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THE EFFECTIVENESS OF IMAGE-GUIDED INTERVENTIONS IN PAIN MANAGEMENT AND MINIMALLY INVASIVE PROCEDURES

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1. Introduction

Photoacoustic imaging is a developing technique that may be used for image-guided interventional treatments. This
imaging technique has a distinctive capability to provide immediate, non-intrusive, economical, and radiation-free assistance in a practical surgical setting. This article provides evidence and highlights promising outcomes of studies using photoacoustic imaging to guide medication distribution, treatment, surgery, and biopsy. Therefore, this minireview will aid in advancing future research and practical implementation of photoacoustic image-guided therapies (1,2).

Photoacoustic imaging (PAI), also known as optoacoustic imaging, is a new therapeutic imaging technique that combines the advantages of optical and ultrasonic imaging. In PAI, a target produces photoacoustic waves when it is exposed to brief laser pulses. The generated photoacoustic (PA) waves will be subsequently captured by an ultrasound transducer to create images. The contrast in photoacoustic imaging (PAI) is determined by the optical absorption and is not affected by the mechanical properties or elasticity. The spatial resolution of PAI can be adjusted to penetrate up to 5 cm, which is significantly deeper than traditional optical imaging methods in soft tissue . (3,4)

Photoacoustic imaging (PAI) has significant promise for clinical diagnosis of a wide range of disorders, including cancer, stroke, atherosclerosis, arthritis, and more. PAI has several applications in the field of cancer, such as early detection, determining the stages and metastases, treatment planning, and assessment. Studies have shown that PAI is effective in diagnosing breast, prostate, thyroid, melanoma, and ovarian cancers (5-8). PAI, or Photoacoustic Imaging, is used in stroke cases to visualize and analyze mechanical thrombolysis, vessel segmentation, and other vessel injuries in the brain (9,10). It is also helpful in assessing plaque distinction and characterization, as well as detecting macrophages and lipids in atherosclerosis plaques. PAI has

also been used in the field of arthritis to identify inflammation stage the disease, and assess its severity.(11-14)

PAI, as a developing technique, has the ability to provide distinct capabilities for seeing tissue in terms of both structure and function. The obtained structural and functional information may immediately assist in various diagnostic and therapeutic treatments. Consequently, PAI has been extensively used to direct further interventions such as medication administration, treatments, tissue sampling, and surgical procedures. Photoacoustic imaging (PAI) is a very promising method for directing treatments due to its several advantages over existing imaging methods such as ultrasound (US), magnetic resonance imaging (MRI), and computed tomography (CT).
PAI provides real-time imaging and offers a wider variety of benefits. The advantages of PAI-guided interventions in real- time can be summarized as follows: (1) The procedure is non-invasive, meaning it does not require any surgical incisions. (2) It allows for continuous imaging of structures during the intervention, providing real-time feedback. (3) PAI is more sensitive, faster, and less expensive compared to MRI and CT scans. (4) It is the only existing modality that can provide non- invasive penetration depth in the order of centimeters, using optical contrast and ultrasound resolution. (5) The spatial resolution of PAI is acoustically dependent and completely independent of optical absorption. (6) PAI can function independently without the need for external contrast agents, using intrinsic agents like hemoglobin and melanin. (7) It is a safe procedure as it does not produce any ionizing emission.
(8) PAI allows for concurrent measurements of functional parameters such as oxygen and hemoglobin levels, temperatures, etc., using only endogenous agents. (9) It provides great optical contrast, making blood vessels easily visible. (10) PAI can be easily incorporated into the current operating environment without requiring extensive efforts.(15-18)

Due to the aforementioned benefits, PAI-guided intervention offers significant promise for improving the efficacy of many treatments and therapies. The application of this technology is wide-ranging, spanning from individual cells to entire organ systems in the body. Various interventions guided by PAI have been developed for use in the cardiovascular system, spinal system, nerves, tendons, fetus, lymph nodes, and tumors occurring at different sites in the body. PAI is extensively utilized for monitoring the delivery of drugs and observing disease conditions, therapeutic outcomes, and subsequent tissue responses.

This study aims to examine the recent advancements in PAI-guided medication administration, operations, treatments, and biopsies. PAI has the ability to accurately direct the release of drugs, track the distribution of drugs, and assess the resulting therapeutic impact. It has the ability to provide both passive and active targeted delivery. Furthermore, it has significant promise in assisting surgical procedures, primarily via the utilization of endogenous contrast agents to locate the desired target and safeguard the adjacent tissues. PAI is a potent tool for directing photothermal treatment (PTT), chemo-PTT, chemo-photoacoustic, and combined PTT and

photoacoustic therapies. It does this by using a range of organic, inorganic, and hybrid nanoparticles. Additionally, it has the capability to provide real-time guidance during biopsies. Therefore, this minireview aims to emphasize the effectiveness of PAI in providing real-time guidance for these treatments (19-21).

