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Concurrent *in vivo* tumor ablation and real-time optoacoustic monitoring with a pulsed 1064 nm laser source

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ABSTRACT

Laser ablation (LA) is gaining acceptance for the treatment of tumors as a viable alternative to surgical resection. In parallel, optoacoustic tomography (OAT) has enabled defining new regimes for diagnosis and characterization of malignant neoplastic lesions with high sensitivity and specificity. Even though pulsed nanosecond lasers are commonly used for both imaging and therapeutic purposes, real-time thermal treatment monitoring with a single laser source has not been previously attempted. Herein, we demonstrate the feasibility of combined OAT and LA by percutaneous irradiation of subcutaneous tumors with a 100 mJ short-pulsed (~5 ns) laser operating at 1064 nm and 100 Hz pulse repetition frequency. The OAT images rendered with a spherical ultrasound transducer array enabled real-time monitoring of the LA lesion progression, which is essential for determining the optimal treatment end-point. Local changes in the optoacoustic signal intensity associated with the induced temperature changes as well as structural alterations in the tumor vasculature could clearly be observed. The optoacoustic volumetric projections further correlated with cross-sections extracted from the excised tumors. This newly enabled capability anticipates new theranostic approaches in cancer research and treatment with potential applicability in a clinical setting.

Keywords: Optoacoustic Imaging, Laser Ablation, Real-time Monitoring, Temperature Mapping.

1. INTRODUCTION

Ablation is gaining acceptance for the treatment of tumors as an alternative to traditional surgical interventions, providing important advantages such as low invasiveness and fast recovery times [1]. Ablation can also represent a viable option for patients not candidates for surgery. Tumor ablation can be performed with laser beams. Lasers are also essential in imaging technologies commonly used for cancer diagnosis and staging due to unique molecular imaging capabilities stemming from specific interactions of light with biological tissues. By combining light excitation and ultrasound detection, optoacoustic (OA) imaging has enabled defining new angiogenetic and other bio-markers of cancer that can greatly impact the diagnosis and characterization of malignant neoplastic lesions [2-4]. Additionally, OA signals are highly sensitive to temperature changes - ~2.7% amplitude variation per °C - and to tissue changes occurring during coagulation [5,6]. These unique properties have been shown to provide unprecedented capabilities for real-time monitoring of tissue heating and ablation [7-12]. Particularly, monitoring of laser heating, coagulation and tissue cutting has been achieved with ultrasound waves generated with light [13,14].

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However, despite the fact that lasers can be used for both OAT monitoring and ablation, the combination of both approaches is hampered by the need of different laser types and energy levels corresponding to different types of laser-tissue interactions [15]. Laser ablation (LA) is generally performed with continuous wave (CW) lasers with sufficient average power to cause a temperature rise beyond the coagulation threshold (~50-60°C depending on the exposure time) [15]. On the other hand, OAT is generally based on non-invasive short-pulsed (nanosecond-duration) lasers with pulse energies and average power below safety standards, which typically cause a temperature rise of a few mK per pulse [16].

Herein, we show that combined OAT and LA can be performed by percutaneous irradiation of subcutaneous tumors with a 100 mJ short-pulsed (~5 ns) laser operating at 1064 nm and 100 Hz pulse repetition frequency (PRF) [17]. The OAT images rendered with a spherical matrix array transducer enabled real-time monitoring of the LA procedure, which is essential to determine the optimal end-point of treatment.

