Mansoura Engineering Journal

Volume 47 | Issue 2 Article 4

4-26-2022

Photoacoustic Imaging in Medicine – A Review

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Faculty of Engineering
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KEYWORDS:
Photoacoustic Imaging (PAI), Photoacoustic Tomography (PAT), Multispectral Optoacoustic Tomography (MSOT), Photoacoustic Microscopy (PAM), Raster-Scan Optoacoustic Mesoscopy (RSOM), Photoacoustic Elastography (PAE), Imaging-Guided Surgery (IGS), Non-Contact Laser Ultrasound (LUS).

***Abstract* — This photoacoustic imaging (PAI) in medicine paper started with an introduction to PAI and the famous photoacoustic techniques including photoacoustic tomography (PAT), multispectral optoacoustic tomography (MSOT), photoacoustic microscopy (PAM), raster-scan optoacoustic mesoscopy (RSOM), and photoacoustic elastography (PAE). A modest review about non-contact laser ultrasound (LUS), having the advantage of operator-independent image quality, has been also demonstrated. A concise review of most of PAI's medical applications is demonstrated including cancer screening (for breast, thyroid, ovarian, prostate, lung, and skin), tissue oxygenation measurements, brain imaging, imaging-guided surgery (IGS), and the guidance of high intensity focused ultrasound (HIFU). Some safety considerations contributed with medical ultrasound and lasers have been then presented. In conclusion, more scientific and clinical development in the field of PAI is expected, and an increase in approved devices that utilize PAI's techniques in medical applications is also expected to serve wide sectors of medicine, whether diagnostic or therapeutic.**

I. INTRODUCTION

PHOTOACOUSTIC imaging (PAI), or optoacoustic imaging, is a biomedical hybrid imaging modality based on the use of laser-generated ultrasound due to the photoacoustic effect [1-2]. The photoacoustic effect as a physical phenomenon was reported in 1880 by A. G. Bell [3-6]. The reason is the energy exchange process which transforms the absorbed light energy into kinetic energy, which in role results in a temperature rise thus a pressure wave or sound [6]. Measuring the sound at different wavelengths produced the origin of the photoacoustic spectroscopy (PAS); also, called optoacoustic spectroscopy (OAS). PAS can be applied to gases, liquids, and solids [6-8]. PAS directly measures the absorbed power of light, which in role serves as a highly sensitive technique with no scattering losses [9]. Photoacoustics' uses have been emerged first in the field of gas spectroscopy and later in biomedical applications [10]. In the last two decades; PAI has rapidly gained wide popularity in more biomedical applications [1]. PAI technique can be roughly expressed as "light in and sound out", merges high-contrast of optical imaging with high spatial resolution and penetration depth of ultrasonography [11-12]. An illustration of the basic principle of PAI is presented in Fig. 1. In PAI: tissue components having different absorption characteristics can be separated spectrally [13]. PAI is sensitive

Received: (28 November, 2021) - Revised: (20 February, 2022) - Accepted: (05 March, 2022)

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(Ser. NO. BFEMU-2111-1199)

for chromophore mapping, whereas these chromophores can be moreover separated into two categories: the 1st like hemoglobin, melanin, and cytochromes, absorbs ultraviolet-visible light by electronic transitions, while the 2nd like lipids and water, absorbs light ranges from near-infrared to mid-infrared by vibrational transitions [14]. In contrast to conventional ultrasonography, PAI has the potential to produce speckle-free images [3]. Functional information can be provided also by PAI as blood flow, temperature, and oxygenation [2]. Recently, a photoacoustic (PA) topography through an ergodic relay (PATER) system, has been introduced to achieve a wide field of view (FOV), snapshot, and high frame rate in a low-cost system [15-17]. At very deep regions, where PAI cannot achieve adequate resolution, the PA probe should be positioned close to the area of interest by the aid of endoscopy [18]. PA endoscopy is aiming to outdo the resolution limitations of endoscopic ultrasound (EUS) which is a clinically available tomographic tool utilized for diagnosing more diseases [19]. From a market point of view, it is forecasted that the PAI market will increase in 2022 [20].

In this review paper the utilized strategy for achieving it was performing a literature search through the Internet, selecting 189 references to build our review, and contacting with two authors of two different references [71, 111] for giving us permission to process and publish their figures' data.

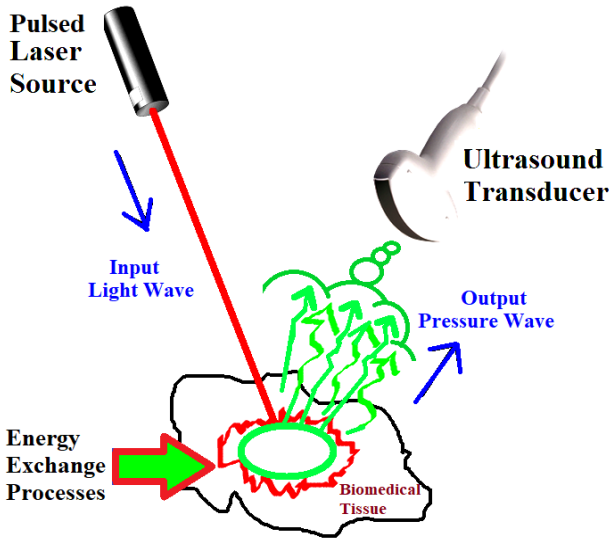

Fig. 1. Illustration of PAI's basic principle.

