



Advances in Application of New Ultrasound Technologies in Prostate-Targeted Biopsy

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Abstract

Transrectal Ultrasound (TRUS)-guided systematic biopsy of the prostate is the current “gold standard” for biopsy of the prostate gland. However, for saturated systematic biopsy, blindness and randomness are inevitable. Prostate-targeted biopsy emerged with the continuous development of precision medicine. This procedure can not only reduce the number of biopsy needles but also improve the accuracy of biopsy; it has become a new trend in the diagnosis of prostate cancer. In this article, the up-to-date research data about new ultrasound technologies in prostate-targeted biopsy, such as contrast-enhanced ultrasound, ultrasound elastography, magnetic resonance imaging-TRUS fusion, and the combination of ultrasound and artificial intelligence, were reviewed to guide targeted biopsy.

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Introduction

Prostate Cancer (PCa) ranks second in the incidence of male malignancies in the world and ranks first in Europe, seriously threatening the health of men [1]. From 1992 to 2017, owing to various factors, such as changes in lifestyle, aging population, and environmental pollution, the crude death rate of male PCa in China (1/100000) rose from 3.39 to 7.17. PCa is known as a “silent killer” and is hard to detect in the early stage. Most patients have progressed to advanced stage at the time of diagnosis, therefore, missing the optimum period for surgical treatment. Consequently, the accurate diagnosis and treatment of early PCa have become new trends in medical development. The consensus statement on early PCa diagnosis by the European Urological Association indicates the following [2,3]: first,

suspected cases are determined through the detection of tumor markers, such as prostate-specific antigen (PSA), and digital rectal examination (DRE); second, based on different situations, further selection of transabdominal or rectal ultrasound, multi-parametric magnetic resonance imaging (mpMRI) and other imaging examinations is performed for the accurate diagnosis of suspected lesions; third, pathological diagnosis is obtained by transrectal ultrasound (TRUS)-guided systematic biopsy. The six-core systematic biopsy has been gradually accepted by scholars from various countries since it was proposed in 1989 [4], and related research based on systematic biopsy has achieved considerable progress. However, TRUS is not sufficiently sensitive nor specific for biopsy procedures because this technology encoun-



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ters difficulty in distinguishing PCa by using standard grayscale or Doppler imaging from the echo performance of diseases, such as benign prostatic hyperplasia and prostatitis [5]. The accuracy of its diagnosis and guidance of biopsy often depends on the physician's experience and skills, which are subjective to a certain extent. The limitation of this approach have been recognized, several experts [6] have put forward an 8-20 core systematic biopsy technology, including saturation biopsy. Increasing the number of biopsies improves the detection rate to a certain extent, but the advantage is offset by the harmful effects, such as bleeding, infection, and anxiety and the increased detection of clinically insignificant PCa (cisPCa), leading to over diagnosis and overtreatment of microscopic tumor foci. Prostate-targeted biopsy technology emerged with the development of precision medicine. The imaging technologies currently available for guiding targeted biopsy include TRUS and MRI. Although TRUS is inferior to MRI in the diagnosis of PCa, the simplicity of guiding prostate biopsy and the popularization and application of new ultrasound technologies in recent years have successfully compensated for this deficiency. Prostate-targeted biopsy guided by new ultrasound technologies, such as contrast-enhanced ultrasound (CEUS), ultrasound elastography, MRI-TRUS fusion, and artificial intelligence (AI), have shown excellent advantages in accurate diagnosis. This article reviews the application and progress of new ultrasound technologies in prostate-targeted biopsy in recent years (Figures 1 & 2).

CEUS-guided targeted biopsy

The increase in the metabolism and oxygen demand of PCa cells depends on the formation of tumor microvessels [7]. If the changes in blood flow in these tissues can be visualized, the accuracy of detecting PCa may be improved. The signal-to-noise ratio can be enhanced by using microbubble ultrasound contrast agents to improve the sensitivity of detection of blood flow. Therefore, CEUS can objectively evaluate the changes in semi-quantitative parameters of blood flow and directly display the microvascular network in PCa lesions. This technology has several potential uses, including guided targeted biopsy, real-time evaluation and confirmation of treatment during cancer ablation, and detection of cancer recurrence after ablation, in the diagnosis and treatment of PCa. Traditionally, the results of PCa angiography are defined as rapid contrast enhancement. PCa with a large lesion area shows uneven enhancement in CEUS, which is caused by the rapid growth of tumors leading to central ischemic necrosis and uneven tumor blood vessel thickness and distribution.