2. METHODS

2.1 Laser ablation and optoacoustic monitoring system

A lay-out of the experimental system used for LA and OAT monitoring is shown in Fig. 1. A subcutaneous tumor was irradiated with a short-pulsed laser (Innolas, GmbH, Krailling, Germany) with wavelength 1064 nm and PRF 100 Hz, providing per-pulse energies of ~100 mJ (10W). The laser beam was guided with a mirror (PF10-03-P01P, Thorlabs, Newton, NJ, USA) and expanded with a diverging lens (LC1715-C, Thorlabs, Newton, NJ, USA) to cover the entire tumor. OAT imaging was performed with a custom-made spherical matrix array transducer placed on the opposite side of the mouse (trans-illumination mode). OA signals were generated with the same laser source used for ablation. The ultrasound array (Imasonic SaS, France) consists of 512 circular elements with ~2.5 mm diameter, has a radius of 40 mm and angular coverage of 140° (1.3π solid angle) [18]. The elements provide >80% detection bandwidth around a center frequency of 5 MHz, corresponding to an almost isotropic resolution of ~150-250 μm within a field of view (FOV) of approximately 10x10x10 mm^3. OA signals were digitized by a parallel data acquisition unit (DAQ, Falkenstein Mikrosysteme GmbH, Germany) operating at 40 megasamples per second and transferred via Ethernet to a personal computer (PC, Intel xeon E5-1630 3.7 GHz processor, 16 GB RAM, 64 bit Windows-10 operating system). Two thermocouples were inserted into the tumor and the peripheral tissue to monitor the temperature during the LA procedure. The thermocouple readings were digitized by a NI 9213 DAQ (National Instruments Corporation, Austin, Texas, U.S.) at 100 Hz and were transferred to the PC.

2.2 Signal and image processing

OAT reconstruction was performed with a graphics processing unit (GPU) implementation of a back-projection formula [19]. Prior to reconstruction, the signals were band-pass filtered using a second order Butterworth filter at cut-off frequencies 0.5 and 7 MHz and deconvolved with the impulse response of the detection elements. Reconstruction was performed in a region of 20x20x20 mm^3 with 100 μm voxel size (200x200x200 voxels). The reconstructed images were normalized to the maximum of the entire sequence for each experiment. The maximum intensity projections (MIPs) of the three-dimensional images were used for visualization. The region of interest was manually segmented in the MIPs, which were subsequently smoothed temporally and spatially.

2.3 *In vivo* mouse experiments

Athymic nude Foxn1 mice (Envigo, Huntingdon, UK) featuring a subcutaneous breast tumor each were used in the experiments. Tumors were induced via injection of 3 million 4T1 breast cancer cells on the mammary fat pad close to the

mammillary glands near the hind paw. The LA and OAT monitoring experiments were performed 12 days after inoculation, when the tumor diameter was ~1 cm. Buprenorphine (0.1 mg/kg) was subcutaneously administered 30 minutes prior to the LA. LA was stopped when the temperature of the thermocouple inserted in the peripheral tissue reached 45ºC. The mice were maintained under isoflurane anesthesia (1.2%–2.0% in oxygen) during the LA procedure. They were euthanized immediately after the laser was stopped. All *in vivo* animal experiments were performed in full compliance with the institutional guidelines of the Helmholtz Center Munich and with approval by the Government District of Upper Bavaria.

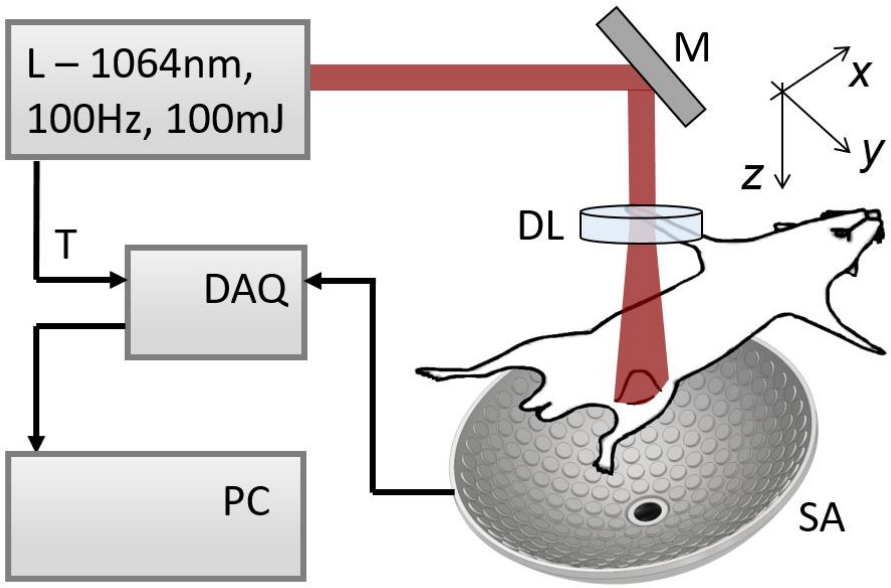

Figure 1. Lay-out of the experimental system used for laser ablation (LA) and optoacoustic tomography (OAT) monitoring. L – laser, DAQ – data acquisition system, PC – personal computer, M – mirror, DL – diverging lens, SA – spherical array.