In the following section II: we will talk about the most famous PA techniques including A. PAT, A.1. MSOT, B. PAM, and C. PAE. In section III, we talk about the recent development of non-contact laser ultrasound (LUS) medical imaging. In section IV, a brief introduction to PAI's applications in medicine mentioned in the following five sections (sections V, VI, VII, VIII, and IX) is presented. In the following section V, most of PAI's applications in cancer screening are presented including A. breast, B. thyroid, C. ovarian, D. prostate, E. lung, and F. skin cancer. Sections VI, VII, VIII, and IX; present in some detail the applications of PAI into tissue oxygenation measurements, brain imaging, Imaging-Guided Surgery (IGS), and PAI's guidance of High Intensity Focused Ultrasound (HIFU), respectively. In section X we will talk about safety considerations for both laser and ultrasound. Finally, in section XI, we concluded that PAI is a promising biomedical imaging tool in more applications in medicine.

II. Most Famous Photoacoustic Strategies

PAI has more techniques to be implemented. Here, we divided PAI's techniques into five main categories: PAT, PAM, PA endoscopy, PATER, and PAE. A concise chart for the PAI's main techniques mentioned in this paper is illustrated in Fig. 2. Where; OD: optical detection, OR: optical resolution, AR: acoustic resolution, MS: multispectral, fcPAT: functional connectivity PAT, LD: light-emitting diode (LED). In the following sub-sections, we will talk in some detail about A. PAT, B. PAM, and C. PAE. PA endoscopy (the third main category) is a very prospective field in PAI, providing molecular contrast at large depths, allowing for simultaneous visualization of structural and functional information [21]. PA endoscopy presents the same strength in spatial resolution of routinely used clinical EUS, whereas introducing more functional information at physiological sites [22]. For more about PA endoscopy, we refer the reader to [18, 19, 21, 23-28]. PATER (the fourth main category) could be considered a combination of computed PAT theory and PAM, trying to achieve a wide-field image with only a single-element ultrasonic detector upon a single laser shot [15-17]. For more about the PATER technique, we refer the reader to [15-17].

A. PAT

PAT technique can be briefly described in four steps [29, 30]:

1. Illumination of the tissue by a pulsed broad laser beam.
2. A small but rapid temperature rise will be generated.
3. The emitted short-wavelength pulsed ultrasonic waves due to thermoelastic expansion will be then detected by unfocused ultrasonic transducers.
4. Image reconstruction process produces tomographic images of optical contrast and high resolution.

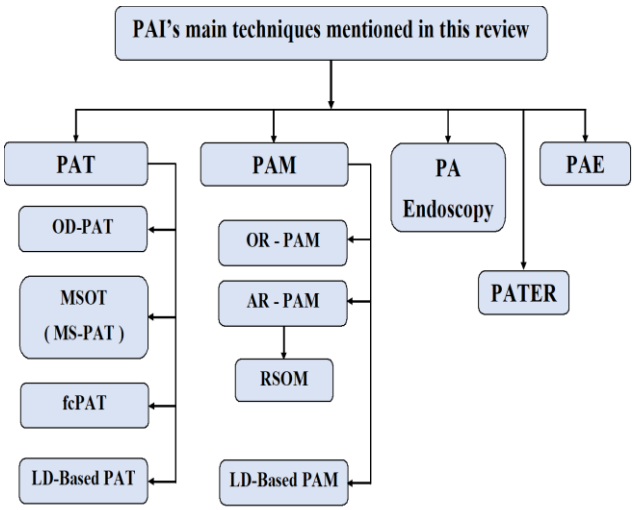

Fig. 2. A concise chart for the PAI's main techniques mentioned in this review.

PAT can image nearly all molecules, fluorescent or not because it doesn't rely on fluorescence emission [31, 32]. PAT is speckle-free unlike ultrasound imaging and optical coherence tomography (OCT) [33]. PAT has the potential to produce fluid-dynamic, functional, molecular, and anatomical imaging, playing an efficient role in biomedical research [34]. PAT has introduced a super-depth combined with high-resolution optical imaging exceeding the optical transport mean free path which is the depth limitation of OCT, confocal microscopy, and two-photon microscopy (~ 1 mm in the skin) [35]. Anatomical and vascular structures imaging can be provided by endogenous hemoglobin contrast. Molecular, functional, and reporter gene imaging can be provided by using exogenous optical contrast [29, 30, 36]. A contrast agent called black mesoporous silicon (BPSi), has been introduced, by Wujun Xu et al [37], for the light-emitting diode (LED) based three-dimensional (3D) PAT, resulting in strong contrast. A United States patent application by James B. Pitner et al [38], has been introduced for Hydroporphyrins as contrast agents for PAI. Another advance to PAT was published by M. Nasiriavanaki et al [39]: developing a functional connectivity photoacoustic tomography (fcPAT) system, allowing non-invasive imaging of the resting-state functional connectivity (RSFC) in a mouse brain, with a large FOV as well as high spatial resolution. RSFC was alerted in many brain disorders [39]. A different technique of PAT is the optical-detection photoacoustic tomography (OD-PAT) in which optical approaches have been used to detect the photoacoustic signals instead of piezoelectric detection in classical ultrasound probes [22].

