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ORIGINAL ARTICLE

Comparison of contrast-enhanced ultrasound targeted biopsy versus standard systematic biopsy for clinically significant prostate cancer detection: results of a prospective cohort study with 1024 patients

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Abstract

Purpose To assess contrast-enhanced ultrasound (CEUS) targeted biopsy (TB) for clinically significant prostate cancer (PCa) detection compared with systematic biopsy (SB).

Methods A total of 1024 consecutive patients scheduled for prostate biopsy were enrolled in this prospective study. CEUS was performed by an experienced radiologist blinded to all clinical data. Suspicious lesions on postcontrast images were sampled in addition to standard 12-core SB. The clinically significant PCa detection rate by CEUS-TB was evaluated in comparison with SB in the total cohort and in different subgroups.

Results In 378 of 1024 patients (36.9%), the diagnosis of PCa was histologically confirmed. PCa was detected by CEUS-TB in 306 patients (29.9%, 306/1024) and SB in 317 patients (31.0%, 317/1024, $P=0.340$). Among 378 PCa patients, 326 (86.2%, 326/378) were diagnosed with significant PCa using Epstein criteria. The significant PCa detection rate of CEUS-TB was 28.7% (294/1024), which was higher than that of SB (25.3%, 259/1024, $P=0.000$). CEUS-TB resulted in 67 additional cases of clinically significant PCa, including 51 patients missed by SB and 16 patients under-graded by SB. Conversely, SB detected 32 additional significant PCa missed by TB. In the subgroup analysis, CEUS-TB yielded a higher significant cancer detection rate than SB in patients with a PSA level ≤ 10.0 ng/ml or prostate volume from 30 to 60 ml.

Conclusion The clinically significant PCa detection rate could be improved by the extra sampling of abnormalities on post-contrast images, especially in patients with a PSA level ≤ 10.0 ng/ml or prostate volume from 30 to 60 ml.

Keywords Prostate cancer · Contrast-enhanced ultrasound · Targeted biopsy · Neoplasm grading

Introduction

The current standard for diagnosing prostate cancer (PCa) relies on systematic biopsy (SB) strategy with a random deployment of biopsy needles to sample the prostate gland. Although the biopsy is performed under ultrasound guidance, there is usually no certainty whether the actual tumor is being biopsied. As a result, SB can miss or under-grade a substantial proportion of significant PCa due to sampling error [1, 2]. In addition, such a random biopsy strategy might also cause the overdiagnosis of clinically insignificant cancers, leading to potentially unnecessary treatment [3, 4]. Thus, it is critical to establish an ultrasound imaging-based targeted biopsy (TB) protocol for the diagnosis of clinically significant cancer early in its course while sparing those with

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clinically insignificant cancer from the morbidity of unnecessary treatment.

Compared with normal tissues, PCa tissues generally have an increased microvessel density [5]. More importantly, the microvessel density in PCa tissues is closely related to the Gleason Score (GS) and pathological T stage, which are important factors contributing to the significance of tumors [6]. The Doppler imaging technique was thus introduced to improve the PCa detection rate by imaging tumor vascularity [7]. However, only the larger feeding vessels and not the microvessels can be visualized using baseline Doppler imaging [8].

Contrast-enhanced ultrasound (CEUS) provides a practical solution to the problem of tumor microvessel imaging via the intravenous administration of microbubble contrast agents [9]. These blood pool contrast agents produce nonlinear scattering and hence allow contrast-specific imaging and the visualization of microvessels from the surrounding tissues. Previous studies have demonstrated that CEUS is more accurate than baseline Doppler imaging in diagnosing PCa [10]. Moreover, studies have also indicated that CEUS could be used to determine the tumor grade and image the extent of infiltration [11, 12]. From this perspective, our hypothesis is that CEUS allows for the accurate detection of clinically significant PCa. We designed a prospective study to compare the utility of CEUS-TB versus standard SB for clinically significant PCa detection in correlation with biopsy pathology.

Methods

This prospective study was approved by the regional ethics committee (no. XHEC-D-2012-004) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients before study inclusion.

Study population

The study was conducted from March 2014 to June 2017. The inclusion criteria were as follows: (a) men with an increased prostate-specific antigen (PSA) level and/or an abnormal digital rectal exam and (b) men scheduled for initial prostate biopsy within 1 week after CEUS. A total of 1094 consecutive patients met these criteria were recruited at our institute. The exclusion criteria were as follows: (a) clinically active urinary tract infection within 3 months ($n=21$); (b) treatment with a 5α-reductase inhibitor ($n=49$). Finally, 1024 patients were enrolled in this study with a mean age of 68.5 ± 8.3 years (35–88 years) and PSA level of 11.2 ± 6.4 ng/ml (0.23–34.84 ng/ml). The flow diagram for patient selection is shown in Fig. 1.