3. RESULTS

The effects of LA can be visualized in the OAT images taken during laser irradiation. The lateral maximum intensity projections (MIPs) of these images for three different mice and five different time points after the beginning of the ablation procedure are shown in Fig. 2. Vascular structures in the tumor are visible in the OAT images taken shortly after starting the laser. Some of these structures, indicated with yellow arrows in Fig. 2, disappear from the image after some time. This arguably corresponds to blood removal and vascular disintegration. A similar effect was observed in OAT monitoring of endovenous laser therapy [14]. The contrast in some tumor areas, labelled with white arrows in Fig. 2, is also clearly enhanced. This is ascribed to a high degree of coagulation as a consequence of heating beyond 60°C [15]. Indeed, the temperature measured with the thermocouples inserted within the tumor core increased to around 85°C over 5 minutes. Overall, the OAT signal intensity increases throughout the tumor volume as a consequence of a combined effect of temperature rise and coagulation.

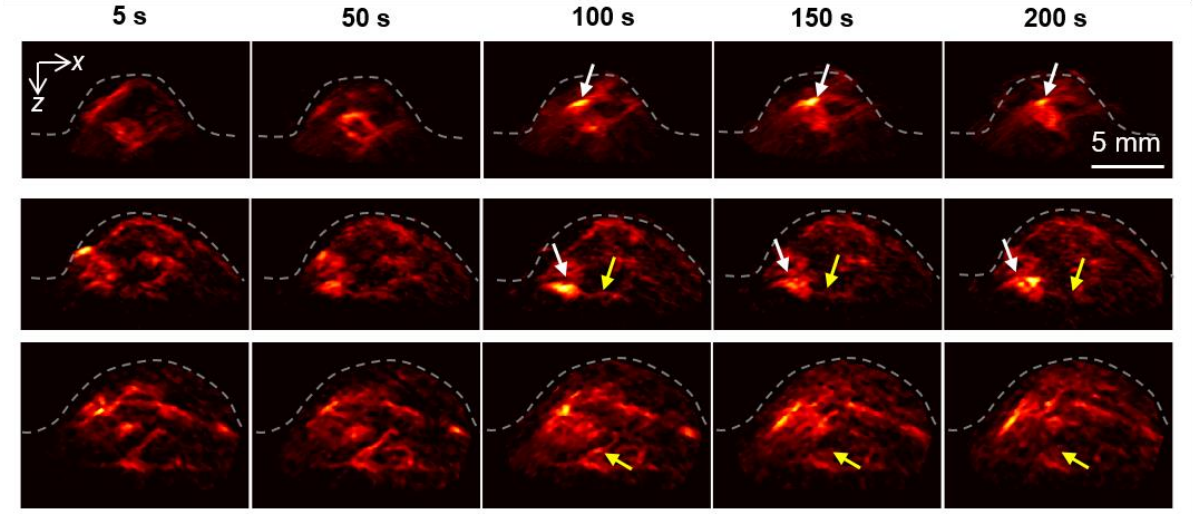

Figure 2. Maximum intensity projections (MIPs) along the lateral direction of the three-dimensional optoacoustic tomography (OAT) images of the tumors acquired at different time points after the beginning of the laser ablation (LA) procedure for three different mice. Coagulated regions are indicated with white arrows and disintegration of vascular structures is indicated with yellow arrows.

4. CONCLUSIONS

The feasibility to perform LA and OAT monitoring of lesion progression with a single short-pulsed 1064 nm laser was demonstrated in a murine breast tumor model *in vivo* by properly selecting the energy per pulse and laser pulse repetition frequency. The free beam was used to percutaneously irradiate the tumor, where the tumor microvasculature was imaged by placing the transducer array on the opposite side of the mouse (trans-illumination mode). Volumetric monitoring of the whole tumor volume during ablation was successfully demonstrated by analyzing the recorded sequence of OA images. Specifically, localized signal increases associated to tissue heating and coagulation as well as disruption of vascular structures was observed. This may facilitate determining an optimal control of laser energy deposition, thus improving the outcome of LA procedures. Simultaneous LA and OAT monitoring opens new theranostic capabilities in cancer research and further facilitates clinical translation due to the deep penetration of light into biological tissues for 1064 nm.

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