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Advancements in Photoacoustic Imaging: Enhancing Cancer Detection and Treatment Monitoring: Review

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Abstract

Background: Photoacoustic imaging (PAI) is an innovative imaging technique that combines optical excitation with acoustic detection, providing significant advancements in clinical diagnostics, particularly in oncology. With its ability to deliver high-resolution images and detailed molecular information without ionizing radiation, PAI is gaining traction in cancer detection and treatment monitoring.

Methods: This review synthesizes recent advancements in PAI and its applications in clinical settings. A comprehensive analysis of peer-reviewed studies from the past two decades was conducted, focusing on PAI's efficacy in various oncological applications, including breast, skin, and prostate cancer. The review also explores the integration of PAI with other imaging modalities and the development of novel contrast agents.

Results: PAI has demonstrated impressive capabilities in identifying and characterizing tumors through its sensitivity to vascular structures and oxygen saturation levels. Studies indicate that PAI can detect early-stage tumors with high specificity and sensitivity,

offering a non-invasive alternative to traditional imaging techniques. The FDA has recently approved a PAI system for breast cancer diagnostics, highlighting its clinical relevance.

Conclusion: The integration of PAI into clinical practice offers a promising avenue for enhancing cancer screening, diagnosis, and treatment evaluation. As research progresses, the standardization of PAI technology and training for healthcare professionals will be crucial for its widespread adoption. Continued advancements in contrast agents and imaging techniques will further solidify PAI's role in precision medicine.

Keywords: Photoacoustic Imaging, Oncology, Contrast Agents, Cancer Detection, Clinical Applications

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1. Introduction

Photoacoustic imaging (PAI), or optoacoustic imaging, is a burgeoning technique that has garnered heightened attention for its applications in clinical research and translation, particularly in the promising care of cancer patients [1,2]. PAI, as a hybrid approach, integrates the benefits of optical excitation with auditory detection, hence enhancing existing technologies. The optical excitation offers significant contrasts that disclose intricate anatomical, functional, and molecular information, including precise vascular architecture, hemoglobin oxygen saturation, and the absorption of contrast agents. Simultaneously, acoustic detection capitalizes on the little dispersion of ultrasound waves in biological tissues, allowing photoacoustic imaging (PAI) to provide high-resolution pictures at the requisite depth (≤4 cm in human breasts crushed against the chest wall) [3-5]. This unique characteristic is facilitated by the photoacoustic phenomenon, whereby absorbed photons are transformed into propagating acoustic waves. Short light pulses irradiating biological tissues cause photon absorption, which thermoelastically generates a temporary pressure rise that propagates as ultrasonic sounds, known as photoacoustic waves. Ultrasonic transducers detect the photoacoustic waves, which may then be used to recreate the optical absorption distribution inside the tissue [6].

In the last twenty years, PAI has facilitated several significant discoveries and applications, spanning from preclinical research to clinical care [6-11]. In preclinical research, PAI has emerged as an indispensable tool, offering rapid in vivo imaging with significant optical contrast, superior spatial resolution, and comprehensive whole-body penetration in tiny animals [12,13]. Translational PAI has garnered increasing attention in cancer, dermatology, pediatrics, neurology, and orthopedics, among other fields of research [7,11,14-17]. PAI has shown a supplementary function in cancer imaging, hence enhancing the screening, diagnosis, and therapy of cancer patients [18-21].

The distinctive physical properties of PAI allow researchers to see the architecture, function, and molecular processes of biological systems in vivo, due to variations in the optical absorption spectra of various endogenous and/or exogenous substances. Consequently, multi-contrast PAI may provide extensive information that aids in cancer

imaging without requiring ionizing radiation, heavy-metal contrast agents, or specialized facilities for radiation protection [22]. The integration of optical absorption contrast with ultrasonic detection imparts PAI several benefits akin to clinical ultrasonography, including an advantageous system geometry facilitated by an open imaging platform and a scalable, high degree of spatial resolution. The swift imaging velocity and operational safety augment the appropriateness of PAI for frequent and recurrent bedside imaging. The scale of PAI imaging can range from organs to organelles, and this methodology has been utilized for imaging breast cancer, skin cancer, prostate cancer, metastatic lymph nodes, and circulating cancer cell clusters, in addition to microscopy of excised tumor samples. With these features, PAI is swiftly advancing into a therapeutically applicable modality [23-30]. In 2021, a company engaged in PAI obtained FDA clearance for an integrated PAI and ultrasonography imaging system, therefore facilitating future clinical translation [31].

