European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:2821–2832
https://doi.org/10.1007/s00259-021-05636-1

ORIGINAL ARTICLE

Dual-tracer PET/CT-targeted, mpMRI-targeted, systematic biopsy, and combined biopsy for the diagnosis of prostate cancer: a pilot study

Dong-Xu Qiu[1] · Jian Li[2] · Jin-Wei Zhang[3] · Min-Feng Chen[1] · Xiao-Mei Gao[4] · Yong-Xiang Tang[2] · Ye Zhang[5] · Xiao-Ping Yi[3] · Hong-ling Yin[4] · Yu Gan[1] · Gui-Lin Wang[1] · Xiong-Bing Zu[1] · Shuo Hu[2] · Yi Cai[1]

Received: 11 October 2021 / Accepted: 24 November 2021 / Published online: 3 December 2021

Abstract

Purpose Growing evidence proved the efficacy of multi-parametric MRI (mpMRI) and prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT)-guided targeted biopsy (TB) in prostate cancer (PCa) diagnosis, but there is no direct comparison between mpMRI-TB and PSMA PET/CT-TB. Gastrin-releasing peptide receptor (GRPR) is highly expressed in PCa, which can compensate for the unstable expression of PSMA in PCa. Therefore, we designed a study to compare the efficiency of mpMRI-TB, dual-tracer (GRPR and PSMA) PET/CT-TB, systematic biopsy, and combined biopsy for the diagnosis of prostate cancer.

Methods One hundred twelve suspicious PCa patients were enrolled from September 2020 to June 2021. Patients with anyone of positive dual-tracer PET/CT or mpMRI underwent TB, and all enrolled patients underwent systematic biopsy (SB) after TB. The primary outcome was the detection rates of PCa in different biopsy strategies. Secondary outcomes were the performance of three imaging methods, omission diagnostic rates, and upgrading and downgrading of biopsy samples relative to those of prostatectomy specimens in different biopsy strategies. McNemar's tests and Bonferroni correction in multiple comparisons were used to compare the primary and secondary outcomes.

Results In 112 men, clinically significant PCa (grade group[GG] ≥ 2) accounted for 34.82% (39/112), and nonclinically significant PCa (GG = 1) accounted for 4.46% (5/112). ^{68} Ga-PSMA PET/CT-TB achieved higher PCa detection rate (69.77%) and positive ratio of biopsy cores (0.44) compared with SB (39.29% and 0.12) and mpMRI-TB (36.14% and 0.23), respectively ($P < 0.005$). Dual-tracer PET/CT screen out patients for avoiding 52.67% (59/112) unnecessary biopsy, whereas dual-tracer PET/CT-TB plus SB achieved high detection rate (77.36%) without misdiagnosis of csPCa.

Dong-Xu Qiu and Jian Li contributed equally to this work.

This article is part of the Topical Collection on Oncology - Genitourinary

Key points **Question:** Although several prostate biopsy strategies are known, the most effective and accurate approach to diagnose PCa, especially for clinically significant prostate cancer (csPCa), remains unestablished.

Pertinent findings: In this prospective and comparative effectiveness study involving 112 patients, the use of dual-tracer PET/CT (^{68} Ga-GRPR + ^{68} Ga-PSMA) was recommended to screen patients from unnecessary biopsy. Dual-tracer PET/CT-TB plus SB achieved a significantly higher PCa detection rate (77.36%) without misdiagnosis of csPCa when compared with the application outcomes of mpMRI-TB and mpMRI-TB + SB.

Implications for patient care: Dual-tracer PET/CT-TB plus SB may be a more effective and promising strategy for accurately diagnosing PCa than mpMRI-TB and mpMRI-TB + SB.

Extended author information available on the last page of the article

Conclusion Dual-tracer PET/CT might screen patients for avoiding unnecessary biopsy. Dual-tracer PET/CT-TB plus SB might be a more effective and promising strategy for the definite diagnosis of clinically significant PCa than mpMRI-TB.

Keywords ^{68} Ga-PSMA · ^{68} Ga-GRPR · PET/CT · mpMRI · Prostate cancer · Diagnosis

Introduction

Prostate cancer (PCa) is the second most common cancer among men across the world [1]. Different stages of PCa directly affect the therapeutic schedule and patients' prognosis [2, 3]. Therefore, it is crucial to design accurate methods for the early diagnosis of PCa.