CEUS can be used to select target patients with high-risk PCa, as recently emphasized in a prospective cohort study by Zhu et al. [8], who compared systematic biopsy with CEUS-targeted biopsy. This study reported that CEUS can improve the detection rate of clinically significant PCa (csPCa), especially for patients with PSA ≤ 10 ng/ml and prostate volume between 30 and 60 ml. Consistent with this notion, Koh et al. [9] compared the positive rate of single-needle PCa with CEUS-targeted and systematic biopsies. The positive rate of single-needle biopsy with targeted biopsy was 16.4%, which was significantly higher than that of systematic biopsy (11.4%). Similarly, a recent comparative study [10] was conducted on 82 patients who were scheduled to undergo prostate biopsy. The results showed that the positive rate of systematic biopsy plus CEUS-targeted biopsy was 72.1%, which was strongly higher than that of systematic biopsy alone (42.8%). Xie et al. [11] argued that CEUS has more advantages than TRUS in detecting PCa in different areas, but CEUS is more likely to miss the lesions in apex; thus, we also need to pay attention to the apex prostate tissue when performing CEUS, and other imaging methods can be possibly combined to improve the visualization of PCa.

Various new-generation contrast agents have been developed in decades to improve the visualization of CEUS. Yuan's team [12] introduced the SonoVue microbubbles carrying six-transmembrane epithelial antigen of the prostate-1 (STEAP-1) for CEUS examination of PCa in nude mouse xenograft models. The results emphasized that SonoVue microbubbles carrying STEAP-1 can improve the ultrasound visualization of PCa and identify tumors more effectively, but further prospective studies are needed to verify the findings. Ding et al. [13] further demonstrated the optimized prostate-specific membrane antigen and used single-chain variable fragment loaded nanobubbles as new targeted ultrasound contrast agent for diagnosis of PCa, thus opening the way for further clinical trials.

One of the disadvantages of CEUS is the potential for human error. CEUS may also be unideal for the diagnosis of early unformed, infiltrative growth, or small-volume PCa, because of the small volume or low Gleason score observed with new blood vessels, similar to the CEUS performance in normal prostate tissue. The contrast agent passes through the prostate tissue for a short time, and only the suspicious section of two-dimensional (2D) gray-scale ultrasound can be used as the observation section. Thus, the diagnosis of gray-scale ultrasound without ab-

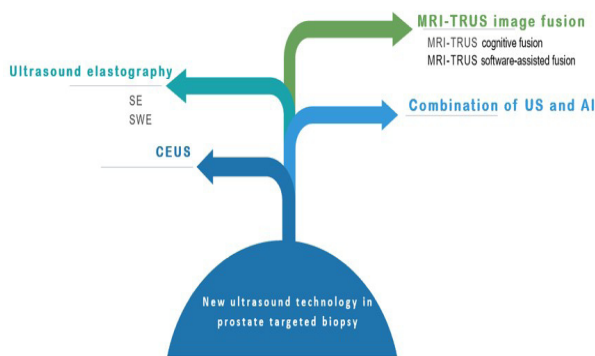


Figure 1: New ultrasound technologies in prostate-targeted biopsy.

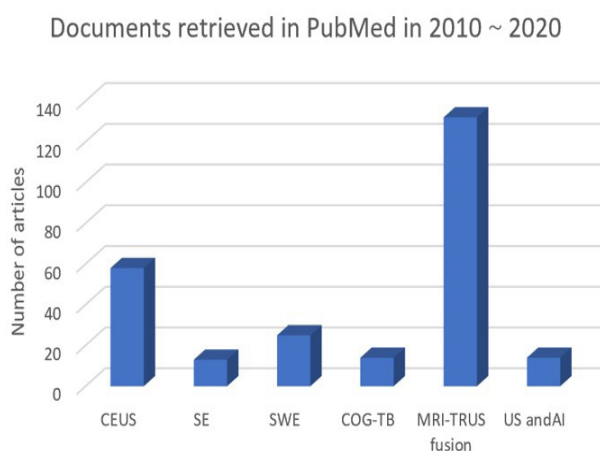


Figure 2: Literature search was performed through the PubMed database using the keywords, "prostate biopsy" combined with "contrast-enhanced ultrasound," "strain elastography," "shear wave elastography," "MRI-TRUS cognitive fusion," "MRI-TRUS fusion," and "artificial intelligence."

