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Towards multimodal detection of melanoma thickness based on Optical Coherence Tomography and Optoacoustics

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ABSTRACT

Melanoma skin cancer has one of the highest mortality rates of all types of cancer if not detected at an early stage. The survival rate is highly dependent on its penetration depth, which is commonly determined by histopathology. In this work, we aim at combining optical coherence tomography and optoacoustic as a non-invasive all-optical method to measure the penetration depth of melanoma. We present our recent achievements to setup a handheld multimodal device and also results from first *in vivo* measurements on healthy and cancerous skin tissue, which are compared to measurements obtained by ultrasound and histopathology.

Keywords: Skin cancer, Tumor depth, Multimodal imaging, Optical coherence tomography, Optoacoustics

1. INTRODUCTION

Melanoma skin cancer is one of the most dangerous types of cancer if not diagnosed at an early stage and treated by surgical excision. It also has one of the lowest incidence rates compared to all types of skin cancer and accounts for approximately three percent of new cancer indispositions but mortality rates are extraordinary high if diagnosed too late. The five year survival rate is highly dependent on the penetration depth of the tumor, which determines the probability for development of metastasis. Suspicious skin lesions are commonly diagnosed by visual inspection (dermoscopy) and excised for pathological analysis which is the gold standard when measuring the penetration depth of a melanoma. If a melanoma is diagnosed by pathology, an additional excision is often required including a safety margin of approximately 1-2 cm [1]. In addition, only less than 10 percent of suspect lesions are in fact cancerous and, therefore, biopsy most often leads to unnecessary excision of healthy skin. Thus, the development of alternative non-invasive methods for melanoma diagnosis and thickness measurement would significantly decrease the amount of surgical interventions.

Suitable alternative approaches are based on tomographic methods among which ultrasound (US) is the most present and established one [2,3]. However, these methods have to fulfill well defined requirements regarding resolution and also maximal measuring depth to be used for dermatological applications. Especially, due to the first aspect common ultrasound devices are operated at high frequencies in the 20 MHz region. To provide higher resolution as required for dermatology, there are also devices available working at 75 MHz or 100 MHz. Recent work also focuses on optical methods such as optical coherence tomography (OCT) and optoacoustics (OA) [4,5]. OCT is an interferometric technique, which relies on light sources with a short coherence length such as superluminescent diodes [4]. Due to the limited coherence of the source, only information within the coherence gate is acquired and, hence, depth discrimination is achieved. The typical volumetric resolution of OCT is in the range of $10 \times 10 \times 10$ μm^3 in air depending on the wavelength of the source and the imaging optics of the specific device. A suitable selection of the center wavelength of the OCT light source is an important prerequisite to achieve a maximal imaging depth in a medium. The latter is limited due to absorption and scattering and, in case of skin imaging, a center wavelength of approximately 1300 nm is often the most suitable choice yielding penetration depths of up to 1 mm. In pilot studies, OCT was proven to be a powerful diagnostic tool for basal cell carcinoma [5]. However, a very precise determination of the penetration depth of cancerous tissue in skin is highly mandatory to provide a reliable alternative to histopathology and often penetration depths larger than 1 mm are of interest to determine the stage of skin cancer. In particular, it is of interest whether the melanocytic lesion invades the dermis where the cancer cells can have access to the blood and lymphatic vessels to spread out. In addition, OCT images only refractive index changes and is not capable of obtaining knowledge of other useful skin properties such as absorption. This, in turn, can be achieved by using optoacoustics. The physical principle of OA is

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based on the absorption of light pulses inside a medium and the subsequent conversion of the absorbed energy into ultrasound waves. OA is not only a complement to OCT, it also yields higher penetration depth since only light propagation in the forward direction is relevant, as opposed to scattering based techniques such as OCT. In OA, volumetric resolutions of down to 20 x 20 x 20 μm^3 were achieved, which is slightly lower compared to OCT. Among other biomedical applications, OA was recently investigated for melanoma thickness measurements and results were compared to ultrasound images and histopathology [7]. The results in [7] showed reasonably good agreement between measured thickness using OA and histopathology. Due to the capability of OA to image absorption profiles in a medium, recent work focusses on the combination of OA and OCT [8] enabling an enhanced reliability due to the capability to image different skin features including the basal membrane but also pathogenic objects such as cancer cells.