This Review delineates the advancements of PAI in clinical translation, emphasizing significant results from diverse oncological applications, and anticipates the future implications of this developing technology. We first present the primary setups of PAI that provide scalability via swift picture gathering. We then examine the contrast processes of PAI and how they elucidate anatomical, histological, functional, and molecular aspects that are not readily discernible or distinctly seen by other modalities. This text delineates exemplary PAI research involving cancer patients, categorizing the functions of PAI into cancer detection, diagnosis, and therapy advice. We end with a recap of the current advancements and provide insights into potential future technological innovations and their therapeutic ramifications.

2. Multiscale Photoacoustic Imaging

PAI has been developed in several configurations, enabling multiscale imaging of physiological parameters [10]. A significant majority of PAI modalities are deemed safe for human use since the radiation exposure or optical fluence on the skin surface typically remains under the safety limits established by the American National Standards Institute (ANSI). The established limitations provide a maximum allowable skin exposure to 1,064 nm light of 100 mJ/cm^2 for each nanosecond laser pulse and 1 W/cm^2 for exposure periods beyond 10 s [32].

3. Principal PAI modes

Photoacoustic imaging (PAI) is often executed via one of three primary modalities: photoacoustic microscopy (PAM), photoacoustic computed tomography (PACT), or photoacoustic endoscopy (PAE) (Fig. 1a). In PAM33, volumetric imaging is performed by two-dimensional raster scanning of the dual foci of optical excitation and ultrasonic detection (Fig. 1b) [33]. At each scanning point, the ultrasonic transducer captures photoacoustic signals along the line stimulated by the laser light, documenting the acoustic time-of-arrival and generating a one-dimensional picture in the depth direction. PACT22 employs an enlarged laser beam to light biological tissue and utilizes an ultrasonic transducer array to simultaneously detect photoacoustic waves from various

angles (Fig. 1c) [34]. Image reconstruction, fundamentally the advanced triangulation of optical absorbers from time-resolved ultrasonic signals, is used to recover PACT pictures. PAE35, a modification of PAM and PACT, is meant to fit into an endoscope for viewing interior organs [35].