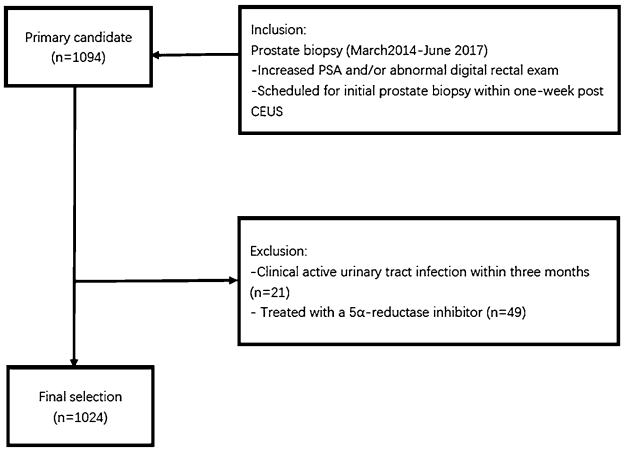

Fig. 1 Flow diagram of patient selection

Imaging protocol

Transrectal ultrasound was performed by an experienced radiologist (Z.Y., 7 years of experience in prostate CEUS) who was blinded to the clinical data. All patients were examined using the Logiq E9 (GE Medical, Wauwatosa, WI) ultrasound system with an IC5-9 endorectal probe. Baseline grayscale imaging was performed from the base to the apex. The prostate volume was calculated using the following formula: volume (ml) = 0.52 × height (cm) × length (cm) × width (cm). The PSA density (PSAD, ng/ml^2) was calculated using the PSA level (ng/ml) divided by the prostate volume (ml). Focal hypoechoic lesions or contour bulges on grayscale images were suspicious for malignancy. Power Doppler imaging was also performed from the base to the apex, and focal asymmetric/increased flow on power Doppler images was suspicious for PCa. After baseline imaging, CEUS was performed using the contrast-enhanced mode, with a probe frequency of RES, a dynamic range of 63 dB, and a mechanical index of 0.13. Post contrast images were obtained at equal trisections starting from the base, followed by the midgland and then the apex. If the patient had suspicious findings on baseline images, the corresponding plane was chosen to include the suspicious findings. A bolus injection of 2.4 ml of contrast agent (SonoVue, Bracco, Italy) was given for each contrast plane via a 20-gauge intravenous catheter, followed by a 5 ml saline flush. Each contrast plane was observed continuously for 90 s. During the examination, the radiologist applied the lowest pressure to the prostate gland from the probe to minimize the influence on blood flow. The time interval between the two contrast planes was approximately 4 min for thorough washout of the microbubbles. The entire examination time was approximately 30 min for each patient. After CEUS, all images were transferred to the workstation in DICOM format for further analysis.

CEUS image interpretation

All CEUS images were initially reviewed by two radiologists (Z. Y., the CEUS examiner, 7 years of experience in prostate CEUS, and J. J., 7 years of experience in prostate CEUS). In cases of discrepancies between the reviewers, the images were further evaluated by another senior radiologist (C.Y., 12 years of experience in prostate CEUS), and finally reached a consensus to determine the suspicious lesion for TB. The reviewers were blinded to all clinical data. The following criteria were used to assess suspicious lesions on CEUS (Fig. 2) [13, 14]: (1) increased focal contrast enhancement compared to adjacent tissue; (2) rapid contrast enhancement after contrast agent administration; and (3) focal no or low enhancement with an ill-defined border.

Biopsy protocol

The biopsy procedure was performed after image interpretation. Preparation for the procedure was performed using a standard method. Two independent groups of radiologists performed the SB and CEUS-TB procedures. For patients with suspicious lesions on CEUS, the TB procedure was performed by the first group of radiologists (C.Y., 12 years of experience in CEUS-TB, and Z.Y., 7 years of experience in CEUS-TB). Usually, 2–3 biopsy cores were sampled for each suspicious lesion. Following the TB procedure, a standard 12-core SB procedure was performed by another group of radiologists who were blinded to the CEUS results (Q.T. and L.W., with 5 years of experience each in prostate biopsy). Each biopsy core was immediately placed in the microbiopsy cassette and labeled to identify the location.