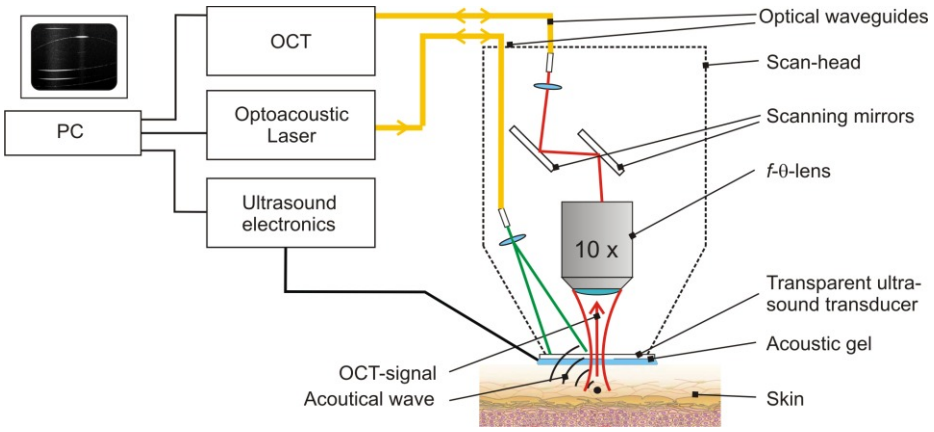

Figure 1.Schematics of the handheld multimodal imaging head and required periphery pursued in this work.

In this work, we aim at the development of an all-optical hand held device to determine the melanoma penetration depth in a non-contact mode. Our method utilizes a multimodal approach based on OCT and OA. We present our recent results on the combination of both modalities in a single hand held device and provide first *in vivo* OCT data obtained on healthy and cancerous skin lesions in a clinical environment, which are compared to measurement results obtained by ultrasound and histopathology. In a future clinical application, our multimodal device will help dermatologists to determine the penetration depth of melanoma, which will decrease the number of surgical interventions and the skin area and reduces unnecessarily excised lesions for safety reasons.

2. EXPERIMENTAL SETUP

A sketch of the handheld OCT and OA device to be developed in this work is shown in Fig. 1. The setup consists of an OCT part, which is based on a commercial swept source OCT (Telesto II, Thorlabs Inc.) with a center wavelength of 1310 nm. The fiber based light source is focused onto the specimen utilizing an *f*-θ-lens (LSM03, Thorlabs). Lateral scanning is achieved by guiding the OCT beam via two galvanic scanning mirrors (Cambridge Inc.). Light which is reflected by the specimen is collected by the same setup and processed by the commercial swept source spectrometer and electronics provided by the manufacturer. For combining OCT and OA, the measuring fields of both methods need to match precisely. To account for this requirement, we developed a transparent piezoelectric sound transducer made from polyvinylidene fluoride (PVDF) which is placed right on top of the specimen, as indicated in Fig. 1 [9]. The PVDF foil is transparent in the wavelength region around 1300 nm, which is the operating wavelength of our OCT system. Hence, the OCT can be used for volumetric measurements by directing the OCT laser beam through the foil to obtain a measurement volume beneath the ultrasound detector such that the OCT and OA measuring volumes coincide.

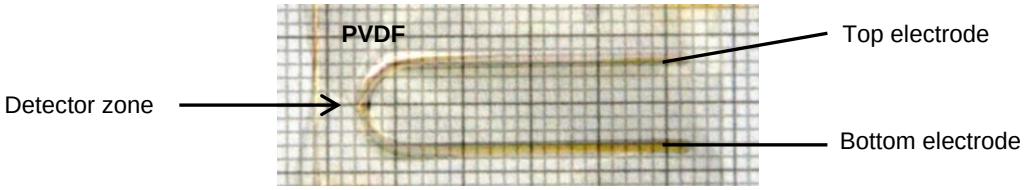

Figure 2.Image of the optoacoustic detector consisting of a PVDF foil and two transparent planar ITO electrodes.