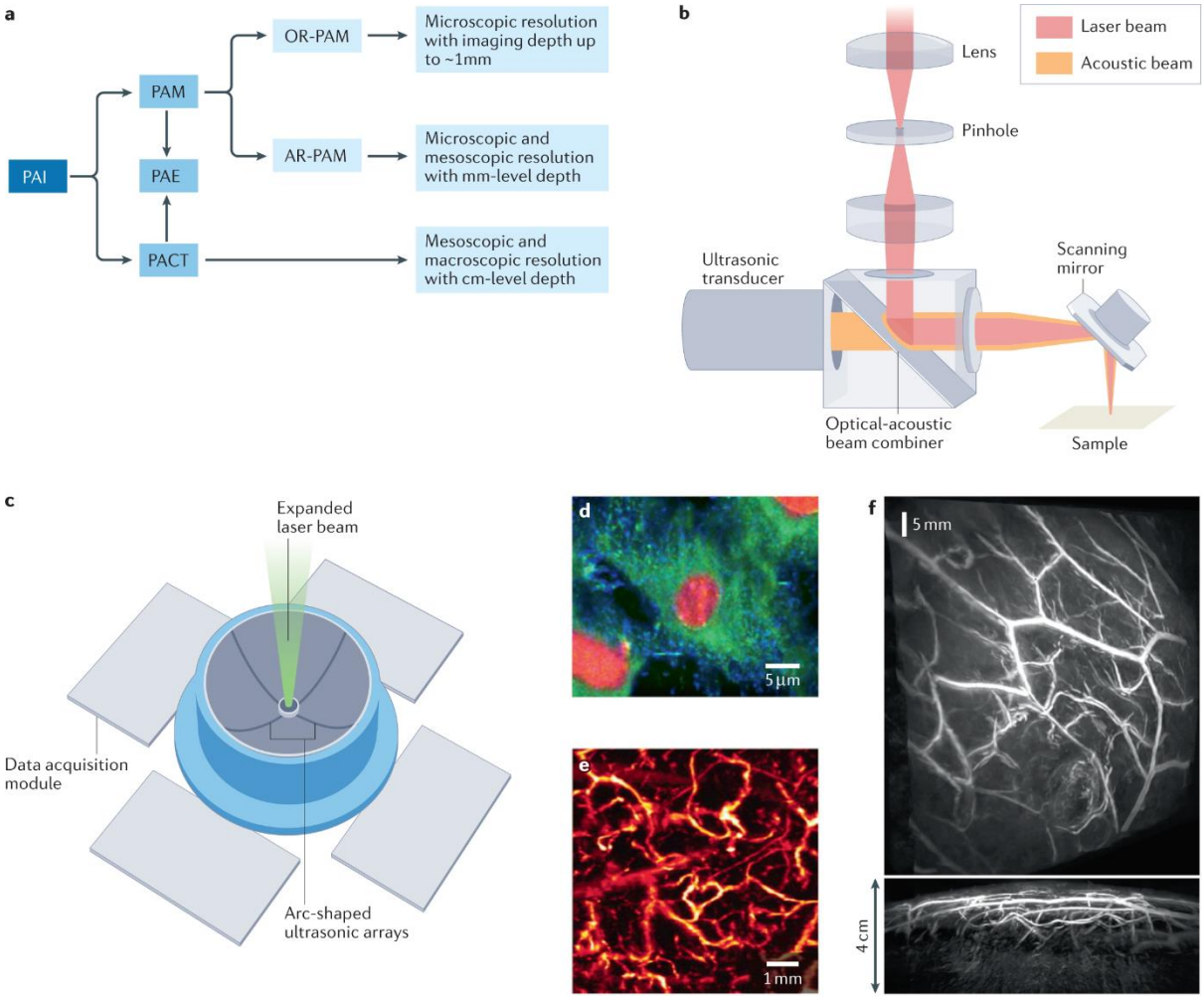

Figure 1: Exemplary setups and illustrations of photoacoustic imaging.

4. Scalable high-velocity imaging

PAM typically offers microscopic and mesoscopic resolution at a millimeter-scale imaging depth (Fig. 1d,e), whereas PACT allows tissue imaging to depths of several centimeters at mesoscopic and macroscopic resolution levels (Fig. 1f). In comparison to PAM, PACT often offers enhanced tissue penetration, an expanded field of view (FOV), and increased imaging speed, albeit this comes with elevated equipment and computational expenses.

PAM may be further categorized into optical resolution (OR) and acoustic resolution (AR) based on whether the optical or acoustic focus is more refined. In OR-PAM, the optical focus laterally restricts photoacoustic excitation at the micrometer scale, with an imaging depth limited by optical diffusion to 1 mm in vivo (Fig. 1d). For imaging at depths beyond 1 mm, AR-PAM utilizes acoustic focusing to laterally restrict photoacoustic detection to tens of micrometers, achieving depths of several millimeters (Fig. 1e), primarily

constrained by frequency-dependent acoustic attenuation. PACT employs lower ultrasonic frequencies for detection, resulting in less susceptibility to acoustic attenuation, although at the expense of resolution compared to PAM [36]. Primarily constrained by light attenuation, PACT typically enables imaging depths of several centimeters with a resolution in the hundreds of micrometers (Fig. 1f). The standard ratio of image depth to spatial resolution in several PAI setups exceeds 100, establishing PAI as a high-resolution modality over extensive length scales [23]. The ideal balance between spatial resolution and imaging depth is contingent upon the application.

Modern high-speed OR-PAM systems, using a high-repetition-rate pulsed laser and a rapid scanner like a galvo mirror to direct optical and acoustic beams, may attain frame rates exceeding several hertz when imaging millimeter-scale three-dimensional areas [37,38]. High-speed PAM allows the visualization of dynamic events, such as blood flow redistribution in mouse models of non-fatal stroke, at microscopic levels; this technique may also be downsized for portable devices for imaging human skin [39-41]. PACT has been used for real-time two-dimensional and three-dimensional imaging by parallel acoustic detection. PACT may conduct a comprehensive scan of an extensive field of view, such as a whole human breast, within the confines of a single breath-hold lasting 10–15 seconds [5]. PACT has been used to assess functional brain activity during motor and linguistic activities in individuals who have undergone hemicraniectomy [42].