normal lesions might be missed. Consequently, Qi et al. [14] used multi-plane ultrasound as a supplement to conventional CEUS, with a sensitivity of up to 92.3%, thus further improving the detection rate of PCa.

These results indicate that CEUS-targeted biopsy provides improved accuracy of prostate biopsy to a certain extent, but it is influenced by the subjective interpretation of physicians. Improving the identification of cancerous lesions and normal tissues is the breakthrough point of future research.

Ultrasound elastography-guided targeted biopsy

Tissue hardness is considered a biomarker of histopathology [15]. Most of the research [16] in prostate has emphasized that compared with the surrounding normal tissues, the average hardness of PCa increases by (2.5 ± 0.8) times with the increase in cell density and the changes in collagen distribution. In normal conditions, urologists understand the hardness of prostate through DRE. However, this finding is highly dependent on the personal experience of urologists, and only cancerous lesions in the peripheral zone of the prostate can be touched. Ultrasound elastography is a novel technology that reflects information about the elasticity and hardness of individual tissues [17]. This technology can express tissue hardness as a proportional-constant Young's modulus (E), which represents the force or strain force per unit area, and the resulting relative change in tissue size or strain. Elastography techniques have been developed based on two principles: the first kind uses quasi-static elastography (SE), and the second utilizes shear wave elastography (SWE).

SE

SE measures tissue hardness by applying external pressure to the tissue. Strain refers to the deformation of tissues due to the application of pressure. The E formula for SE is $E = \sigma/\epsilon$, where σ represents the external applied pressure, and ϵ denotes the strain [18]. The strain ratio is the ratio of the strain in the target tissue area to that in the tissue reference area, and it is commonly used in clinical practice because the calculation of strain ratio requires no prior knowledge of the applied pressure [19]. SE was first used to detect the elasticity of superficial organs; its maximum tissue penetration depth is 3-4 cm, which is insufficient to correctly distinguish benign and malignant prostate deep tissues with large volume [20].

Zhu et al. [21] pointed out that compared with systematic biopsy, SE-guided targeted biopsy has a higher detection rate of PCa. Moreover, their study revealed a negative correlation between prostate volume and targeted biopsy detection rate. Chang et al. [22] examined the addition of SE and CEUS to guided targeted biopsy; the area under the receiver operating characteristic curve of the PCa detection when combining the application of the two methods reached (0.921 ± 0.023) , which is higher than that of CEUS and SE (0.88 ± 0.029) and (0.80 ± 0.038) , respectively. Nygard et al. [23] combined SE and PCa gene 3 scores of 124 patients with suspected PCa and demonstrated that the combination of the two methods compensates for the lack of gray-scale ultrasound imaging, thus improving the visualization of malignant regions in the prostate. These results indicate that the SE-guide targeted biopsy alone cannot yield a satisfactory detection accuracy, but the joint inspection of other methods can obtain a desirable detection rate.

Both elastography ultrasound technologies have limitations. SE-guided targeted biopsy has high requirements for operating

physicians. In addition to the limited range of motion of the probe in the rectal cavity and attenuation of force conduction, the application of pressure to the prostate to maintain uniform force on all parts is difficult, which will affect the accuracy of targeted biopsy. Therefore, the role of SE in PCa needs further investigation.

SWE

SWE is a new ultrasonic elastic quantification technology, which uses multi-beam focused ultrasound to generate shear wave in tissues [24]. This technology needs no applied pressure to the tissue, thus avoiding the error caused by different pressures of the human body. Consequently, this method has the advantage of being objective. SWE can quantitatively measure E of the tissue. The larger the E , the faster the shear wave speed and the greater the hardness of the biological tissue [25]. However, the cut-off point for the best diagnostic efficiency between PCa and prostate benign disease remains uncertain [26].