A.1. MSOT

MSOT, a Multispectral PAT (MS-PAT) technique, has been able to introduce a generation of biomedical imaging. A particular advantage of MSOT is its ability to scale with different tissue sizes [40]. MSOT has been succeeded to visualize fluorochromes in tissues that are not visible with conventional single wavelengths' PAI [41]. A fast acquisition MSOT whole-body scanner has been introduced by Rui Ma et al to visualize small animals' molecular markers with multi-wavelength illumination [42]. Razansky et al [43], have introduced their protocol of volumetric real-time MSOT of biomarkers; assuring MSOT's ability in visualizing tissue biomarkers and optical contrast with speed and resolution representative of ultrasound. A fast MSOT platform for dynamic imaging of pharmacokinetics and bio-distribution in multiple organs has been demonstrated by Adrian Taruttis et al [44]; introducing fast and high-resolution in vivo imaging's capabilities. Semi-quantitative MSOT for volumetric Pharmacokinetic (PK) imaging of gastric emptying had been demonstrated by S. Morscher et al; using MSOT in monitoring gastrointestinal motility in mice given indocyanine green (ICG) by oral gavage aiming fate of ICG be monitored in the gastrointestinal tract [45]. Not only ICG, but MSOT also visualize a range of exogenous contrast agents e.g., methylene blue (MB) [46]. The performance of an MSOT system equipped with 2D vs. 3D handheld probes has been demonstrated by Neuschmelting et al [47], for potential clinical translation. First in vivo clinical use of MSOT non-invasively has been introduced by S. Y. Chuah et al [48], for Structural and functional 3D mapping of skin tumors, confirming the benefit of that imaging method for surgical intervention guidance. Over the last few years, MSOT has succeeded in more than one application in medicine such as imaging of breast cancer [49], particle size-dependent intratumoral distribution of polymeric micelles [50], thyroid disorders [51], drug-induced liver injury (DILI) [52], neural dynamics and organization of the intact mouse brain [53], and orally-administered particles within the gastrointestinal tract of murine models [54]. MSOT has the potential to achieve real-time tracking in vivo of magnetic nanoparticles quantitatively [55]. A co-registration of MSOT and magnetic resonance imaging (MRI) data from murine tumor models, has been introduced by M. Gehrung et al [56], assuring feasibility of hardware and software-based registration framework for MRI and MSOT images.

B. PAM

PAM technique can be briefly described as focusing a pulsed laser beam into the tissue, ultrasonic waves will be then generated, and finally, a focused ultrasonic transducer will detect the generated waves to form a depth-resolved one-dimension (1D) image [29, 30]. Also, three-dimension (3D) high-resolution tomographic images can be generated by raster scanning [29, 30]. L. V. Wang has illustrated in [57] that: PAM can image up to 3 mm into scattering tissue with 15 micrometers axial resolution while working at 50 MHz ultrasonic detection frequency. Whereas working at 5 MHz, PAM can image ~10 times as deep but with ~10 times axial resolution [57].

PAM has the potential to image the microvascular network in the skin, which is invaluable in dermatology and related cancer research [58]. Weak acoustic scattering in tissue is an advantage of PAM, unlike pure optical microscopic techniques [59]. PAM breaks through the optical propagation limit (~1 mm in soft tissue); providing images with high-resolution at imaging depths up to a few millimeters, with excellent scalability [59].

There are two different techniques of PAM: Optical-resolution photoacoustic microscopy (OR-PAM) and Acoustic-resolution photoacoustic microscopy (AR-PAM).

OR-PAM: this technique uses focused light to spatially limit the stimulation, producing an optical diffraction-limited resolution in the lateral direction.

AR-PAM: in this technique a relatively large area is illuminated, rather than focus light to an optically diffraction-confined spot, so more laser energy is allowed in AR-PAM than in OR-PAM, increasing the chance of photons to reach a much greater depth [22].

In AR-PAM, the illumination can be either **dark-field** or **bright**: The dark-field approach has the advantage to reduce surface interference to deeper PA signals, whereas the bright-field method can carry higher fluence to a targeted volume [22].

A most famous technique that belongs to the AR-PAM family is the **RSOM** (raster-scan optoacoustic mesoscopy).

Optoacoustic mesoscopy is, optoacoustic (or photoacoustic) imaging having acoustic resolution and wide-bandwidth ultrasound detection. RSOM's placement is like a bridge in-between optoacoustic microscopy and optoacoustic macroscopy [60]. Optoacoustic mesoscopy or macroscopy qualifies deeper imaging than optical or optoacoustic microscopy methods which use focused light [46]. A classification of microscopy, mesoscopy, and macroscopy concerning their penetration depth, had been stated by V. Ntziachristos in [61], as: (< 1 mm), (0.5 mm to 10 mm), and (> 1 cm); respectively. Another penetration-based classification had been stated by A. Taruttis, G. M. van Dam, and V. Ntziachristos in [46], as: (< 1 mm), (1–5mm), and (beyond 5 mm); respectively. Over the last decade, more papers have been published concerning optoacoustic mesoscopy [62-69].

In recent years, several applications in medicine have been reported using advanced PAM imaging systems (Such as Laser Diode (LD) based PAM systems) towards a low-cost and aiming for a portable PAM system for point-of-care and wearable applications [70, 71]. LD-based PAM imaging has been investigated to reduce the size of bulky lasers usually used in PAM and also for economic issues [71]. A sample image generated from an original 4060 by 2700 pixels data (taken with permission from [71]) for in vivo LD-based PAM microvasculature imaging of an 8.12 mm by 5.4 mm area from a mouse ear is illustrated in Fig. 3.