Histopathological assessment

All biopsy cores were analyzed by an experienced pathologist (G.W., 10 years of experience in prostate pathology) who was blinded to the imaging findings. Each biopsy core was reported as benign prostatic hyperplasia, inflammation, prostatic intraepithelial neoplasia or PCa with an assigned GS and tumor length. The GS was reported according to the recommendations of the International Society of Urological Pathology (ISUP) Consensus Conference [15]. The cancer core length was measured as the maximum length of cancer within the core in millimeters. For biopsy cores with discontinuous cancer, we measured the discontinuous cancer from one end to the other without subtracting out the intervening benign prostate tissue based on recommendation by Karram S. [16].

Clinically significant PCa was defined using Epstein criteria as any GS pattern 4 or greater, or GS 3 + 3 disease with core cancer involvement ≥ 50% or more than two cores positive [17]. Besides Epstein criteria, the significant PCa detection rate of CEUS-TB versus standard SB was also reevaluated using University College London (UCL) definition 1 (GS 4 + 3 and/or maximal cancer core length ≥ 6 mm, and/or total cancer core length ≥ 6 mm),

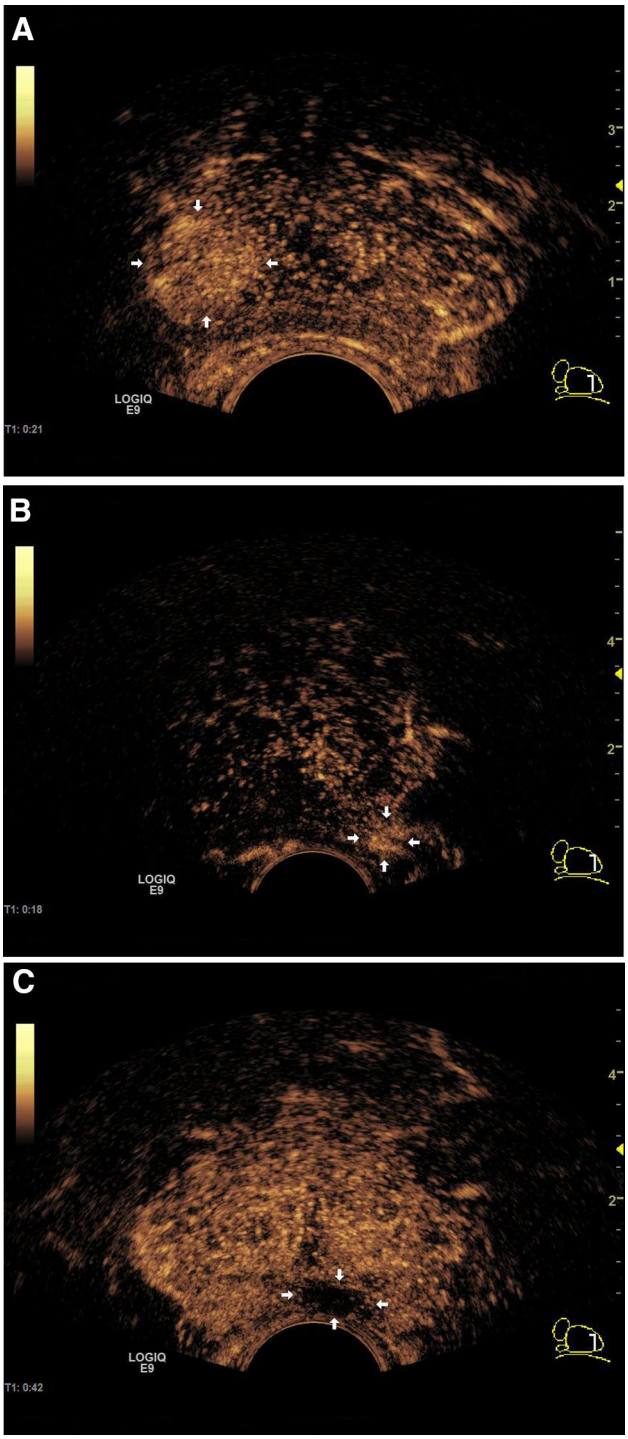

Fig. 2 Diagnostic criteria for PCa. **a** Increased focal contrast enhancement in comparison to adjacent tissue, **b** rapid contrast enhancement after contrast agent administration, **c** focal low enhancement with ill-defined border

UCL definition 2 (GS 3 + 4 and/or maximal cancer core length ≥ 4 mm, and/or total cancer core length ≥ 6 mm), and GS ≥ 3+4 [18, 19].