5. Contrasting mechanisms

Due to the unique optical absorption spectra of each fundamental biological component in an image, photoacoustic imaging (PAI) facilitates the in vivo mapping of diverse endogenous or exogenous chromophores by swiftly adjusting the excitation light to various wavelengths. Haemoglobin, myoglobin, melanin, water, lipids, and nucleic acids may all be imaged endogenously in this manner. The use of exogenous contrast ants, including nanoparticles and organic dyes, broadens photoacoustic imaging into the realm of molecular imaging [43,44].

6. Comparative anatomy and histology

Haemoglobin is a significant absorber among the chemical constituents of most tissues in the visible and short-wavelength near-infrared (NIR) spectra [45]. Consequently, PAI is inherently adept at distinguishing angiographic architecture without the need for ionizing radiation or injected contrast chemicals and has a high sensitivity for imaging tiny vasculatures, such as skin capillaries or breast arterioles. Angiogenesis, a pivotal factor in cancer progression, invasion, and metastasis, is a hallmark of cancer and may be identified and defined by PAI [46-50]. Moreover, PAI facilitates spectral distinction among several compounds, including water, lipids, proteins, and melanin. PAM utilizes the robust UV absorption characteristics of nucleic acids (including DNA and RNA) to photograph the nuclei of individual cells without staining, offering a label-free alternative to conventional ex vivo histological staining techniques [30].

7. Functional and molecular differentiation

Besides anatomical components, spectroscopic PAI allows the assessment of functional and molecular attributes, hence providing a more complete representation of the underlying physiological and pathological states. Functional imaging often demonstrates physiological activity at the organ or tissue level, while molecular imaging mostly depicts biological and pathological processes at the molecular level. Functional imaging typically assesses endogenous contrast, whereas molecular imaging employs exogenous contrast to designate in vivo biomarkers [51]. We categorize the functional contrast of PAI into hemoglobin oxygen saturation (sO2) and dynamic information and classify the molecular contrast agents into nanoparticles and organic dyes.

8. Oxygen saturation of hemoglobin

Haemoglobin is crucial for tissue metabolism as the principal oxygen transporter. By distinguishing the separate contributions of oxyhaemoglobin (HbO2) and deoxyhaemoglobin (HbR), the overall concentration (HbT) and degree of sO2 may be evaluated [45]. These two parameters are the most often used indicators of blood perfusion and oxygenation, respectively. sO2 may not be exclusively associated with the partial pressure of oxygen, however, sO2 maps have shown a strong association with cellular indicators of hypoxia [52,53]. In contrast to conventional sO2 measuring techniques, which often rely on diffuse optics, PAI offers superior spatial resolution within the optical diffusive domain [23].

9. Dynamic contrast

Due to its high imaging speed, PAI can capture hemodynamics, and tissue deformation, and give thermodynamic data, including temperature fluctuations, mostly in real time [54]. PACT has effectively been used to assess tissue deformation caused by respiration, revealing disparities in compliance between malignant and adjacent non-malignant tissues, hence offering a contemporaneous contrast-based technique for cancer detection. By using both static and dynamic contrast, PAI may elucidate variations in metabolic activity. For instance, by assessing artery diameter, hemoglobin total (HbT), oxygen saturation (sO2), the tissue volume of interest, and blood flow velocity, Photoacoustic Imaging (PAI) facilitates the evaluation of oxygen metabolism [55,56].

10. Nanoparticles and organic pigments

Nanoparticles may be tailored for a specific absorbance spectrum, and their bioconjugation facilitates the targeting of biomarkers in molecular imaging and medication administration [57,58]. Organic dyes may be swiftly eliminated from the body due to their diminutive molecular size, and several have received approval for therapeutic use. Alterations in tumor vascular permeability may be evaluated by imaging the extravasation of indocyanine green (ICG) [59]. Exogenous contrast chemicals may be advantageous in imaging structures with restricted optical absorption at certain wavelengths, such as lymph nodes, and in labeling diseased conditions [60].

