA, USA) mixed with oxygen and remained fully anesthetized during surgery. During imaging experiment, dog was anesthetized again using the same process to acquire images. The laser energy on the rectal surface was 13 mJ, yielding a laser fluence of 12.4 mJ/cm², which is well below the ANSI safety limit [23]. All the animal handling were followed according to the protocol approved by the Animal Study Committee of Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences.

3. Results and discussions

The Monte Carlo simulation results of laser energy distribution in the scattering medium, mimicking the biological tissues, are shown in Fig. 4 for our probe design and the conventional design. The laser fluence distribution at different imaging depths, i.e., at different lateral cross-sections perpendicular to the probe axis, are shown in Fig. 4(a). The white rectangle in each image in Fig. 4(a) indicates the detection area of the ultrasound transducer at the corresponding depth. The quantitative comparison of the averaged laser fluence within the ultrasound detection region at various depths between our probe design and the conventional probe design, are shown in Fig. 4(b). The solid and dashed lines are the fitting curves of the quantification. The imaging depths within the purple box in Fig. 4(b) is zoomed out and is shown in Fig. 4(c). The laser fluence of our probe design is higher for all imaging depths compared to the conventional design, indicating a better imaging sensitivity.
for our probe. The laser energy in our design is more efficiently utilized to excite the photoacoustic signals for all imaging depths. In the conventional design, almost no laser energy distribution occurs at the shallower depths of the imaging sample, which may result in the loss of key information within this shallower region of the sample.

![Laser fluence comparison](image)

Fig. 4. The Monte Carlo simulation result of laser fluence in the imaging sample mimicking biological tissues for our probe design and the conventional design. (a) Laser fluence distribution at different imaging depths, i.e. at different lateral cross-sections perpendicular to the probe axis. The white rectangle in each image indicates the detection area of the ultrasound transducer at the corresponding depth. (b) Quantitative comparison of the averaged laser fluence within the ultrasound detection region at various depths between our probe design and the conventional design. (c) Zoomed-in view of the purple rectangle in (b).

The cross-sectional B-scan image of the black strings is shown in Fig. 5(a). The photoacoustic probe proposed in this study has a field of view (or view angle) larger than 145 degrees. The signal to noise ratios (SNR) of all the black strings in the image are between 21 dB and 41 dB. The quantified lateral and axial resolutions of the central black string (white box in Fig. 5(a)) are shown in Fig. 5(b) and 5(c), respectively. The lateral resolution is 1.29 mm, and the axial resolution is 0.42 mm. Both resolutions are close to the theoretical values (1.21 mm for lateral resolution and 0.35 mm for axial resolution). It should be noted that only 32 elements at the center of the ultrasound transducer were employed for calculating the theoretical lateral resolution due to the curvature of the transducer and limited view angle of each element.
Fig. 5. The results of black strings custom-designed phantom experiments. (a) The cross-sectional B-scan image of the black strings. The quantified lateral (b) and axial (c) resolutions of the central black string (white box) in (a).

The imaging results of the phantom mimicking the prostate cancer and labeled by the exogenous contrast agent are shown in Fig. 6. Figure 6(a) is the real photo of the phantom. The egg-shaped agar phantom simulating the prostate organ is visualized in the ultrasound image as shown in Fig. 6(b). However, the ICG and agar mixture mimicking the prostate cancer tissue cannot be easily seen in the ultrasound image. On the other hand, the photoacoustic image in Fig. 6(c) and the fused photoacoustic and ultrasound image in Fig. 6(d) clearly show the mimicked cancer tissue due to the laser energy absorption by the contrast agent (i.e., ICG) yielding the strong photoacoustic signal. This phantom result confirms that the prostate cancer can be well visualized in photoacoustic imaging after appropriate targeting and labeling by exogenous contrast agents. In practice, targeting and labeling can be achieved by intravenous injection of photoacoustic contrast agent before the photoacoustic imaging. The contrast agent is selectively accumulated in the tumor region due to either active targeting or the enhanced permeability and retention (EPR) effect of the tumor tissue.