The American Urological Association (AUA) and the European Association of Urology (EAU) guidelines recommend 12-core systematic transrectal ultrasound-guided biopsy (TRUS-SB) as the standard method for definitive diagnosis and grading of PCa [4, 5]. However, 18% of clinically significant cancer (csPCa) cases are misdiagnosed, while 32% nonclinically significant cancer (ncsPCa) cases are incorrectly diagnosed by TRUS-SB [6]. Several prospective trials have proven that multi-parametric magnetic resonance imaging (mpMRI)-guided TB can improve the detection of csPCa and avoid unnecessary biopsy [6–11]. However, mpMRI cannot easily detect small foci in the central gland of prostate, which results in 35% cases of misdiagnosis of csPCa [12]. Moreover, the prostate imaging reporting and data system (PI-RADS), which was used to interpret prostate mpMRI results, exists in high inter-reader variations in terms of score and lesion location [13], thus reducing the diagnostic efficacy of mpMRI-targeted biopsy (mpMRI-TB). Moreover, patients cannot undergo mpMRI sometimes because of claustrophobia or its absolute/relative contraindications [14, 15]. Therefore, alternative imaging examination is in need to overcome the limitations of mpMRI in PCa diagnosis [15, 16]. Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is overexpressed in most primary and metastatic castration-resistant PCa cases [17]. The ^{68} Ga-labeled inhibitor of PSMA is an ideal imaging target of positron emission tomography/computed tomography (PET/CT) and positron emission tomography/magnetic resonance imaging (PET/MRI) demonstrating high sensitivity and specificity for PCa diagnosis and staging [18–21]. The advantages of ^{68} Ga-PSMA PET/CT in accurately determining the lesion location and extent may help in achieving better diagnostic efficacy compared with mpMRI [22–24]. Prospective trials also have proved that ^{68} Ga-PSMA PET/CT-targeted biopsy (^{68} Ga-PSMA PET/CT-TB) improves the detection rate of csPCa compared with SB [25, 26]. Therefore, ^{68} Ga-PSMA PET/CT was regarded as the most promising alternative to mpMRI for prostate cancer (PCa) diagnosis, especially in patients with claustrophobia, or absolute/relative contraindications of MRI examination, or high suspicion of PCa, or a previously negative biopsy [27, 28]. However, there is no study directly comparing the diagnostic accuracy of ^{68} Ga-PSMA PET/CT-TB and mpMRI-TB. On the other way, PSMA is highly expressed in PCa with higher Gleason score (GS) or prostate-specific antigen (PSA) level, but about 5–10% PCa have no or low PSMA expression [29], which may decrease the diagnostic accuracy of ^{68} Ga-PSMA PET/CT-TB [19].

Gastrin-releasing peptide receptor (GRPR), which regulates the physiological functions of organs by acting through gastrin-releasing peptide, is overexpressed in PCa in the early stages, and ^{68} Ga-GRPR PET/CT is another promising imaging technique detecting and localizing primary PCa [30–32]. Prospective studies identified that GRPR expression is not associated with GS and PSMA expression, suggesting that ^{68} Ga-GRPR- and ^{68} Ga-PSMA PET/CT may be complementary in PCa diagnosis and staging [18, 33]. However, there is no clinical data proving the advantage of ^{68} Ga-GRPR PET/CT-targeted biopsy (^{68} Ga-GRPR PET/CT-TB).

An ideal prostate biopsy should improve the detection rate of csPCa in the early stages and minimize the detection of ncsPCa with fewer upgrading or downgrading compared with radical prostatectomy [34–36]. This prospective study was designed to compare the diagnostic efficacies of different imaging techniques (mpMRI, ^{68} Ga-GRPR PET/CT, and ^{68} Ga-PSMA PET/CT)-guided TB, followed by the identification of the optimal strategy for accurately diagnosing PCa.

Materials and methods

Patients and study design

All participants were enrolled in outpatient clinics and operated on by a urologist (with extensive surgical experience of over 1,000 cases of transperineal prostate systematic biopsy and 300 cases of prostate targeted biopsy) if they have been referred with a clinical suspicion of prostate cancer based on PSA level > 4 ng/mL, and/or digital rectal examination abnormality, and/or imaging abnormality with or without prostate biopsy previously. Above suspicious patients who were treated with tamsulosin or finasteride ($n = 34$) or underwent prostate biopsy previously ($n = 9$) were enrolled, and all patients denied the prostate cancer familiar history. All were eligible for enrollment with the ability to understand the study procedures and volunteer to participate in

this study with written and signed informed consent. The exclusion criteria included the history of PCa pathological diagnosis and treatment; the use of known medications that affect PSA levels; and the general contraindications in MRI (including claustrophobia or electronically, magnetically, and mechanically activated implants or devices). Patients with cochlear implants, insulin pumps, nerve stimulators, cardiac lead wires, prosthetic heart valves, and hemostatic clips are regarded as the relative contraindications [15, 16] or biopsy operation, with examinations suggesting extracapsular (T3) disease (stage > T3a). Patients first underwent mpMRI and then dual-tracer PET/CT within 15 days. The time interval between imaging examinations and prostate biopsy was < 4 weeks.