Statistical analysis

Sample size The primary goal of the study was to compare the benefits of CEUS-TB versus SB for significant PCa detection. Our initial cohort indicated that the proportion switching from no-event to event was approximately 7% and that the proportion switching from event to no-event was approximately 4%. According to a type I error rate of 5% and a power equal to 80%, the required sample size was approximately 955 patients.

Data analysis Continuous quantities are reported as median with interquartile range. The by-patient cancer detection rate for the different biopsy techniques was compared using McNemar's test. For the biopsy core analysis, differences between the groups were compared by the Wilcoxon rank-sum test or chi-square test. *P* values less than 0.05 were considered significant, and all statistical analyses were performed using Stata version 15.1 (Stata Corp LLC, TX, USA).

Table 1 Cohort demographics and clinical and biopsy characteristics

No.	1024
Age (year)[a]	68 (63–75)
Abnormal digital rectal exam (%)	207 (20.2%)
PSA (ng/ml)[a]	9.89 (6.72–14.07))
Volume (ml)[a]	48.13 (34.00–70.10)
PSAD (ng/ml^2)[a]	0.19 (0.12–0.31)
PCa, No. (%)	378 (36.9%)
GS, No. (%)	
GS 6	122 (32.3%)
GS 7	188 (49.7%)
GS 8	17 (4.5%)
GS ≥ 9	51 (13.5%)

PSA prostate-specific antigen, *PSAD* prostate-specific antigen density, *PCa* prostate cancer, *GS* Gleason Score

[a]Data are the median and interquartile range

Results

The clinical and pathological characteristics of patients enrolled in this study are summarized in Table 1. In the final cohort of 1024 patients, prostate biopsy revealed PCa in 378 cases (36.9%, 378/1024).

Of 1024 patients, 754 patients with 991 suspicious lesions on CEUS (range 1–3) underwent combined CEUS-TB and SB, the remaining 270 patients with negative CEUS only underwent standard SB. PCa was detected by CEUS-TB in 306 patients (29.9%, 306/1024) and by SB in 317 patients (31.0%, 317/1024). No significant differences were found between SB and CEUS-TB in overall cancer detection ($P = 0.340$). In the biopsy core analysis, 2334 cores were sampled targeting suspicious lesions on CEUS, with a mean of 2.4 (range 2–3) cores for each lesion. For SB, a total of 12,288 cores were sampled. The biopsy core positive rate for CEUS-TB was significantly higher than for SB (39.8%, 929/2334 versus 10.3%, 1265/12,288, $P < 0.001$). In our study, there were discrepancies between two readers in 247 of 1024 patients, and the biopsy was performed after the consensus was reached together with a senior investigator.

Prostate biopsy revealed insignificant PCa in 52 of 378 PCa patients (13.8%), and significant PCa in 326 of 378 PCa patients (86.2%) using Epstein criteria. Considering clinically significant cancers only, the results of CEUS-TB were positive in 294 patients (28.7%, 294/1024), which was higher than SB (25.3%, 259/1024, $P < 0.001$). Using Gleason ≥ 3+4, UCL definition 1 and UCL definition 2 for reevaluation, the proportion of clinically significant PCa was 25.0% (256/1024), 29.8% (305/1024) and 33.9% (347/1024), respectively. The results indicated that CEUS-TB yielded a higher clinically significant PCa detection rate than SB using these definitions (Table 2). A comparison of the biopsy results from standard 12-core SB versus CEUS-TB using Epstein criteria is shown in Table 3. As shown in Table 3, CEUS-TB resulted in 67 additional cases of clinically significant PCa, including 51 patients missed by SB and 16 patients under-graded by SB. Conversely, an additional 32 significant cancer cases missed by CEUS-TB were detected by SB. In comparison, ten patients with insignificant cancer

Table 2 Comparison of different biopsy protocols for significant PCa detection with stratification by age, PSA level and prostate volume

Definition	No. of significant PCa	Significant PCa detection rate by TB	Significant PCa detection rate by SB	*P* value (SB vs TB)
Epstein criteria	31.8% (326/1024)	28.7% (294/1024)	25.3% (259/1024)	<0.001
UCL definition 1	29.8% (305/1024)	27.8% (285/1024)	23.5% (241/1024)	<0.001
UCL definition 2	33.9% (347/1024)	29.3% (300/1024)	27.1% (277/1024)	<0.001
Gleason ≥ 3+4	25.0% (256/1024)	23.0% (236/1024)	19.9% (204/1024)	<0.001

