Photoacoustics 3 (2015) 100–106

Contents lists available at ScienceDirect

Photoacoustics

journal homepage: www.elsevier.com/locate/pacs

Research article

Real-time Near-infrared Virtual Intraoperative Surgical Photoacoustic Microscopy

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ARTICLE INFO

Article history:
Received 11 May 2015
Received in revised form 16 July 2015
Accepted 7 August 2015
Available online 12 August 2015

ABSTRACT

We developed a near infrared (NIR) virtual intraoperative surgical photoacoustic microscopy (NIR-VISPAM) system that combines a conventional surgical microscope and an NIR light photoacoustic microscopy (PAM) system. NIR-VISPAM can simultaneously visualize PA B-scan images at a maximum display rate of 45 Hz and display enlarged microscopic images on a surgeon's view plane through the ocular lenses of the surgical microscope as augmented reality. The use of the invisible NIR light eliminated the disturbance to the surgeon's vision caused by the visible PAM excitation laser in a previous report. Further, the maximum permissible laser pulse energy at this wavelength is approximately 5 times more than that at the visible spectral range. The use of a needle-type ultrasound transducer without any water bath for acoustic coupling can enhance convenience in an intraoperative environment. We successfully guided needle and injected carbon particles in biological tissues *ex vivo* and in melanoma-bearing mice *in vivo*.

1. Introduction

During microsurgeries, visualization of sub-surface information is crucial to improve the accuracy of incisions and suturing, and to prevent unintentional accidents such as copious bleeding and tissue damage. Thus, since the early 20th century, intraoperative surgical microscopes have been regarded as essential devices for microsurgeries in ophthalmology, orthopedic surgery, neurosurgery, plastic surgery, and so forth [1–3]. Although the use of an optical microscope increases the surgical accuracy and efficacy during the microsurgery, it only provides magnified surface images within the region of interest; it cannot provide sub-surface information. To overcome this limitation, intraoperative imaging methods such as X-ray imaging, computed tomography (CT), ultrasound (US) imaging, and magnetic resonance imaging (MRI) have been adapted for use in surgical environments before, during, and after surgery [4–7]. However, these intraoperative imaging methods cannot maximize the surgical capabilities due to either ionizing radiation, low spatial resolution, low sensitivity, inconvenience, bulkiness or slow image acquisition.

Photoacoustic microscopy (PAM) is an emerging medical imaging modality based on optical excitation and US detection via light induced thermoelastic expansion [8,9]. PAM is capable of supplying sub-surface anatomical as well as functional, metabolic, molecular, and genetic information in real time [10]. Thus, this imaging method has been used in both clinical and preclinical research in several medical fields [11–21].

A virtual intraoperative surgical photoacoustic microscope (VISPAM) has been developed and used to guide needle insertion into live animals [22], but this system has several disadvantages. It uses a green (i.e., wavelength $\lambda = 532$ nm) laser beam as a PA excitation source, and this visible light significantly disturbed the surgeons' vision during *in vivo* experiments. Further, the VISPAM B-scan image was displayed at 2 Hz, which was not fast enough for real-time imaging. In addition, VISPAM entails use of a water bath for acoustic coupling, and this device limits the maximum capability of the system in surgical conditions.

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http://dx.doi.org/10.1016/j.pacs.2015.08.002

In this article, we describe a real-time near-infrared virtual intraoperative surgical photoacoustic microscopy (NIR-VISPAM) system that combines commercial surgical microscopy and PAM with an invisible NIR laser source (i.e., λ = 1064 nm). By sharing the same optical path, the NIR-PAM system was easily adapted to the conventional optical microscope; the NIR laser light is invisible, so it did not annoy the operators during surgery. Other benefits include a deeper penetration of NIR light than green light into tissue, and a higher laser safety limit (i.e., 100 mJ/cm^2 at λ = 1064 nm vs. 20 mJ/cm^2 at λ = 532 nm). Further, the conventional microscopic and PA B-scan images were displayed concurrently on the microscopic view plane using augmented reality. The PA B-scan image display rate reached maximally up to 45 Hz, so the real-time imaging capability was achieved. Moreover, a custom-made needle US transducer eliminates the need to use a water bath, which is closer to real clinical practice. The axial and lateral resolutions were 61 ± 1.4 and 36 ± 0.9 μm, respectively. We used the system to guide needle insertion and to monitor injection of carbon particles into chicken tissue *ex vivo* and into melanoma-bearing mice *in vivo*.

2. Material and methods

The NIR-VISPAM system (Fig. 1a, b) consisted of an NIR pulsed laser source (Teem photonics, SNP-20F-100) as a main PA excitation source; a per-pulsed laser energy of 4 μJ, a repetition rate of 20 kHz, a pulse width of 0.7 ns, and λ = 1064 nm. Initially, 10% of the laser light was deflected by a beam splitter (Thorlabs, CM1-BP108) and directed into a photodetector (Thorlabs, PDA36A-EC) to trigger a galvo-scanning mirror and a data acquisition (DAQ) system. The remaining 90% of the light was delivered to the NIR-VISPAM system. Then the NIR-VISPAM system was implemented by modifying a commercial surgical microscope (Carl Zeiss, OPMI). The NIR-VISPAM system consisted of three main divisions: (i) a customized PAM scanning [D1], (ii) a beam-projecting [D2], and (iii) a beam-splitting [D3].