Multi-parametric MRI (mpMRI) protocol

MRI was performed at 3 T with an external coil (Siemens Healthineers, GE), and mpMRI protocol included T1-weighted imaging in axial plane, T2-weighted imaging in three planes, diffusion-weighted imaging with the calculation of apparent diffusion coefficient (ADC) maps, and dynamic contrast-enhanced imaging. The images were interpreted according to PI-RADS v2.1 standard (Supplementary Table 1) by two genitourinary radiologists (XP Yi and JW Zhang) independently without information about the patients' clinical data [37]. The lesions were evaluated by PI-RADS score of 1 to 5 (higher scores signified more clinically evident lesions). Patients with PI-RADS score ≥ 3 underwent mpMRI-TB. Consensus assessments were used to decide the discordant PI-RADS scores and the need for mpMRI-TB.

Radiologists labeled a maximum of 2 highest scoring lesions per patients by using the BK Fusion software before conducting the prostate biopsies (Fig. 1). Prostate volume was determined by mpMRI, and PSA density (PSAD) was calculated by dividing the PSA level value by MRI prostate volume.

68 Ga-PSMA PET/CT and 68 Ga-GRPR PET/CT protocol

The precursor PSMA-617 was obtained from Huayi Isotopes Company (China), and the

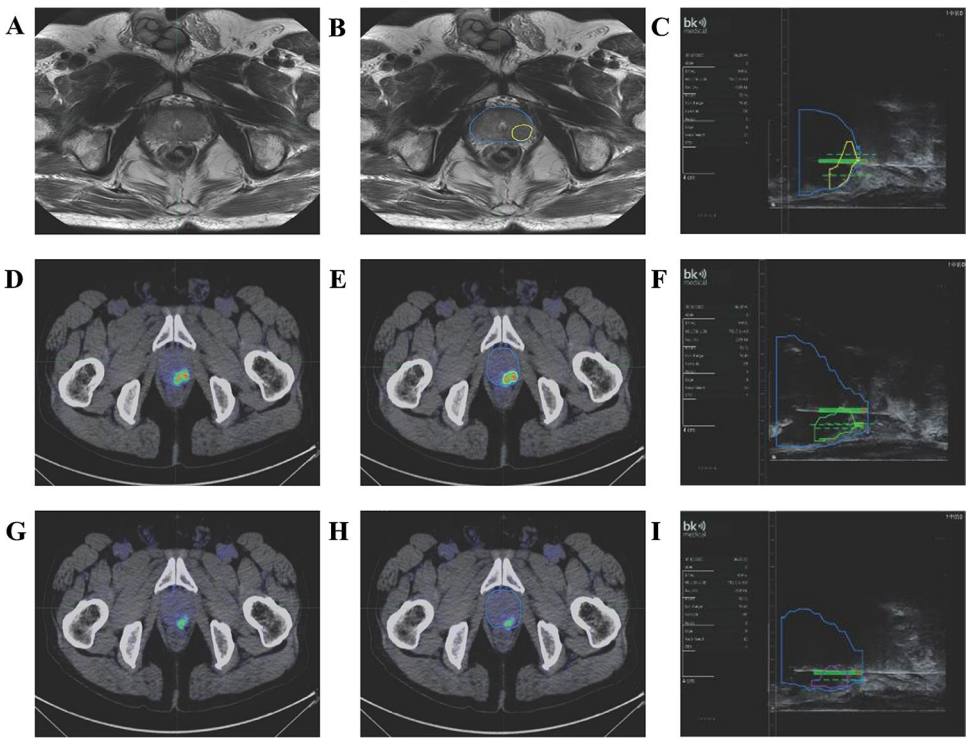

Fig. 1 Schematic demonstrating steps to achieve mpMRI, ^{68} Ga-GRPR PET/CT, and ^{68} Ga-PSMA PET/CT-targeted biopsy. (1) Suspicious patient underwent mpMRI (**A**), ^{68} Ga-GRPR PET/CT (**D**), and ^{68} Ga-PSMA PET/CT (**G**). (2) Radiologists and nuclear medicine specialists independently labeled prostate with blue line and region of interests (ROIs) in mpMRI (**B**), ^{68} Ga-GRPR PET/CT (**E**), and ^{68} Ga-PSMA PET/CT (**H**) with yellow, green, and purple lines, respectively. (3) Urologist matched labeled mpMRI (**C**), ^{68} Ga-GRPR PET/CT (**F**), and ^{68} Ga-PSMA PET/CT (**I**) images with real-time prostate ultrasonography scans to obtain samples by BK Fusion Biopsy System (green rectangle and green dotted line means puncture paths). mpMRI, multi-parametric magnetic resonance imaging; PSMA, prostate-specific membrane antigen; GRPR, gastrin-releasing peptide receptor; PET/CT, positron emission tomography/computed tomography

precursor GRPR (NOTA-P2-RM26) was supplied by Prof. Xiaoyuan (Shawn) Chen (Yong Loo Lin School of Medicine and Faculty of Engineering, National University of Singapore) [32]. PSMA and GRPR were radiolabeled using an automated module (ITM). Each patient received an intravenous injection of 68 Ga-PSMA (median dose, 153.55 MBq; range, 128.02–203.87 MBq) and 68 Ga-GRPR (median dose, 146.52 MBq; range, 109.89–198.32 MBq) in two different days (time interval < 3 days), followed by PET/CT scans at 40 ± 10 min using a General Electric Discovery PET/CT 690 Elite scanner (General Electric Healthcare, Waukesha, WI, USA). The image acquisition parameters are reported in Supplementary Table 2.