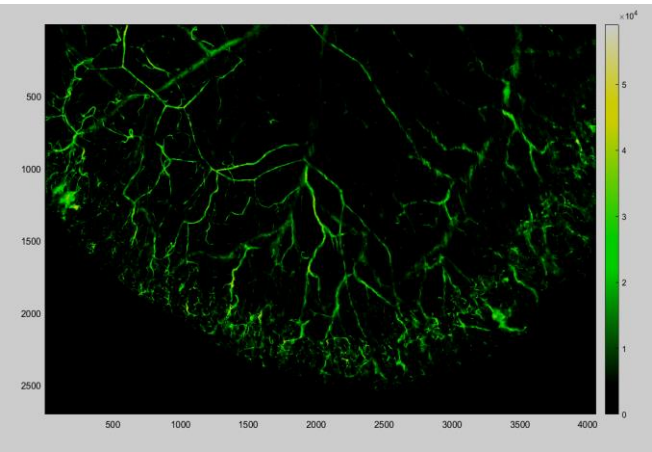

Fig. 3. A sample image produced with permission from [71], illustrating an in vivo LD-based PAM imaging of a mouse ear. Where the numerical values on each X-axis and Y-axis are referring to the pixels' coordinates in the image (where each pixel has a size of 2 μm by 2 μm).

C. PAE

Elastography imaging can be described as art to measure and posterior graphical representation of the spatial allocation of tissue's stiffness [72]. The elasticity distribution in biological tissue can be noninvasively mapped by Elastography to reveal disease conditions [73]. Published studies on PAE imaging (PAEI) are so limited [72]. The start was in 2011, when G. Gao et al, had published their development of a system of PA viscoelasticity imaging, obtaining a high contrast image, reflecting information of the tissue viscoelasticity with the PA phase projection [74]. In the same year 2011; K. J. Parker et al, have stated their 20 years' perspective on Imaging the elastic properties of tissue [75]. In 2015; Pengfei Hai et al, have proposed Vascular elastic photoacoustic tomography (VE-PAT) to measure blood vessel compliance in humans [76]. A PAT imaging system called quantitative photoacoustic elastography (QPAE) imaging system helping in tissue elastic properties' recovery nondestructively and noninvasively, has been developed by Pengfei et al [72, 77, 78]. Till now, PAE is in the upbringing stage of its development [72].

III. LUS MEDICAL IMAGING

The non-contact laser ultrasound (N-CLUS) medical imaging technique is based on the concept of optical detection of ultrasound (OD-US) [79, 80]. OD-US can play an important role in PAI for biomedical study and clinical diagnosis [80]. In full N-CLUS technique; PA sources are employed on the skin surface, in combination with laser interferometric detection instead of piezoelectric ultrasound detectors used in most PA systems [81]. The main difference between PAI and N-LUS is the detection mechanism (piezoelectric or optical), we can name the technique of N_LUS by optical detection PAI (OD-PAI). Historically, ultrasound generation with lasers nearly goes back to the first laser invention (the ruby laser) [82], which was used for generating ultrasound or shock waves in materials [83]. Recently, more studies have been emerged clarifying the medical applicability of N-CLUS's concept [81-90].

IV. PAI'S APPLICATIONS IN MEDICINE

PAI has a wide variety of applications in more branches in biomedicine [184-189]. In the following sections V, VI, VII, VIII, and IX, a concise review is presented for most PAI's applications in cancer screening, tissue oxygenation measurements, brain imaging, guiding surgeries, and HIFU's guidance, respectively.

V. PAI'S APPLICATIONS IN CANCER SCREENING

In 2020, more than 1.8 million new cancer cases and more than 0.6 million cancer deaths were expected to occur only in the United States [91]. Screening can detect some cancers early when treatment is more often successful [92]. Important elements in cancer control are cancer detection in its early stages and supplying immediate appropriate treatment [93]. PAI can play a role in cancer diagnosis and therapy guidance [94, 95].

A. Breast cancer

A group of diseases in which cells in breast tissue change and divide uncontrolled, typically resulting in a lump or mass, is called breast cancer [96]. Breast cancer is the second common cancer worldwide after lung cancer, the fifth common cause of cancer death [97, 98].

X-ray-based Mammography [97], Breast ultrasound (BUS) imaging [99-101], and Magnetic resonance imaging (MRI) [102, 103], are the three most famous imaging techniques utilized for breast cancer screening. X-ray-based screening mammography, beginning in the 1980s, helps in the early detection of breast cancer [97]. But it uses ionizing radiation, painful breast compression, and has poor performance in radio-dense breasts. BUS imaging can be utilized as mammography's adjunct [100, 101]. However, X-ray and BUS imaging are both suffer from having non-optimal sensitivity and specificity [104]. MRI could be used for breast imaging in cases of uncertain findings in X-ray and BUS imaging [104]. However, MRI suffers from limited specificity, requires contrast agents, excludes more patients for instance who have pacemakers, or claustrophobia, moreover it is a little obstructed in pre-menopausal women by the requirement to time imaging during certain phases of the menstruation cycle [104]. PAI, a nonionizing modality, has the potential to achieve higher specificity in the diagnosis of malignant and benign breast masses, helping to reduce the number of false-positive scans and unnecessary biopsies of benign [104]. Over the last few years, there were various breast' PAI systems have been proposed [105-110]. Recently, Li Lin et al [111], have introduced a high-speed 3D Photoacoustic computed tomography (PACT) system for both preclinical and clinical applications, achieving an in vivo imaging depth of 4 cm in the human breast within a single breath-hold (SBH) of 10 s. Figure 4 is illustrating a sample image of a healthy human subject's right and left breasts in vivo taken by the 3D-PACT system introduced in [111].