The PAM scanning [D1], used three devices: (1) a two-dimensional galvanometer (Thorlabs, GVS002) to scan the laser beam in the X-Y plane; (2) an objective lens (Thorlabs, AC254-075-B; diameter: 25.4 mm, focal length: 75 mm, NA: 0.17); and (3) a dichromatic mirror (Edmund optics, NT55-233) to reflect the NIR PA excitation light to the sample and to transmit the native visible light from the sample surface to the surgical microscope. Pulsed NIR irradiation stimulated emission of PA waves, which were detected by a homemade needle-type transducer with a length of 48.5 mm, a diameter of 1 mm, and a central frequency of 41 MHz (University of Southern California). Instead of a water tray, the needle transducer was directly coupled to the targets by ultrasound gel. The acquired PA signals were amplified by two successive amplifiers (Mini-Circuits, ZFL-500LN +), then digitized by the DAQ board (NI instrument, PCI-5124). One-dimensional optical scanning along the X-axis acquired data for one depth-resolved PA B-mode image. The typical pixel numbers along X and Z axes in one PA B-mode image were 200 and 1800, respectively. The Hilbert transform was applied along each PA A-line. The maximum image display rate of one reconstructed PA B-mode image was 45 Hz. To increase the signal to noise ratio (SNR), two and three PA B-mode images were averaged for *in vitro* and *in vivo* experiments, respectively.

Beam projection [D2] used a beam projector (Optoma, PR320) with a size of 15 cm × 14 cm × 7 cm (X, Y, and Z axes, respectively) and two mirrors. Beam splitting [D3] used a customized beam splitter inside the surgical microscope system. The main functions of divisions [D2] and [D3] are to back-project the acquired PA B-mode image onto the surgical microscopic view plane through the ocular lens.

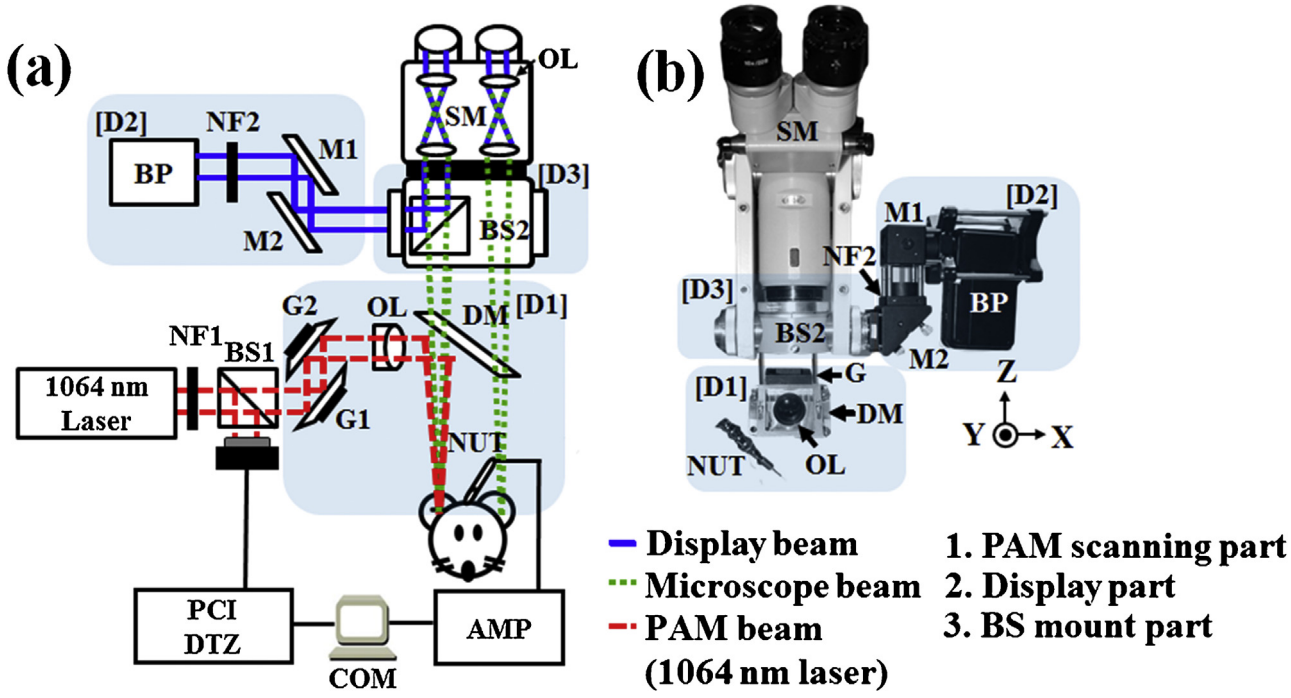

Fig. 1. (a) Schematic of the near-infrared virtual intraoperative surgical photoacoustic microscopy (NIR-VISPAM) system. (b) Photograph of the NIR-VISPAM system. COM, computer; PD, photodiode; BS, beam splitter; NF, neutral density filter; AMP, amplifier; BP, beam projector; M, mirror; G, galvo-scanner; OL, object lens; NUT, needle type ultrasonic transducer; and PCI DTZ, PCI digitizer.