PCa prostate cancer, *SB* systematic biopsy, *TB* targeted biopsy

Table 3 Cross-tabulation of biopsy results comparing TB to SB

SB	No suspicious lesions on CEUS	TB			Overall total
		Benign	Insignificant PCa	Significant PCa	
Benign	255	391	10	51	707
Insignificant PCa	3	37	2	16	58
Significant PCa	12	20	0	227	259
Overall total	270	448	12	294	1024

SB systematic biopsy, *TB* targeted biopsy, *PCa* prostate cancer

were additionally detected by CEUS-TB, whereas an additional 40 patients with insignificant cancer were detected by SB. The insignificant PCa detection rate was higher for SB than CEUS-TB (4.1%, 42/1024 versus 1.2%, 12/1024; $P < 0.001$).

The detection rate of significant cancer was further investigated with stratification by age, PSA level, and prostate volume (Table 4). Notably, CEUS-TB yielded a higher significant cancer detection rate in patients with a PSA level ≤ 10.0 ng/ml or prostate volume from 30–60 ml ($P < 0.05$).

The biopsy GS, the number of positive cores and core cancer involvement contribute to the significance of PCa. By additional CEUS-TB, GS upgrading was observed in 27 cases. In the converse scenario, GS upgrading by SB was observed in six cases. Compared with PCa patients underwent SB alone, the number of positive cores in patients underwent both CEUS-TB and SB was significantly higher (median: 6, interquartile range: 4–8 versus median: 1, interquartile range: 1–2, $P < 0.001$). Cancer core length was also significantly higher in CEUS-TB than SB (median: 9 mm, interquartile range: 5–11 mm versus median: 6 mm, interquartile range: 3–9 mm, $P < 0.001$).

Discussion

There has been considerable concern regarding both the overdiagnosis of clinically insignificant cancer and the underdiagnosis of significant cancer with current random biopsy strategies. With the development of prostate imaging modalities, TB strategy under imaging guidance could potentially provide a practical solution. Multiparametric magnetic resonance imaging (MRI) has emerged as an accurate modality in detecting PCa in correlation with radical prostatectomy histopathology [20]. The suspicious lesions on MRI could be accurately sampled under MRI guidance or MRI/US fusion guidance [21, 22]. However, MRI-guided biopsy is an expensive and time-consuming solution that is still limited to only a few academic centers. MRI/US fusion targeted biopsy also requires specific equipment and software. Moreover, not all patients are suitable for MRI

Table 4 Comparison of different biopsy protocols for significant PCa detection with stratification by age, PSA level and prostate volume

	No. of patients	No. of significant PCa	Significant PCa detection rate by TB	Significant PCa detection rate by SB	*P* value (SB vs TB)
Age group					
≤ 60	177	21.5% (38/177)	20.9% (37/177)	16.9% (30/177)	0.020
> 60 ≤ 70	443	23.7% (105/443)	20.8% (92/443)	18.7% (83/443)	0.128
> 70	404	45.3% (183/404)	40.8% (165/404)	36.1% (146/404)	0.010
PSA level group					
≤ 4.0	52	17.3% (9/52)	17.3% (9/52)	9.6% (5/52)	0.046
> 4.0 ≤ 10.0	471	23.4% (110/471)	21.7% (102/471)	16.8% (79/471)	< 0.001
> 10.0 ≤ 20.0	394	39.8% (157/394)	35.3% (139/394)	34.0% (134/394)	0.435
> 20.0	107	46.7% (50/107)	41.1% (44/107)	38.3% (41/107)	0.439
Prostate volume group					
≤ 30	192	63.0% (121/192)	56.3% (108/192)	55.7% (107/192)	0.847
> 30 ≤ 60	499	31.7% (158/499)	29.3% (146/499)	24.2% (121/499)	< 0.001
> 60	333	14.1% (47/333)	12.0% (40/333)	9.3% (31/333)	0.606
Overall	1024	31.8% (326/1024)	28.7% (294/1024)	25.3% (259/1024)	< 0.001

PSA prostate-specific antigen, *PCa* prostate cancer, *SB* systematic biopsy, *TB* targeted biopsy

imaging. Implant, pacemaker, or claustrophobia is contraindications to MRI. As an imaging modality, CEUS could be safely performed in most of patients with contraindications to MRI. More importantly, suspicious lesions on CEUS could be directly biopsied under postcontrast imaging guidance with no specific devices. In the present study, we investigated whether CEUS-TB was more sensitive for clinically significant PCa detection in comparison with standard SB.