B. Thyroid cancer

In 2020, the expected number of new cases of thyroid cancer diagnosed only in the United States (US) is estimated at 52,890. The incidence rate is about 3 times higher in women than in men [92]. Thyroid cancer was the most rapidly increasing cancer in the US till now [92]. In 2012, there were an estimated 40,000 deaths globally due to thyroid cancer [93]. The thyroid gland, normally located in the lower front of the neck, is a butterfly-shaped endocrine gland [112]. Ultrasound combined with fine-needle aspiration cytology (FNAC) is the primary diagnostic tool for thyroid cancer, followed by histology [10]. PAI can augment, FNAC combined ultrasound, for molecular imaging of thyroid nodules. It is because the thyroid gland is superficial (2–3 cm deep) allowing sufficient penetration of light [10]. Recently, more researches have been introduced discussing PAI's utilization in thyroid cancer diagnosis [113-115].

C. Ovarian cancer

In 2020, an expected 21,750 new cases of ovarian cancer will be diagnosed only in the United States and about 13,940 women are expected to die from the disease [92]. Globally, ovarian cancer is the eighth most frequent cause of cancer death among women with 152,000 deaths, as stated by the 2014's world cancer report [93]. Ovarian cancer is rarely detected at an early stage because of its low spread in the general population [116], Bin Rao et al, have investigated the feasibility of "optical biopsy", using high OR-PAM to quantify the microvasculature of ovarian and fallopian tube tissue [116]. Through the last decade, there was more than one prototype PAI-based system studying the ability of PAI to enhance ovarian cancer diagnosis [116-119].

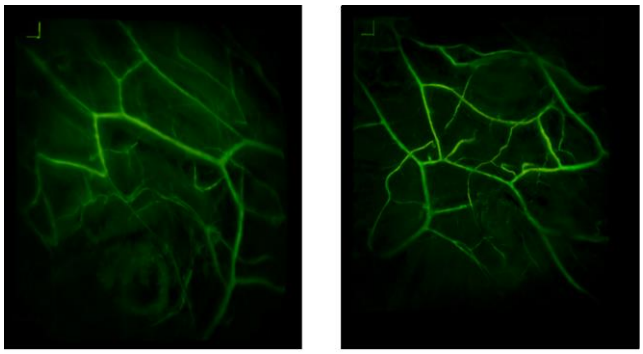

Fig. 4. 3D-PACT of a healthy human subject's breast in vivo (Taken and Processed with permission from [111]). A is a processed perspective angiogram of the Right breast. B is the Left breast image of the same human subject.

D. Prostate cancer

Globally, prostate cancer (PCa) is the second most common cancer in men worldwide [76]. In 2020, the expected new cases of prostate cancer are estimated at 191,930 only in the United States, and 33,330 men are expected to die from the disease [92]. To visualize prostatic anatomy and guide needle biopsy, transrectal ultrasound (TRUS) has been routinely used since the 1980s [120]. A trial in validating if ex-vivo multispectral PAI can characterize malignant prostate tissue, benign prostatic hyperplasia (BPH), and normal human prostate tissue, has been proposed by Dogra et al [121], concluding that multispectral PAI had the potential to differentiate between malignant prostate, BPH and normal prostate tissue. B. L. Bungart et al [122], have published their success in providing prostate biopsy targets by 1064 nm PAT and ultrasonography texture-based feature analysis. Through the last few years, more researches have been emerged concerning enhancing PAI's applications on the prostate [120-125].

E. Lung cancer

Lung cancer is the most frequent cancer worldwide; it is the most common cancer in men and the third in women [93]. As estimated in 2012: there were more than 1.8 million new cases and almost 1.6 million deaths [93]. Only in the United States: the expected new cases of lung cancer in 2020 were estimated at 228,820, whereas the expected mortality from the disease was estimated at 135,720 [92]. Early detection could be a reason for decreasing mortality from lung cancer because most diagnoses occur in a late stage of cancer with a low survival rate [126]. PAI has been studied to help in lung cancer diagnosis

through more than one study during the last decade assuring its promising role in lung cancer diagnosis [126-129].

F. Skin cancer

In recent years, skin cancer cases number has risen globally [1]. Melanoma, Basal cell carcinoma, and squamous cell carcinoma; are the three main types of skin cancer, in which the last two types are called non-melanoma skin cancers (NMSCs) and are seldom life-threatening, whereas the first type: melanoma skin cancers are rare but aggressive and start in pigmented lesions like a mole or birthmark [1]. Nearby lymph nodes are the first site of metastasis where melanoma can spread throughout the body [1]. For precise melanoma prognosis, ascertaining, staging, and planning treatment; the pathological status of the sentinel lymph node is significant [130]. Initial results using PAT by Jose et al [130], suggested that PA could develop into an intraoperative imaging method for detecting melanoma metastases in sentinel lymph nodes. Recently, more researches have been emerged discussing PAI's utilization in skin cancer imaging [131-135].