Wildeboer et al. [27] examined the PCa detection rate of B-mode, SWE, and CEUS. For the per-patient comparison, SWE alone showed no overwhelming improvement in the overall performance over that of B-mode and CEUS. Meanwhile, the combination of three methods demonstrated a higher PCa localization capability compared with SWE alone. Xiang et al. [28] reported that for suspected PCa patients who are negative for MRI, increasing the SWE test can improve the diagnosis rate and reduce the false negative rate. Shoji et al. [29] advocated that prostate imaging-reporting and data system (PI-RADS) combined with 3D SWE measurement of E can significantly improve the diagnosis of csPCa. Their study also implied a significant correlation between the tissue elasticity of the lesion and Gleason score. In recent years, medical experts have also conducted a number of related studies [30]. Most of the studies indicated that SWE can provide important information for PCa detection, thus improving the guiding capability and reducing the requirement of unnecessary core biopsies.

A disadvantage of SWE is that the sampling frame needs to be left in the area of interest for 3 s, and the patients need to temporarily hold their breath, because the frame is easily affected by respiratory movement during operation. Second, false positives will be present if calcification occurs in the elastic region, because the shear wave propagates fast in solids. Third, when the PCa lesion is located in the deep side, the color filling defect in the SWE sampling frame is large, and poor image quality is likely to cause missed diagnosis.

In conclusion, SWE can reliably display the elastic characteristics of PCa, providing information for the detection of PCa and biopsy guidance reasonably [31,32]. However, systematic diagnostic criteria and more large samples of data are needed to achieve more accurate diagnosis results. Still, we strongly believe that the use of SWE will create a new era of cancer diagnosis, especially for PCa.

MRI-TRUS image fusion-guided targeted biopsy

MRI has evident advantages in identifying local infiltration and peripheral metastasis of PCa [33]. The joint application of multi-sequence imaging in decades has greatly improved the diagnostic capability for PCa. A previous study [34] stated that obtaining mpMRI information of patients before biopsy can improve the detection of csPCa, but the need for systematic biopsy cannot be avoided. However, MRI-directed targeted biopsy is not routinely used due to its cost, time-consumption,

and complicated operation. Despite the availability of related studies [35], its wide application in clinical practice is difficult. Thus, several scholars have proposed that patients with negative TRUS but positive MRI can undergo TRUS combined with MRI to perform targeted biopsy in suspicious malignant areas. MRI-TRUS image fusion technology allows urologists to progress from blind, systematic biopsy to targeted and tracked biopsy. At present, this method is recommended in international guidelines [36]. MRI-TRUS image fusion has been described either cognitively or assisted by software.

Cognitive fusion-targeted biopsy (COG-TB)

In COG-TB, a physician carefully reads the patient's MRI image to form an impression of the suspected lesion in the mind and simply aims the biopsy needle at the suspected prostate area. This technique is the same as a general TRUS-guided prostate biopsy but requires no additional training and facility beyond MRI and conventional ultrasound equipment. Although simple and low-priced, this method is prone to errors because of the wrong registration caused by the incorrect judgment of the lesion location. American Urological Association and Society of Abdominal Radiology stated that COG-TB is still an equitable method in resource-poor circumstances [37]. Kuliš et al. [38] performed COG-TB on patients who persistently presented elevated PSA despite prior negative systematic biopsy. Although the data are limited, COG-TB yields improved accuracy over systematic biopsy and provides a valuable supplement to systematic biopsy. However, COG-TB is inferior to other MRI-targeted biopsy [39,40]. According to a previous study [41], COG-TB missed more than 50% csPCa lesions, whereas MRI-TRUS fusion accurately identified all lesions. However, Xu et al. [42] suggested that in patients with high PI-RADS score and large lesion volume, the accuracy of COG-TB in locating suspicious lesions is consistent with that of MRI-TRUS fusion.