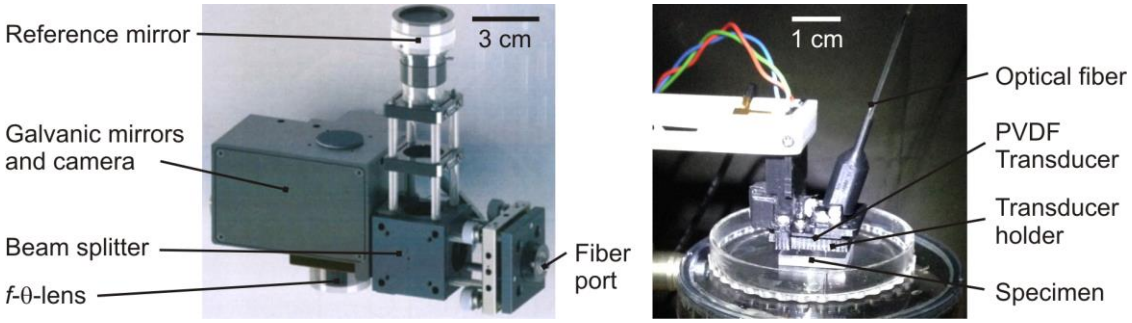

Figure 3. Images of the OCT setup (left) and the OA setup utilizing a single PVDF detector

Prior to combining OCT and OA, we developed two separate measuring devices for performance tests and enhancement. The OCT head shown in Fig. 3 (left) consists of a Michelson interferometer with a reference arm including an adjustable mirror and an object arm which consists of two integrated galvanic scanning mirrors and an additional camera. The *f*-θ-lens is mounted beneath the galvanic mirrors.

At the current stage, the OA setup consists of a single PVDF detector, which will be extended to a detector array and combined with the OCT setup in future work to enable photoacoustic tomography. The single detector setup is depicted in Fig. 3 (right), where the detector is illuminated by a pulsed solid state laser which runs at a wavelength of 532 nm, a pulse duration of 9 ns and a repetition rate of 10 Hz. For illumination purposes, the laser light is launched from a multimode fiber and collimated by a single lens. The PVDF detector foil is mounted on a polymeric holder with a circular recess to enable the laser pulse to reach the specimen, which is placed in contact with the detector. The PVDF detector foil was fabricated in cooperation with the Institut für Hochfrequenztechnik, Technische Universität Braunschweig, Germany. For fabrication, Indium Tin Oxide (ITO) was sputtered on both sides of a 10 µm thick piezoelectric PVDF film (Precision Acoustics) in the shape of a "J"s. ITO is electrically conducting and transparent for wavelengths longer than 400 nm. The area where the tips of the "J"s overlap forms the circular ultrasound detector while the other parts serve as electrodes as shown in Fig. 2. To improve the signal-to-noise ratio, a self-build electrical preamplifier with a flat amplitude response from 0 Hz to over 100 MHz is used. Due to the high frequencies involved we use a high-speed data acquisition card (Agilent U1065A) which is capable of acquiring up to 8 Giga samples per second.

3. EXPERIMENTAL METHOD AND RESULTS

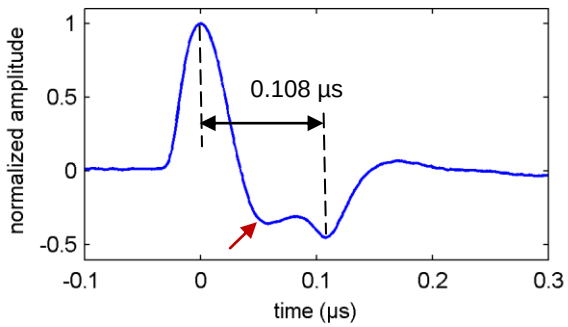

Figure 4.Detector signal of the optoacoustic setup obtained at a two layer phantom with a measured thickness of 119,78 µm; red arrow indicates an additional feature due to interference of sound waves.