Images were interpreted by visual assessment. Any focal tracer uptake greater than the surrounding background and not associated with physiological uptake was considered a possible malignancy. Two nuclear medicine specialists (YX Tang and J Li) reviewed all images independently without information about the patients' clinical data and mpMRI reports. PET images and PET/CT fusion images were viewed in the axial, coronal, and sagittal planes. The region of interests (ROIs) was drawn around the primary prostatic lesion with 40% maximal standardized uptake values (SUVmax) cut-off in the 40-min post-injection fusion image. SUV_{max} of the prostate lesion, normal prostate background, and liver background (SUV_{BGp} and SUV_{L}, respectively) was measured concurrently. $SUV_{T/BGp}$ signified the calculated uptake ratio of the prostate lesion versus the normal prostate background, whereas SUV_{ratio} signified the calculated uptake ratio of the prostate lesion versus liver background.

No more than two most suspicious lesions were labeled by the nuclear medicine specialists using BK Fusion software for each patient before conducting prostate biopsies (Fig. 1). A consensus assessment decided the final ROIs and the need for PET/CT-TB when discordance existed.

Prostate biopsy protocol

BK Fusion Biopsy System was used to match labeled images with real-time prostate ultrasonography scans for achieving image identification and TB of lesions. All suspicious lesions in mpMRI and PET/CT were fused and targeted in real time with the TRUS (transrectal ultrasound) images using a biplane 6/9/12 MHz Pro Focus Transducer 8848 ultrasound system (BK Ultrasound, Peabody, MA), which permit both transrectal prostate biopsy and transperineal prostate biopsy with rigid fusion in mpMRI or PET/CT transrectal ultrasound fusion prostate biopsy (Fig. 1). No more than two most suspicious lesions were labeled in mpMRI, 68 Ga-PSMA PET/CT, and 68 Ga-GRPR PET/CT PET/CT, and each suspicious lesions underwent targeted biopsy with 2–4 cores.

A 12-core transperineal systematic biopsy (SB) was adopted, and the distribution of 12 regions was shown in Supplementary Fig. 1 [38–40]. A urologist (with extensive surgical experience of over 1,000 cases of transperineal prostate systematic biopsy and 300 cases of prostate targeted biopsy) blinded to imaging results performed prostate biopsy in the order of ^{68} Ga-GRPR PET/CT-TB, ^{68} Ga-PSMA PET/CT-TB, mpMRI-TB, and SB. If the image results were negative, the corresponding TB was skipped, whereas SB was conducted in all enrolled patients.

Prostatectomy cohort

PCa-diagnosed patients underwent radical prostatectomy (RP) for comparing the grade group (GG) between the prostatectomy specimens and the biopsied specimens. Here, PCa patients who received other treatments (including hormonal therapy, radiation, focal therapy, and chemotherapy) were excluded.