VI. PAI IN TISSUE OXYGENATION MEASUREMENTS

Oxygen was named by Joseph Priestley and Antoine Lavoisier who had isolated it. Carl Scheele had discovered oxygen in the late eighteenth century. Living cells obtain oxygen through air inhaled into the respiratory system from where it is absorbed into the bloodstream. In red blood cells (RBCs), oxygen is bound to hemoglobin. In some tissues such as muscle, oxygen is also stored bound to myoglobin [136]. William G. K., Peter J. R., and Gregg L. S. have been awarded the 2016 Albert L. basic medical research award for the discovery and clarification of pathways by which humans and other multicellular organisms sense and respond to changes in oxygen availability [137]. The Nobel prize for Physiology or Medicine for 2019 had been given to the same three men for discoveries on the mechanisms by which animals cells respond to changes in oxygen levels [136]. To facilitate blood oxygenation, a specialized oxygen-binding molecule (hemoglobin) is needed since oxygen does not dissolve readily in the plasma because plasma is 93% water [138]. Tissue oxygenation can be imaged by PA based on the oxygen-dependent light absorption characteristics of hemoglobin [139]. Molar extinction coefficient (cm-1/M) spectra curves for HBO2 and HB are shown in Fig. 5. Where: M is referring to the molar concentration in moles/liter. Where HbO2 (red): refers to Oxygenated Hemoglobin, and HB (blue): refers to Deoxygenated Hemoglobin.

Oxygen saturation (sO2) can be described by equation (1) taken from [138]; Where THb: refers to Total Hemoglobin Concentration.

$$sO2 = HbO2/THb \quad ; THb = HbO2 + Hb \qquad (1)$$

Blood oxygenation measurements by PAT are an important application been widely carried out in PA studies of tumor hypoxia, brain functions, cancer therapy, and wound healing [140]. PAM has been able to image sO2 in the microvasculature of biological tissues [141]. PAI can deduce the spatial allocation of sO2 in blood, and be co-registered with ultrasonography images of the surrounding anatomy [142]. sO2 can be expected from the partial pressure of blood's oxygen (pO2) based on a standard dissociation curve shown in [142]. Real-time assessment of tissue hypoxia in vivo can be achieved by combining PA and high-frequency ultrasound [143]. In blood flow measurements, PAI has an efficient role [144-146].

VII. PAI IN BRAIN IMAGING

The absorption spectra of deoxyhemoglobin (Hb) and oxyhemoglobin (HbO2) enabled PAT to provide label-free functional brain images of oxygen saturation (sO2) and total hemoglobin concentration (THb) [13]. For improving the visibility of the neurovascular structures, optical contrast agents, like nanoparticles and organic dyes can be used [13]. Different PAI brain imaging techniques have emerged through the last few years [13, 147]. Visualizing Alzheimer's disease of a mouse's brain has been reported by Park SJ et al [148], applying the MSOT technique utilizing an optical imaging probe (CDnir7: Compound of Designation near-infrared 7). Recently, more researches have been emerged discussing different types of PAI schemes, techniques, and applications in brain imaging [148, 149-162].

VIII. PAI IN IMAGING-GUIDED SURGERY (IGS)

Imaging-guided surgery (IGS) is a branch of the concept of Image-guided therapy (IGT) which includes any intervention or surgery that utilizes improved imaging for monitoring, localizing, controlling, and targeting procedures [163]. Due to PAI's ability in noninvasive diagnosis of various types of tissues including bone: PAI could be applied in IGS providing real-time visualization and analysis abilities during more than one type of surgery, for instance: cancer surgery and spinal surgery, helping surgeons in avoiding pedicle breaches by choosing an adequate starting point before drilling or pedicle probe insertion [164]. An intraoperative breast cancer screening by PA has been demonstrated by Ivan K. et al [165], producing a new perspective for malignant cancer visualization moreover surgical guidance. In 2020, a United States patent by M. Bell et al has been dated for a system and method of transcranial PAI to guide skull base surgeries [166]. For more about PA-guided surgery, we refer the reader to [167].

IX. PAI'S GUIDANCE OF HIFU

Providing non-invasive heating and ablation for a wide range of applications, HIFU was rapidly obtaining clinical approval with only a single session required usually for

treatment (day case procedure) [168]. An integrated HIFU drive system on a chip has been introduced by Omid F. et al [169], proposing the feasibility of their system of HIFU based integrated catheter ablation that containing a drive signal generator integrated circuit (IC), and a capacitive micromachined ultrasound transducer (CMUT) ring array. Since, Tumors in organs partially becloud by the rib cage are a challenge for HIFU therapy because of HIFU's beams distortion reducing the focusing gain at the target, Mohamed A. and Emad E. have introduced a new method of refocusing that can steer power towards the target, whereas limiting the deposition of power on the ribs using the semidefinite relaxation (SDR) technique in approximating the original (non-convex) optimization problem [170]. Through the last few years, more researches have emerged concerning the applications of combining PAI and HIFU [171-174].