3.1 Optoacoustics

To demonstrate the functionality of the OA setup, we performed measurements on a stripe of black insulation tape (BT) made from polyvinyl chloride (PVC) attached to a polystyrene petri dish. A layer of polyvinyl alcohol hydrogel (PVA) is used for acoustic coupling of the detector and the BT. An excerpt of the measured ultrasound signal is shown in Fig. 4.

Disregarding the first peak at 0 µs in the sound signal, we observed two additional features. The first feature (indicated by the red arrow in Fig. 4) is due to soundwave diffraction whereas the later feature corresponds to the thickness of the BT. Acoustic waves being reflected by a soft boundary, from high to low impedance (such as the BT-dish boundary), change the sign of the acoustic signal, which yields a negative pressure wave in this case. Using the maximum at 0 µs and the second feature (minimum) as characteristic points (see dashed vertical lines in Fig. 4) one can determine the time for the pressure wave to cross the BT twice. By multiplying the transit time with the speed of sound of PVC one obtains the thickness of the BT: 0.108 µs/2 *x* 2218 m/s[ndt] = 119,78 µm. Caliper measurements on a stack of 10 BT gave a thickness of 121 µm per sheet.

3.2 OCT, ultrasound and histopathology

For a first study on melanoma thickness assessment using OCT, we conducted a series of OCT and comparative US (DUB 100-12Bit, taberna pro medicum GmbH, Germany) measurements on ten suspicious skin lesions identified by dermoscopy on five female and three male volunteer patients. The clinical measurements were carried out at the Clinic for Dermatology, Venereology, and Allergology at the University Medical Center Göttingen. Each skin lesion was imaged by OCT and US, excised by medical doctors subsequent to the measurements and analyzed by histopathology.