Pathology protocol

All biopsy samples were reviewed by two experienced uropathologists (HL Yin and XM Gao) blinded to patients' clinical data and image reports. The analyzed biopsy features included pathological type, length of tissues involving lesions, and length of whole biopsy specimens. For each positive sample, GG and GS were determined according to the 2019 International Society of Urologic Pathology (ISUP) criteria [41]. Prostatectomy specimens were reviewed by experienced general pathologists.

Definitions of terms

According to EAU guidelines and ISUP scoring system, csPCa was defined as GG ≥ 2 (GS ≥ 3 + 4) [4, 41], and ncsPCa was defined as GG = 1 (GS 3 + 3 = 6). Combined biopsy was defined as the combined use of TB and SB in a patient. The GG and GS of combined biopsy were the higher GG and GS of composed biopsy strategies. If PCa-diagnosed patients underwent RP, GG and GS were adjusted to that of prostatectomy specimens. Upgrading or downgrading was assessed by comparing the GG of prostate biopsy with that of prostatectomy specimens. Upgrading indicated a higher GG of prostatectomy specimens when compared with that of biopsy specimens, whereas downgrading indicated a lower GG.

Outcomes

The primary outcome was the csPCa and ncsPCa detection rates in different biopsy strategies. The secondary outcomes were the performance of different imaging methods,

omission diagnostic rates, positive ratio of biopsy cores, and the upgrading and downgrading rates in different biopsy strategies.

Data analysis

Mean (± standard deviation [SD]) and Student's *t* test were used for continuous variables with normal distribution, whereas median (interquartile range) and Mann–Whitney *U* test were used for discrete distribution. The McNemar test was used to compare the cancer detection rates of different biopsy strategies. The adjusted Wald interval was applied to calculate the differences and confidence intervals for PCa detection rates of different biopsy strategies. Bonferroni correction was used to adjust for multiple comparisons. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 25.0, IBM Corp., Armonk, NY, USA). $P < 0.05$ indicated statistical significance.

Results

Patients

A total of 112 patients underwent mpMRI and dual-tracer PET/CT from September 2020 to June 2021 at Xiangya Hospital. Thirty-four patients were treated with tamsulosin or finasteride, and nine patients underwent prostate biopsy previously. All patients denied the prostate cancer familiar history. There were 41, 13, and 10 enrolled patients with hypertension, diabetes, and coronary heart disease, respectively. A total of 83, 40, and 43 patients showed suspicious lesions in mpMRI, ^{68} Ga-GRPR PET/CT, and ^{68} Ga-PSMA PET/CT, respectively, and underwent TB. All 112 patients underwent SB in the same clinical setting. Baseline characteristics and image characteristics of all 112 patients are summarized in Table 1 and Supplementary Table 3, respectively. In 112 recruited patients, 44 (39.29%) men were diagnosed with PCa, and 7 (6.25%) men developed hematuria after biopsy. Of the 44 PCa patients, 36 (81.81%) underwent RP. The main process of this analysis is presented in Fig. 2.

Imaging performance

In all 112 patients, 83, 40, 43, and 53 male patients had positive mpMRI, ^{68} Ga-GRPR PET/CT, ^{68} Ga-PSMA PET/CT, and dual-tracer PET/CT result, respectively. In these four groups, mpMRI group had the lowest PCa rates (csPCa rate, 40.96%; ncsPCa rate, 4.82%) ($P < 0.05$). And dual-tracer PET/CT group achieved the lowest PCa misdiagnosed rate (5.08%) without misdiagnosis of csPCa ($P < 0.05$). More detailed information was displayed in Fig. 3. And the discrepancy between mpMRI and dual-tracer PET/CT was displayed in the Supplementary Fig. 2.

Table 1 Baseline characteristics

Variable	Value
Number of patients	112
Age, years, median (IQR)	64 (59–70)
PSA level, ng/mL, median (IQR)	11.09 (6.18–15.94)
Comorbidity, no. (%)*	
Hypertension	41 (36.60)
Diabetes	13 (11.61)
Coronary heart disease	10 (8.93)
Tumor stage, no. (%)*	
No cancer	68 (60.71)
cT1c	23 (20.54)
cT2a	7 (6.25)
cT2b	6 (5.36)
cT2c	8 (7.14)
Prostate volume on mpMRI, cm^3, median (IQR)	42.97 (29.44–68.74)
PSA density, ng/mL/mL, median (IQR)	0.19 (0.13–0.42)
Prostate biopsy strategy, *n* (%)	
Systematic biopsy	112 (100.00)
mpMRI-targeted biopsy	83 (74.11)
^{68} Ga-GRPR PET/CT-targeted biopsy	40 (35.71)
^{68} Ga-PSMA PET/CT-targeted biopsy	43 (38.39)
Biopsy cores per strategy	
Systematic biopsy	12 (12–12)
mpMRI-targeted biopsy	
Overall	4 (3–4)
Per lesion	3 (3–4)
^{68} Ga-GRPR PET/CT-targeted biopsy	
Overall	3 (3–4)
Per lesion	3 (2–3)
^{68} Ga-PSMA PET/CT-targeted biopsy	
Overall	3 (3–4)
Per lesion	3 (2–3)