11. Integrating with other imaging modalities

Integrating PAI with data from other recognized imaging modalities, such as ultrasonography and MRI, enhances the comprehensiveness of clinical imaging [61]. The integration of an ultrasonic scanner with the optical transmitting components necessary for photoacoustic imaging (PAI) effectively produces a hybrid ultrasonography and photoacoustic computed tomography (PACT) apparatus, using identical acoustic detection and data collecting methods. The morphological, functional, and molecular differences offered by PACT may be seamlessly coregistered with the ultrasound images [61]. In addition to the integration of ultrasonography, PACT may be integrated with additional imaging modalities. For instance, in a combined MRI and photoacoustic picture, centripetal blood veins are discernible in the tumor's center, illustrating the coexistence of two contrast processes within a single image [62]. PACT has been merged with fluorescence tomography for the concurrent collection of optical absorption and fluorescent or bioluminescent data [63]. PAM has been integrated with optical coherence tomography, as well as two-photon and confocal microscopy, to enhance image contrast via optical scattering and fluorescence [64-67].

12. Oncological identification

The majority of tumors do not exhibit significant morphological alterations in the first stages of growth. Consequently, physiological data is essential for the precise early identification of cancer [68,69]. Leveraging the heightened sensitivity of photoacoustic imaging (PAI) for tumor-associated hypoxia and angiogenesis, early cancer detection is now one of the most promising uses of PAI and is nearing clinical translation [70,71]. This debate categorizes research using PAI for cancer detection into four groups: breast cancer screening, skin cancer imaging, prostate cancer detection, and early investigations of other malignancies.

13. Screening for breast cancer

Breast cancer is the most often diagnosed malignancy and the second primary cause of cancer-related mortality among women in the USA. Timely identification of breast cancer facilitates enhanced patient care and survival rates. An optimal breast cancer screening method facilitates cancer diagnosis with elevated sensitivity and specificity, little risk of adverse events, reduced operator reliance, rapid acquisition speed, and cheap operating expenses. At now, all FDA-approved imaging systems can only partly meet these requirements, offering supplementary information and benefits derived from various cancer screening approaches. Mammography is widely employed for breast cancer screening; however, its sensitivity diminishes in women with dense breast tissue (24–47% in those with heterogeneous dense breasts versus 71–78% in women with fatty breasts) and involves ionizing radiation, thereby elevating the risk-to-benefit ratio [72-74]. Ultrasonography has been used as a supplementary method to mammography-based screening; nevertheless, there is significant potential for enhancement due to its poor specificity (65–89%), operator reliance, and the possibility of speckle artifacts [73,75].

Similar to other solid tumors, breast cancers need the development of new blood vessels (via neovascularization or angiogenesis) to expand beyond a few millimeters in diameter

[76]. A plethora of clinical data demonstrates that angiogenesis begins at the breast cancer in situ stage or earlier. Evidence also suggests an elevation in blood channel density in the pathophysiology of simple breast hyperplasia [77,78]. Alongside the heightened density and irregular appearance, these newly created capillaries often exhibit higher permeability, facilitating the delineation of the tumor by the extravasation of gadolinium (or ICG), detectable using contrast-enhanced MRI (CE MRI) (or PACT). Angiogenesis and its underlying stimulation, local hypoxia, may serve as natural sources of imaging contrast for PACT, irrespective of breast density, hence providing further physiological information to existing breast screening techniques. From a technical standpoint, an effectively constructed breast PACT system must include optimum setups for optical illumination and auditory detection [79].

14. Conclusions

In the last decade, the clinical use of PAI has advanced due to enhanced availability to multichannel data collecting systems and customized large-scale ultrasonic arrays. Multiscale PAI with uniform contrast may significantly impact biomedicine by offering scalable high spatial resolution and imaging depth, hence facilitating a comprehensive comprehension of biological activities, ranging from organelles to organs. PAI has shown potential in offering direction for cancer screening, diagnosis, and therapy. PACT has been effectively utilized to identify breast tumors through their associated angiogenesis and relative stiffness, has facilitated the diagnosis of these lesions by evaluating blood oxygen saturation and vascularity, and has been employed to assess treatment responses by analyzing alterations in anatomy and function.

In early 2021, the FDA authorized the first PAI system for breast cancer diagnostics. PAM and PACT have been used in human skin to outline skin cancer lesions, monitor circulating cancer cells, and identify melanoma metastases in sentinel lymph nodes (SLNs). PAE has shown efficacy in identifying prostate cancer and the capability to see additional interior organs. PAM has shown potential as an intraoperative technique for evaluating cancer margin status, hence eliminating the need for fixation, staining, or sectioning of the excised specimens. When used with contrast agents, photoacoustic molecular imaging is anticipated to enhance precision medicine by delivering a more accurate diagnosis that facilitates more effective therapy.