COG-TB is easy to operate and requires no additional economic and time costs. However, this method lacks the use of a software image fusion. Thus, this procedure highly depends on the physician's prostate anatomy, imaging knowledge and spatial imagination. Therefore, in the actual biopsy operation, false negative biopsies may be obtained for lesions with small size and lesions in special parts such as the urethra.

Software-assisted targeted biopsy

MRI-TRUS software-assisted fusion-guided targeted biopsy requires pre-biopsy mpMRI data, which are obtained and stored in a specific device. During the biopsy session, the fusion software enables the real-time TRUS imaging, and pre-stored MRI images are fused to locate the lesion and guide the targeted biopsy. This method plays a complementary role in systematic biopsy and provides an objective basis for the development of clinical diagnosis and treatment plans. This condition was recently implied in a prospective cohort study by Siddiqui et al. [43], who studied 1003 suspected PCa patients with elevated PSA or abnormal DRE results. Their study examined the PCa detection rate of MRI-TRUS software-assisted fusion-guided targeted biopsy, systematic biopsy, and combined biopsy (targeted + systematic). Patients with high-risk PCa (Gleason score $\geq 4+3$) diagnosed by targeted biopsy showed superior results to those who underwent systematic biopsy; the combined biopsy additionally diagnosed 22% of PCa patients. The study stated that MRI-TRUS software-assisted fusion-targeted biopsy demonstrated high detection rate of csPCa, but systematic biopsy should not be eliminated. Fourcade et al. [44] demonstrated

that the positive detection rate of targeted biopsy using MRI-TRUS software-assisted alone showed no significant increase compared with systematic biopsy, whereas the combined application of these methods are of great value for the diagnosis and prognosis of PCa but limited in the diagnosis of cisPCa. A recent study [45] indicated that the best choice for patients who undergo MRI-TRUS software-assisted fusion-targeted biopsy is the targeted biopsy-added lateral six-core systematic biopsy. In a study by Mischinger et al. [46], a comparative study of MRI-TRUS robotic-assisted and software-assisted fusion-guided targeted biopsy and systematic biopsy suggested that the two methods had no statistically significant difference in the detection rate of PCa, but the number of targeted biopsy needles of the former was significantly less than that of systematic biopsy, which will become one of the forefronts of prostate-targeted biopsy.

Scanning the prostate with an ultrasound cavity probe will inevitably squeeze the prostate, which will cause the calibration deviation of the prostate MRI and TRUS images. Therefore, image registration is a critical component of MRI-TRUS software-assisted fusion owing to the huge appearance difference between the two methods. In the past, several scholars implanted markers in the prostate for registration. However, this method is invasive and unsuitable for clinical promotion. A recent study [47] showed that the similarity metric of learning with deep neural network can be used to evaluate the MRI-TRUS registration, which can reduce the image reconstruction time, improve image accuracy, and reduce operation complexity. The hardware and software equipment and biopsy platforms for MRI-TRUS image fusion-targeted biopsy, such as Artemis (Eigen, USA), BiopSee (Pi Medical, Greece), and Logiq 9 (GE Healthcare, UK), are gradually becoming commercially available [48]. However, the use of a fusion device, makes the MRI-TRUS software-assisted fusion-targeted biopsy costlier than systematic biopsy.

Through the continuous maturation and development of image fusion algorithms, combining the advantages of high intrinsic contrast of MRI with TRUS, which is convenient, fast, and enables real-time imaging, MRI-TRUS software-assisted fusion-guided prostate-targeted biopsy is likely to show extremely high clinical application prospects.

Combined ultrasound and AI-guided targeted biopsy

Currently, TRUS-guided prostate systematic biopsy still mainly relies on traditional computer vision technology. Human error is inevitable in biopsy, and the accuracy of diagnosis has not reached the desired effect. The application of AI technology can provide new solutions to the current dilemma of PCa diagnosis. In the auxiliary diagnosis of prostate diseases, studies [49,50] are focused on the intelligent analysis and processing of prostate MRI. With the development of computer and information technology, a variety of ultrasound image intelligence-assisted diagnosis and analysis systems are being developed to predict benign and malignant prostate lesions, which have become a tendency in PCa diagnosis. The first and best clinical test result to date comes from the artificial neural network (ANN) analysis computerized TRUS (ANNACTRUS) system. An ANN is a system that uses a physical operating system to imitate the structure and working mode of the human brain neural network; it is also an outstanding representative of using machines to simulate human brain intelligent activities [51]. As early as 1999, the team of Professor Loch of Kiel University in Germany acted as pioneer in applying ANN to TRUS images for analysis and labeling and attempted to build an ANNACTRUS prostate-targeted bi-