Fig. 6. The imaging results for egg-shaped agar phantom simulating the contrast agent labeled prostate cancer. The real photo (a), an ultrasound image (b), photoacoustic image (c) and their merged image (d) of the phantom.

The feasibility of the transrectal photoacoustic probe for *in vivo* imaging application was demonstrated by imaging the prostate of a healthy canine model implanted with the suture to mimic tumor angiogenesis. Figures 7(a) and 7(b) are the real photos of the prostate before and after suture implantation, respectively. Figures 7(c)-7(e) each show the ultrasound image, photoacoustic image (counterpart of ultrasound), and their merged image of the *in vivo* prostate obtained after 2 days of surgery. The rectal wall and the profile of the prostate (yellow circle in Fig. 7(c)) can be clearly visualized in the ultrasound image. In the
photoacoustic image, strong photoacoustic signals were observed at the rectal site, which is mainly due to the bleeding from surgery that has not been fully absorbed by the tissue. This bleeding from surgery attenuated most of the laser energy, resulting in almost no photoacoustic signal observed in the prostate. However, due to the relatively higher absorbance in the black suture, they can still be visualized in the photoacoustic image. It is to be noted that the imaging time point is set to day 2 rather than longer time for bleeding to absorb, because suture degrade over time, which would weaken the photoacoustic signal of the suture. The SNR at the bleeding site of the rectal wall and the suture was calculated to be 41.3 dB and 35.2 dB respectively, without any frame averaging. Two black sutures out of three are seen in the photoacoustic image because not all sutures could be captured by the same imaging B-scan plane. As shown in the fused image, both sutures correlate well with their counterparts in the ultrasound image. In the ultrasound image, similar features to sutures were observed outside the prostate. These features are presumably due to other anatomical structures such as calcifications that have high acoustic impedance. Given that the ultrasound imaging can provide anatomical information of the prostate and the photoacoustic imaging can provide blood abnormality and exogenous contrast agent labeled information in the tumor tissues, the combination of photoacoustic imaging and ultrasound imaging would have high potential for early diagnosis of prostate cancer. Because of this hybrid capability of photoacoustic imaging, the imaging result would have higher specificity to distinguish tumor angiogenesis compared to the ultrasound imaging alone, such as BW-mode and Doppler ultrasound.

Fig. 7. The imaging results for a healthy dog implanted with a suture into the prostate to simulate tumor angiogenesis. The real photo of the prostate before (a) and after (b) suture implantation. The ultrasound image (c), photoacoustic image (d) and their merged image (e) of the canine prostate region.
4. Conclusions

A novel design for transrectal photoacoustic imaging probe was proposed and implemented in this study. Due to the optimized laser illumination and high utilization efficiency of the laser energy, our photoacoustic probe design possesses higher imaging sensitivity compared to the previous system. The Monte Carlo simulation of photon propagation in scattering medium showed superior laser energy delivery using our system compared to the previously reported probe designs. The performance of the probe was experimentally characterized by imaging the black strings in water. The potential of the probe for clinical prostate cancer imaging was demonstrated by imaging tumor mimicking phantom and in vivo canine imaging. High-quality images were obtained at large imaging depth with relatively low laser energy, which is well below the ANSI safety limit. The photoacoustic probe remains compact for in vivo application, and the compact size makes it user-friendly for clinical application.

The combination of photoacoustic imaging and ultrasound imaging, demonstrated in this study, will enhance the diagnostic accuracy and precise localization of prostate cancer. This will also benefit the guidance of needle biopsy, potentially reducing the unnecessary painful repeated biopsy and more importantly improving the biopsy accuracy. In addition to early cancer diagnosis, the probe also has the potential to be used for intraoperative navigation during cancer surgery. Further enhancement in imaging is possible because the laser energy used in this study is mainly limited by the maximum output of the laser source and the low coupling efficiency of the fiber bundle. By using a different laser source, the performance of the photoacoustic probe can be enhanced further by increasing the laser energy. Thus, the work presented here has a potential to be improved and enhanced further for routine clinical use in near future, e.g., targeted surgery to avoid unnecessary prostatectomies, the real-time guidance of ablation therapy, and postoperative treatment evaluation.

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Disclosures

The authors declare that there are no conflicts of interest related to this article.

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