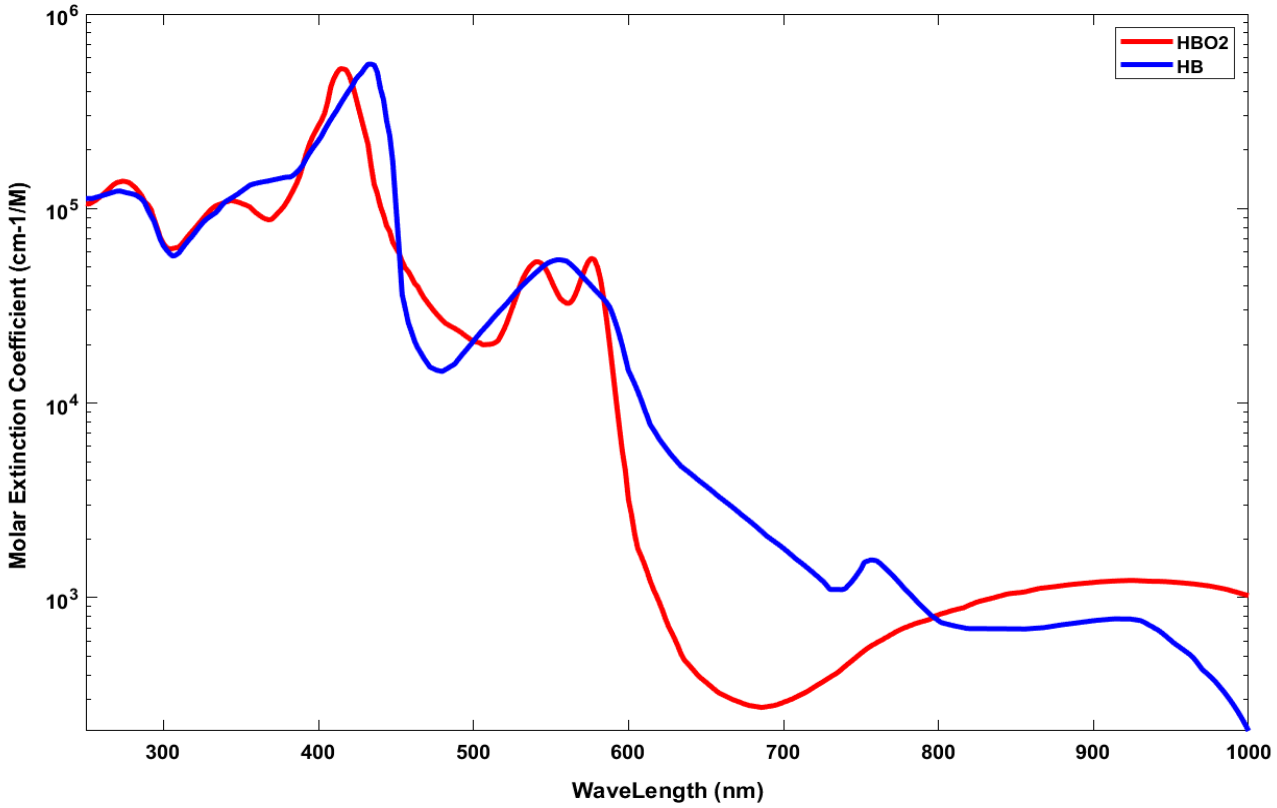

Fig. 5. Molar extinction coefficient (cm-1/M) spectra curves for HBO2 (red) and HB (blue) through different wavelengths (nm). Where: M is referring to the molar concentration in moles/liter (The raw data for these two curves have been taken from: https://omlc.org/spectra/hemoglobin/summary.html).

X. Safety Considerations

In most traditional ultrasound imaging the ultrasound prob does a dual job: transmitting and receiving ultrasound in both directions as shown in Fig. 6 – A, so more studies concerning ultrasound safety have been emerging concerning this topic, however, diagnostic ultrasound has been widely accepted with an impressive safety record since the 1950s [175-176]. For more about the factors contributing to this record, ultrasound thermal and non-thermal or mechanical (cavitation) induced bio-effects, ultrasound safety considerations, and exposure practice and levels; we refer the reader to [176 – 181].

In PAI: the existence of ultrasound is just the output from the biological tissue due to the PA effect and the ultrasound probe is just utilized for receiving the induced ultrasound waves as illustrated in Fig. 6 -B, so the ultrasound safety consideration illustrated is not applicable here in PAI's. Instead, Laser safety is so important in PAI. In PAI the used laser type, class, and exposure limit must be included in the safe range standards of the laser. laser's safety standards for use vary in their scope and design, for more about international standards for using laser, American National Standards Institute (ANSI) standards for using laser, laser safety exposure limits, and laser hazard classification classes we refer the reader to [182]. Wherever it is located, a laser is as safe or as hazardous as the user; hence, well and safely a clinical practice operates can be defined by the user's knowledge and skill [183].

XI. Summary and Conclusion

Photoacoustic Imaging (PAI) has wide applications in medicine. There are more techniques of PAI including; PAT,

MSOT, fcPAT, OD-PAT, OR-PAM, AR-PAM, RSOM, PA endoscopy, PATER, and PAE. In the last two decades: the medical applications of photoacoustics have been widely spread. In cancer diagnosis; PAI has a big role, for instance in cancers detection of breast, thyroid, prostate, and skin. Visualizing Alzheimer's disease could be possible by PAI's Brain imaging. PAI could help in a real-time assessment of tissue hypoxia. PAI's guidance plays a strong role in more applications of IGS and HIFU. Our conclusion is the expectation of more future applications of PAI in medicine. Moreover, OD-PAI or N-CLUS, LED-based PAI, PATER, and PA endoscopy systems can generate promising techniques opening the door for more researches in this field.

ACKNOWLEDGEMENTS

1- Authors hereby thank Dr. Terence T. W. Wong, and Xiufeng Li, for providing the original data of their paper [71] to us and giving us permission to process and publish. Also, thanks to the rest co-authors of [71]: Victor T. C. Tsang, Lei Kang, and Yan Zhang.

2- Authors hereby thank Prof. Dr. Lihong V. Wang, for providing us a permission to process and publish the original breast figure's data of his paper: [111]. Also, thanks to the rest co-authors of [111]: Li Lin, Peng Hu, Xin Tong, Shuai Na, Rui Cao, Xiaoyun Yuan, David C. Garrett, Junhui Shi, and Konstantin Maslov.