2. Drug distribution directed by artificial intelligence (AI)

Photoacoustic imaging (PAI) is a highly promising technique for guiding drug delivery due to its ability to provide optical contrast with deep penetration. PAI can take advantage of the strong optical contrast of the drug itself to enhance contrast, especially when there is a significant difference in optical absorption between the drug and surrounding tissue. PAI also offers excellent sensitivity and high spatial resolution. Furthermore, PAI is a cost-effective alternative to MRI and CT, and can be used for real-time monitoring. Moreover, PAI can seamlessly integrate with existing clinical protocols and is user- friendly for doctors to run (22).

Photoacoustic imaging (PAI) has been utilized to track the path of drug administration and monitor the release of drugs from their carriers, as well as the subsequent diffusion process and final distribution. PAI has also been employed to observe the real-time therapeutic effects of drugs. PAI-guided drug delivery has demonstrated success in various medical treatments, including cancer therapy, anticoagulation therapy, bipolar disease treatment, and coronary heart disease treatment. The investigation and validation of PAI for continuous monitoring have been conducted on tissue/tumor phantoms, animal models, and cell cultures, either by directly using the drug/therapeutic agents or by employing a dye that mimics the drug.

While free agents may sometimes be used, nanoparticles with a size range of 93 to 96 are the predominant exogenous contrast agents employed for enhancing contrast in PAI-guided medication administration. Numerous inorganic nanomaterials, including metallic and carbon-based ones, have been created because of their specific optical characteristics, which make them suitable for use as contrast and medicinal agents. In recent times, organic and semiconducting nanomaterials have been used in photoacoustic theranostic applications (23-25). Additionally, drug administration may be achieved using either passive or active targeted delivery methods. In passive drug delivery, the effectiveness of a medicine is determined by its duration in circulation, whereas in active drug delivery, nanoparticles are custom-designed to selectively bind to a particular target.

3. Passive medication administration guided by PAI

PAI facilitates both passive and active targeted medication delivery. PAI can facilitate the passive transportation of drugs by taking advantage of the enhanced permeability and retention effect. Additionally, nanoparticles can be coated with materials such as polyethylene glycol (PEG) to further enhance this process. In a study, micelles containing doxorubicin (DOX) were utilized to examine the passive drug delivery guided by

PAI. The investigation was conducted in simulated acidic lysosome environments using human breast cell lines. PAI effectively tracked the release of DOX and offered immediate viewing of micelles that entered the lysosomes via endocytosis. The investigation focused on the use of photoacoustic sensors to passively monitor the quantity of heparin. These sensors, composed of cellulose and Neil blue A, were used for real-time monitoring of heparin content in plasma and blood. PAI was able to accurately determine the concentration of heparin in plasma within 3 minutes and in blood within 6 minutes .(26-28)

4. PAI-guided PTT employing organic nanoparticles

Organic nanoparticles are used as contrast agents in PAI- guided PTT because to their exceptional biocompatibility and high drug packing capacity. These nanoparticles include of polymers, conjugated polymers, and micelle-based nanoparticles. Polypyrrole is an organic polymer that exhibits exceptional conductivity, stability, and high absorption in the near-infrared (NIR) region. On the other hand, chitosan, an organic polymer derived from marine sources, provides favorable attributes such as biocompatibility, affordability, abundance, stability, and non-toxicity.

The use of chitosan-polypyrrole nanoparticles is highly recommended for localized tumor photothermal therapy (PTT) because to its desirable characteristics such as biocompatibility and rapid conversion of PTT. These were used in the process of PAI-guided photothermal ablation of a tumor, whereby the cells experienced apoptotic cell death upon reaching a tissue temperature of 62°C, facilitated by PAI for precise tumor localization. The usage of conjugated polymeric nanoparticles in PAI-guided PTT resulted in cell necrosis. These nanoparticles were modified with an amino acid ligand. These nanoparticles enhanced the process of photoacoustic imaging (PAI) by improving the contrast and signal-to-noise ratio. This enabled the visualization of deeper anatomical features.

Furthermore, these nanoparticles effectively served as a photothermal therapy (PTT) agent, specifically targeting and destroying localized tumors. Melanin-based micelles are advantageous due to their biocompatibility, environmental friendliness, and high photothermal therapy (PTT) efficacy. A study shown that PTT may be enhanced by utilizing melanin- based micelles with poly-L-lysine loaded with a medication, which mimics the surface of the micelles. The enhanced efficacy of PTT was attributed to the role of PAI in optimizing the duration of NIR irradiation on the tissue, resulting in the induction of cell necrosis specifically in the tumor (29,30).