opsy system [52]. Thorsten et al. [53] and Antoine et al. [54] further verified the feasibility of ANN intelligence-assisted prostate biopsy. Experimental studies have demonstrated that ANNACTRUS targeted biopsy can not only improve early PCa diagnosis sensitivity, specificity, cost-effectiveness, and patient comfort but also detect low-risk PCa easily. More recent studies by Tokas [55] followed up 71 patients with suspected PCa and who underwent ANNACTRUS targeted biopsy for 12 years; the results showed that ANNACTRUS is an effective method for monitoring suspicious PCa patients and can be used as an alternative for repeated systematic biopsy. A recent study [56] enabled a targeted prostate biopsy system by improving architecture and training of the network to provide a real-time prostate segmentation. Wang et al. [57] used four methods: ANN, support vector machine (SVM), least squares SVM, and random forest (RF) to construct a PCa prediction model. The study advocated that the accuracy of ANN in the detection of csPCa, sensitivity, and F1 scores were the highest, and RF is suitable to distinguish malignant and non-malignant prostate lesions and further identify csPCa. Feng et al. [58] innovatively proposed a deep learning framework based on 3D convolutional neural network to uniformly extract spatiotemporal features from continuous CEUS images to detect PCa; the specificity and average accuracy of this method for PCa CEUS image detection reached 91% and 90%, respectively. This finding suggests that the combination of AI and other ultrasound modalities is expected to improve the visualization of PCa and can be used as the focus of further research.

AI can not only analyze the imaging information of PCa but also integrate a patient's other diagnosis and treatment information, thus improving the accuracy of prostate-targeted biopsy and effectively monitoring the progress of PCa. However, AI still needs to overcome the limitations of PCa diagnosis, such as the lack of extensive multi-center test, unified industry standards and sharing and privacy issues. With the continuous development of AI, the development of new ultrasound imaging intelligence-assisted diagnosis technology will bring huge changes to the diagnosis process and treatment mode of PCa [59,60]. At the same time, we can use the commonality of medical images to promote the development of AI in the field of medical image analysis.

Summary and outlook

The development process of prostate biopsy is inextricably linked with the rapid development of modern science and technology. In the present era, TRUS-guided systematic biopsy still occupies an irreplaceable position in the diagnosis of PCa despite its limited sensitivity. Prostate-targeted biopsy is receiving clinical attention due to its advantages, such as excellent accuracy, low number of needles, and low complications. However, no evidence indicates that targeted biopsy can be used as a substitute for systematic biopsy. CEUS and ultrasound elastography-guided prostate-targeted biopsy improves the accuracy of prostate biopsy to a certain extent, but several PCa lesions are not displayed under ultrasound. MRI-TRUS fusion-guided targeted biopsy takes advantage of two imaging tests, avoids the blindness of biopsy, and reduces overdiagnosis and is worthy of clinical application. AI, as a highly innovative scientific field, has become a research topic and has received considerable attention in the diagnosis of PCa. Multiparametric ultrasound technologies, such as the combination of CEUS and SWE, have been widely investigated in the diagnosis of PCa [61]. This condition prompts us to select the most favorable diagnosis scheme based

on the comprehensive evaluation and analysis of patient condition. However, several problems remain unresolved for the new ultrasound technologies in prostate-targeted biopsy. At this stage, data support from multiple centers and large samples are needed to achieve the accurate diagnosis of PCa.

With the increase in operator expertise and reduced costs, the broad prospects of new ultrasound technologies in prostate-targeted biopsy are undoubted. As increasing evidence becomes available, we can look forward to the bright future of ultrasound prostate-targeted biopsy with the ultimate aim of replacing "blind" systematic biopsy with trustworthy targeted biopsy.

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