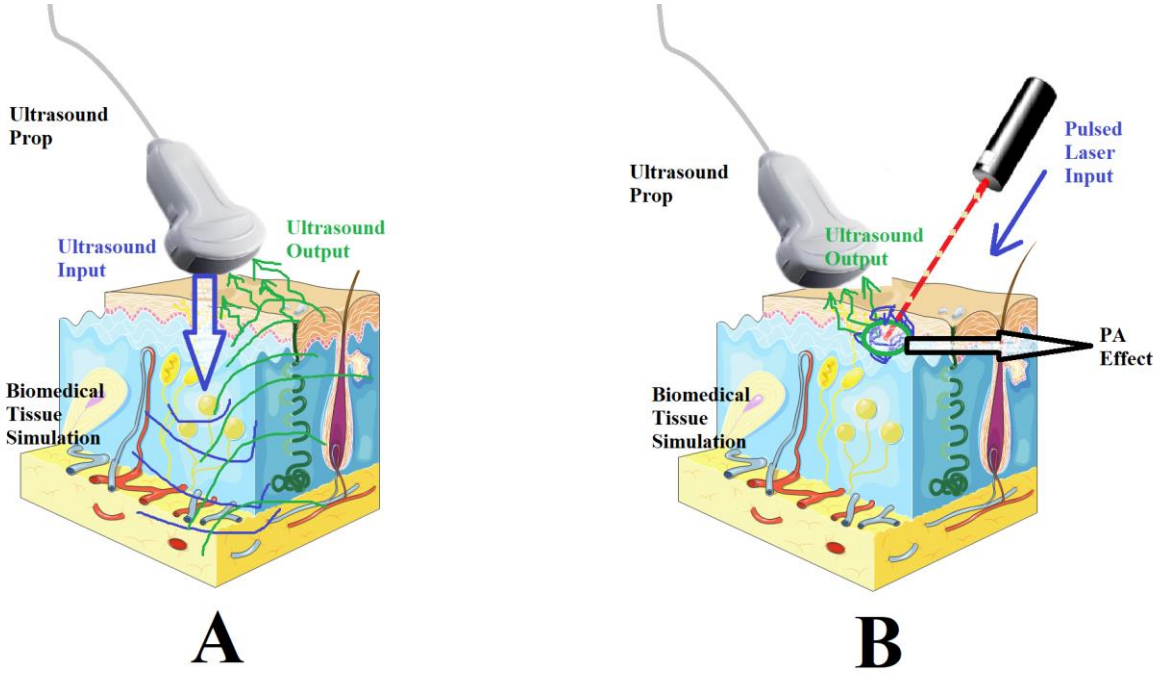

Fig. 6. A and B: simple illustration for the basic principle of ultrasound imaging and PAI, respectively. (The picture of the simulated skin tissue shown in the figure is taken from: https://smart.servier.com)

AUTHORS CONTRIBUTION

The following is authors' statement outlining their individual contributions to the paper using the relevant roles:

1. *Samir M. Badawy:* Supervision, Investigation, Conception and design of the work, Data analysis and interpretation, Methodology, Drafting the article, Critical revision of the article, and Final approval of the version to be published.
2. *Mohammed T. GadAllah:* Conception or design of the work, Data collection and tools, Data analysis and interpretation, Investigation, Methodology, Resources, Software, Drafting the article, Critical revision of the article, and Final approval of the version to be published.
3. *Abd El-Naser A. Mohamed, Alaa A. Hefnawy, Hassan E. Zidan, and Ghada M. El-Banby:* Supervision.

FUNDING STATEMENT:

The author received no financial support for the research, authorship and/ or publication of his article.

DECLARATION OF CONFLICTING INTERESTS STATEMENT:

The author declared no potential conflicts of interest with respect to the research, authorship or publication of his article.

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Arabic Title:

التصوير الصوتي الضوئي في الطب – مراجعة

Arabic Abstract:

بدأت هذه الورقة البحثية الخاصة بالتصوير الصوتي الضوئي (PAI) في الطب بمقدمة للتصوير الصوتي الضوئي والتقنيات الصوتية الضوئية الشهيرة بما في ذلك التصوير المقطعي الصوتي الضوئي (PAT) ، والتصوير المقطعي الصوتي الضوئي متعدد الأطياف (MSOT) ، والفحص المجهري الصوتي الضوئي (PAM) ، والتنظير النقطي الصوتي الضوئي (RSOM) ، و تصوير المرونة الصوتي الضوئي (PAE). تم أيضًا عرض مراجعة متواضعة حول الموجات فوق الصوتية بالليزر بدون تلامس (LUS) ، والتي تتمتع بميزة جودة الصورة المستقلة عن المشغل.كما يتم عرض مراجعة موجزة لمعظم التطبيقات الطبية للتصوير الصوتي الضوئي بما في ذلك فحص السرطان (للثدي والغدة الدرقية والمبيض والبروستاتا والرئة والجلد) ، وقياسات أكسجة الأنسجة ، وتصوير الدماغ ، والجراحة الموجهة بالتصوير (IGS) ، وتوجيه الموجات فوق الصوتية المركزة (HIFU). بعد ذلك تم تقديم بعض اعتبارات السلامة المتعلقة باستخدام الموجات فوق الصوتية الطبية والليزر. و في الختام ، من المتوقع المزيد من التطوير العلمي والسريري في مجال PAI ، ومن المتوقع أيضًا أن تخدم زيادة الأجهزة المعتمدة التي تستخدم تقنيات PAI في التطبيقات الطبية قطاعات واسعة من الطب ، سواء كانت تشخيصية أو علاجية.

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