5. PTT-guided by PAI employing inorganic nanoparticles

The types of inorganic nanoparticles used for photoacoustic imaging (PAI)-guided photothermal therapy (PTT) include metallic nanoparticles, plasmonic nanoparticles, carbon-based nanoparticles, and quantum dots. Gold nanorods, which are metallic nanoparticles, can serve as both photoacoustic imaging (PAI) and photothermal therapy (PTT) agents due to their strong

optical absorption and surface plasmon resonance (SPR). However, there are safety concerns associated with their long-term use. To address this, silica-coated gold nanorods with enhanced thermal stability have been developed. These nanorods significantly amplify the photoacoustic signal and have been successfully employed in PAI-guided PTT, leading to cell death in tumor tissue.

PAI carefully monitored the whole process using temperature monitoring. The combination of photoacoustic imaging (PAI) and ultrasound-guided photothermal therapy (PTT) demonstrated that these nanoparticles are capable of generating targeted heat during medical treatments. Plasmonic nanoparticles are commonly used in photothermal therapy (PTT) because their absorbance peaks can be adjusted by controlling their surface plasmon resonance during synthesis. Therefore, by synthesizing these nanoparticles with a specific resonating wavelength in the near-infrared (NIR) region, they can be used as effective contrast agents in photoacoustic imaging (PAI) and as photothermal agents in PTT. Gold nanoparticles are exemplary plasmonic nanoparticles used in PAI-guided PTT. Specifically, gold nanorods, which possess high PTT efficiency and NIR absorbance, were combined with graphene oxide, known for its exceptional drug packing capacity. These nanocrystals demonstrated successful cancer therapy at the tumor site of nude mice. At first, PAI facilitated the release of drugs by responding to the change in the pH of the surrounding environment.

Subsequently, PTT was conducted using the same gold nanorods. In another research, it was shown that gold nanostars, which were linked to CD44v6 antibodies, a surface marker seen on stomach cancer cells, were effective in eliminating cancer cells utilizing photothermal therapy (PTT) with guidance from photoacoustic imaging (PAI). The research showed that tumor development was effectively stopped and the lifespan of mice with tumors was improved using photothermal therapy (PTT). Additionally, photoacoustic imaging (PAI) was utilized to measure the reaction of the cells to PTT. Superparamagnetic carbon-based nanoparticles have various applications, such as in MRI and PAI imaging, as well as in PTT therapies. One specific type of these nanoparticles is Hägg iron carbide, which exhibits exceptional absorption in the NIR range and high PTT conversion efficiency. This may be used to effectively treat the tumor while minimizing damage to the
surrounding tissue. The nanoparticles effectively elevated the temperature of tumor tissue to around 47°C, resulting in necrotic and apoptotic cell death during photothermal therapy (PTT). The utilization of nanoparticles in PAI has allowed for improved contrast enhancement and subsurface tissue organization in PAI-guided PTT. Copper chalcogenides, a type of quantum dot, possess exceptional NIR absorption and confined SPR, making them suitable for use as both PTT and PAI agents. These quantum dots can be combined with iron oxide to create small, biocompatible, and adaptable nanodots, which have been successfully employed in both MRI and NIR imaging (31-35).

6. Summary and Future study

While PAI has notable benefits, it also has drawbacks when it comes to clinical translation. One disadvantage is the reliance on external contrast agents. PAI sometimes necessitates the use of exogenous contrast agents, which introduces several safety problems. The long-term effects of dyes and their removal from the body are significant concerns due to the potential for these substances to induce several harmful consequences in the body. Image artifact reduction is a significant challenge when reconstructing photoacoustic images from signals. This task necessitates intricate algorithms and entails a substantial amount of time for processing. The imaging depth of photoacoustic imaging (PAI) is restricted due to the significant scattering of light in soft tissue, which hampers its delivery.

Photoacoustic imaging (PAI) offers an expanded range of translation possibilities, including novel applications such as light emitting diode-based PAI (LED-based PAI) and wearable PAI. LED-based photoacoustic scanners have shown the ability to measure reactive oxygen and nitrogen species. This capability has been confirmed in live mice. Wearable optical resolution photoacoustic microscopy (W-ORPAM) is a kind of portable imaging system called a wearable PAI system. It is used to capture real-time images of the cerebral cortex. This technique takes advantage of changes in blood vessels under various physiological situations and has been tried on mice. A different wearable device using Periodontal Attachment Index (PAI) to monitor periodontal health has been shown to be effective and this has been verified in human subjects.(36)

Ultimately, although there are other imaging techniques that may be used to guide therapies in real-time, PAI stands out due to its non-invasive nature, safety, real-time capabilities, great optical contrast, and sometimes lack of need on external contrast chemicals. Similar to other methods of medical imaging, photoacoustic imaging (PAI) also has some limits, one of which being the depth at which it can effectively
capture images. However, due to its low cost, simplicity of use, and high imaging contrast, PAI-guided intervention has significant promise for rapid clinical implementation and may be favored over other modalities in some circumstances. PAI has been actively involved in exploring new applications and continuously improving its present uses. It has the potential to become a widely used imaging technique for real-time guidance during interventions in the near future.

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