For patients with biopsy-proven PCa, the biopsy GS and cancer core length have been recommended as important variables for determining the significance of PCa. In our series of patients, CEUS-TB was correlated with both of these variables. Improved targeting with CEUS resulted in more accurate grading of PCa. GS upgrading was observed in 27 cases by additional CEUS-TB in comparison with SB. Moreover, cancer core length was also significantly higher in CEUS-TB than in SB. Our results were consistent with those of Halpern et al., who reported that CEUS achieved an AUC of 0.90 for high-grade PCa with greater than 50% biopsy core involvement in a randomized double-blind trial of dutasteride pretreatment for CEUS evaluation [11]. These results demonstrate that CEUS might be more sensitive in depicting PCa with a higher GS and a higher volume and thus potentially contribute to the diagnosis of clinically significant PCa.

In this study, the clinically significant PCa detection rate of CEUS-TB versus standard SB was evaluated in patients who underwent initial biopsy. Compared with SB, the significant PCa detection rate for CEUS-TB was higher (28.7% versus 25.3%, Epstein criteria). The use of CEUS-TB as an adjunct to the standard SB resulted in additional diagnoses of 67 cases of clinically significant PCa. More importantly, only ten cases of clinically insignificant PCa were detected solely on CEUS-TB. These data indicated that CEUS-TB improved the clinically significant PCa detection rate without remarkably increasing the diagnosis of insignificant disease. Our results also raise the larger question of interest regarding whether CEUS-TB could be performed in lieu of standard SB. In the converse scenario, although standard SB inevitably detected 40 additional cases of clinically insignificant PCa, it did detect 32 significant cancers missed by CEUS. Therefore, the optimal biopsy strategy is to add CEUS targeted cores to standard SB, rather than replacing SB.

The prostate volume, serum PSA level and patient age were the potential confounders in PCa detection. In our cohort, we found a trend toward a higher significant PCa detection rate with increasing age and PSA level and decreasing prostate volume. Compared with standard SB, CEUS-TB achieved a higher significant PCa detection rate in patients with a PSA level ≤ 10 ng/ml and a prostate volume from 30 to 60 ml. Our subgroup results are consistent with those of Mitterberger et al., who reported that the overall PCa detection rate was significantly higher for CEUS-TB than SB in patients with relatively low PSA levels and medium-sized prostate glands in a cohort of 1776 men [23]. Based on these data, CEUS-TB would be strongly recommended in patients with PSA levels ≤ 10 ng/ml and prostate volumes from 30 to 60 ml.

Our study has several limitations. First, the real number of cancer-negative cases cannot be assessed in the current study. As a result, verification bias was more likely to occur in benign patients and thus might cause overestimation of the sensitivity of prostate biopsy [24]. Second, the current criteria for clinically significant PCa based on biopsy parameters are not perfect and might misclassify some of the patients who would have unfavorable pathological features in their whole-gland prostatectomy specimen [25]. However, radical prostatectomy is not suitable for all patients, and whole-gland prostatectomy specimens can only be assessed after surgery. For the purpose of treatment decisions, the biopsy histopathology would thus be the ideal reference standard. Third, this study was carried out in a single center; multicenter studies would reduce the selection bias and provide more information about the diagnostic performance of CEUS.

Conclusion

Given the limitations of systematic prostate biopsy, a diagnostic test that could detect and localize significant PCa is needed. Our study demonstrates that CEUS-TB can improve the significant PCa detection rate without remarkably increasing the diagnosis of insignificant disease. Additional CEUS-TB is recommended for significant PCa diagnosis, especially in patients with a PSA level ≤ 10.0 ng/ml or prostate volume from 30 to 60 ml. In the future, with the development of targeted contrast agents binding specifically with PCa tissues, CEUS will play an important role in PCa detection, biopsy guidance and risk stratification.

Author contributions ZY: data collection and management, data analysis, manuscript writing. CY: project development, manuscript editing. JJ: data collection, data analysis, manuscript editing. QT: data collection, data analysis. LW: data collection. QY: data collection. GW: data collection. WL: data collection. QJ: project development, data collection.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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