In conclusion, PAI has been engineered to provide superior imaging capabilities and may serve as the foundation for several extensive clinical applications. Nonetheless, extensive and committed comparative clinical research is necessary to determine the additional benefits of certain uses. Integrating evidence-based practices into healthcare processes is crucial. From the application standpoint, substantial efforts are being undertaken to achieve effective clinical translation. To enhance cancer screening, the dependability of PAI must be augmented by the standardization of both the technology and its implementation. Radiologists are expected to be the first adopters of this technology, requiring specialized training to evaluate the novel information and picture

characteristics obtained from PAI devices, which can be seamlessly linked with ultrasonography.

To enhance cancer detection, more comparative clinical data are necessary to create a diagnostic model that demonstrably improves and can be included in the existing workflow. In addition to direct cancer detection, PAI may enhance current diagnostic techniques, such as core needle biopsy sampling, via the creation of bespoke PAI systems. PAI may provide insights into the impact of treatments in cancer therapy. For instance, anti-angiogenesis medication has shown efficacy just in a subgroup of cancer patients208, who may possess similar angiographic anatomy. Consequently, PAI may serve as a predictive instrument and enhance therapy results by prompt monitoring. The advancement of these diverse methodologies in clinical settings necessitates a shift from fragmented and limited feasibility studies to comprehensive, application-focused, large-scale prospective clinical trials aimed at pinpointing particular enhancements to current processes.

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التطورات في التصوير الصوتي الضوئي: تعزيز اكتشاف السرطان ومراقبة العلاج

الملخص

الخلفية :يُعد التصوير الصوتي الضوئي (PAI) تقنية مبتكرة تجمع بين الإثارة البصرية والكشف الصوتي، مما يوفر تقدمًا كبيرًا في التشخيصات السريرية، لا سيما في مجال الأورام. بفضل قدرته على تقديم صور عالية الدقة ومعلومات جزيئية مفصلة دون استخدام الإشعاع المؤين، يكتسب التصوير الصوتي الضوئي زخمًا في اكتشاف السرطان ومراقبة علاجه.

الطرق :يُقدم هذا الاستعراض تحليلًا للتطورات الحديثة في التصوير الصوتي الضوئي وتطبيقاته في الإعدادات السريرية. تم إجراء تحليل شامل للدراسات التي تمت مراجعتها من قبل النظراء خلال العقدين الماضيين، مع التركيز على كفاءة التصوير الصوتي الضوئي في التطبيقات المختلفة في مجال الأورام، بما في ذلك سرطان الثدي والجلد والبروستاتا. يستعرض الاستعراض أيضًا دمج التصوير الصوتي الضوئي مع تقنيات التصوير الأخرى وتطوير عوامل تباين جديدة.

النتائج :أثبت التصوير الصوتي الضوئي قدراته المذهلة في تحديد وتوصيف الأورام من خلال حساسيته للهياكل الوعائية ومستويات تشبع الأكسجين. تشير الدراسات إلى أن التصوير الصوتي الضوئي يمكنه الكشف عن الأورام في مراحلها المبكرة بدقة وحساسية عاليتين، مما يوفر بديلًا غير جراحي لتقنيات التصوير التقليدية. وقد وافقت إدارة الغذاء والدواء الأمريكية (FDA) مؤخرًا على نظام تصوير صوتي ضوئي لتشخيص سرطان الثدي، مما يؤكد أهميته السريرية.

الاستنتاج :يُعد دمج التصوير الصوتي الضوئي في الممارسات السريرية مسارًا واعدًا لتعزيز فحوصات السرطان وتشخيصه وتقييم العلاج. ومع تقدم الأبحاث، سيكون توحيد تقنية التصوير الصوتي الضوئي وتدريب المهنيين الصحيين أمرًا بالغ الأهمية لاعتماده على نطاق واسع. ستُعزز التطورات المستمرة في عوامل التباين وتقنيات التصوير دور التصوير الصوتي الضوئي في الطب الدقيق.

الكلمات المفتاحية :التصوير الصوتي الضوئي، الأورام، عوامل التباين، اكتشاف السرطان، التطبيقات السريرية.