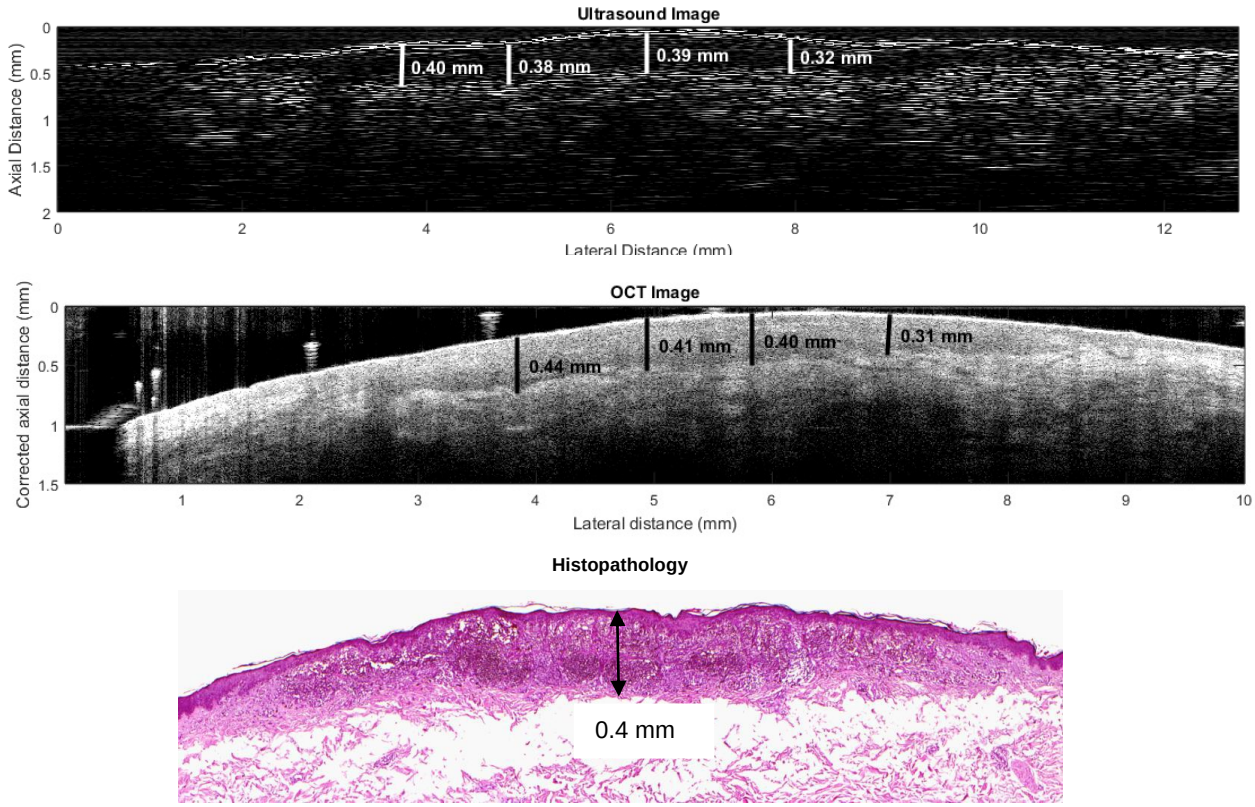

Figure 5. Preliminary results of clinical melanoma thickness measurement: ultrasound (top) and OCT measurements (middle) as well as histopathology data (bottom) taken at the same region of a cancerous mole.

One of the excised skin lesions was found to be cancerous at an early stage. Images of B-scans obtained from US and OCT measurements as well as microscope images of thin sections taken from histopathology are shown in Fig. 4. Each image was taken at approximately the same cross-section of the skin lesion. The tumor thickness at the current project stage was determined manually by visual inspection of the OCT and US B-scans as well as on the histopathological thin sections. Prior to the thickness measurements using the OCT images, we performed a distortion correction to the OCT images to account for unwanted scaling due to the refractive index of skin [10,11], which was assumed to be $n = 1.36$.

The results of the thickness measurements are also shown in Fig. 4. We found the largest tumor thickness to be 0.4 mm, 0.44 mm and 0.4 mm in US, OCT and histopathological measurements, respectively. The deepest melanocytic nest,

which was identified in the histopathological thin section, had a depth of 0.6 mm. We found that the identified tumor depth is approximately the same in US and OCT images compared to the gold standard histopathology. While OCT yielded a slightly larger maximum tumor thickness, this deviation may be due to an unwanted variation of the measuring field when comparing all three modalities. Also, the fixation of the skin sample required for histopathology may reduce the thickness and, thus, lead to smaller thickness values compared to the case for the *in vivo* measurements. To yield more reliable results on the comparison between the different methods, we will carry out a more thorough measurement campaign including more patients and malignant melanomas at different cancer stages.

4. CONCLUSIONS

We presented our recent results on combining optical coherence tomography (OCT) and optoacoustics (OA) into a single handheld measuring device for skin cancer tumor thickness assessment. To operate OCT and OA in a single device, we designed and fabricated a transparent ultrasound foil transducer made from polyvinylidene fluoride (PVDF). Due to the transparency of the foil, it can be placed in contact to the skin lesion to be examined and provides the capability to operate OCT directly through the foil such that OCT and OA share the same measuring volume. The OCT is based on a commercial swept source OCT operated at a wavelength of 1310 nm. At the current stage, the OA setup consists of a single transducer, which will be extended to a detector array in future work to enable for photoacoustic tomography (PAT). Acoustical waves inside the specimen are excited by laser pulses with pulse durations of 9 ns and a wavelength of 532 nm and are detected by the transducer. To demonstrate the functionality of our approach, we presented first results on phantom measurements, which are made from black insolation tape. We were able to measure the correct tape thickness from the transducer signal. In addition to the OA measurements, we conducted a first clinical study on melanoma thickness assessment using OCT. The results were compared to ultrasound measurements and results obtained from histopathological thin sections. We found that all three methods yielded the same maximum melanoma thickness with a maximum deviation of 40 µm. In future work, we expect to establish a reliable correlation between melanoma thickness measurements from histopathology, which is the clinical gold standard, and measured thicknesses utilizing the combined OCT and OA setup. We expect, that our results open new ways for non-invasive alternatives to histopathology, which will reduce the amount of excisions and unnecessarily removed skin lesion drastically.

5. ACKNOWLEDGEMENTS

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