IQR, interquartile range; *PSA*, prostate-specific antigen; *mpMRI*, multi-parametric magnetic resonance imaging; *PSMA*, prostate-specific membrane antigen; *GRPR*, gastrin-releasing peptide receptor; *PET/CT*, positron emission tomography/computed tomography

*Tumor stage is reported as the clinical stage in the biopsy cohorts

Comparison of prostate cancer detection rate, omission diagnostic rate, and biopsy cores

Among all 112 patients, 39 (34.82%) were diagnosed with csPCa (GG ≥ 2) whereas 5 (4.46%) with ncsPCa (GG = 1) (Table 2). ^{68} Ga-PSMA PET/CT-TB achieved a significantly higher PCa detection rate (30/43, 69.77%) compared with SB (39/112, 34.82%) and mpMRI-TB (30/83, 36.14%). Dual-tracer PET/CT-TB plus SB achieved a significantly

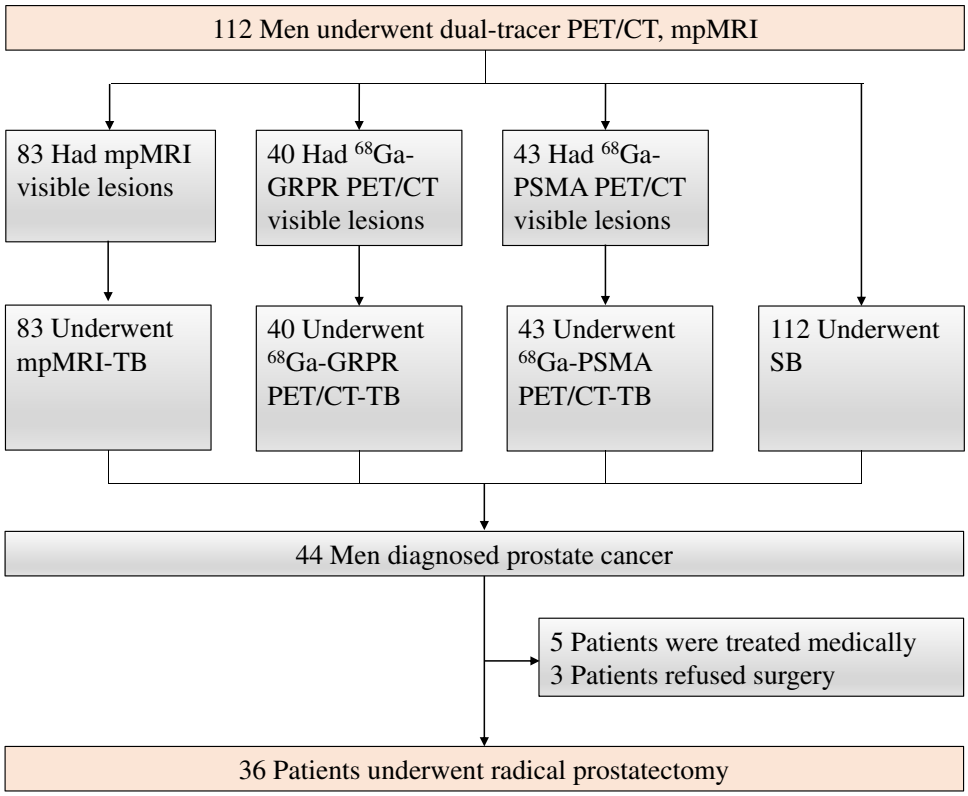

Fig. 2 Flowchart of this study. TB, targeted biopsy; SB, systematic biopsy; mpMRI, multi-parametric magnetic resonance imaging; PSMA, prostate-specific membrane antigen; GRPR, gastrin-releasing peptide receptor; PET/CT, positron emission tomography/computed tomography

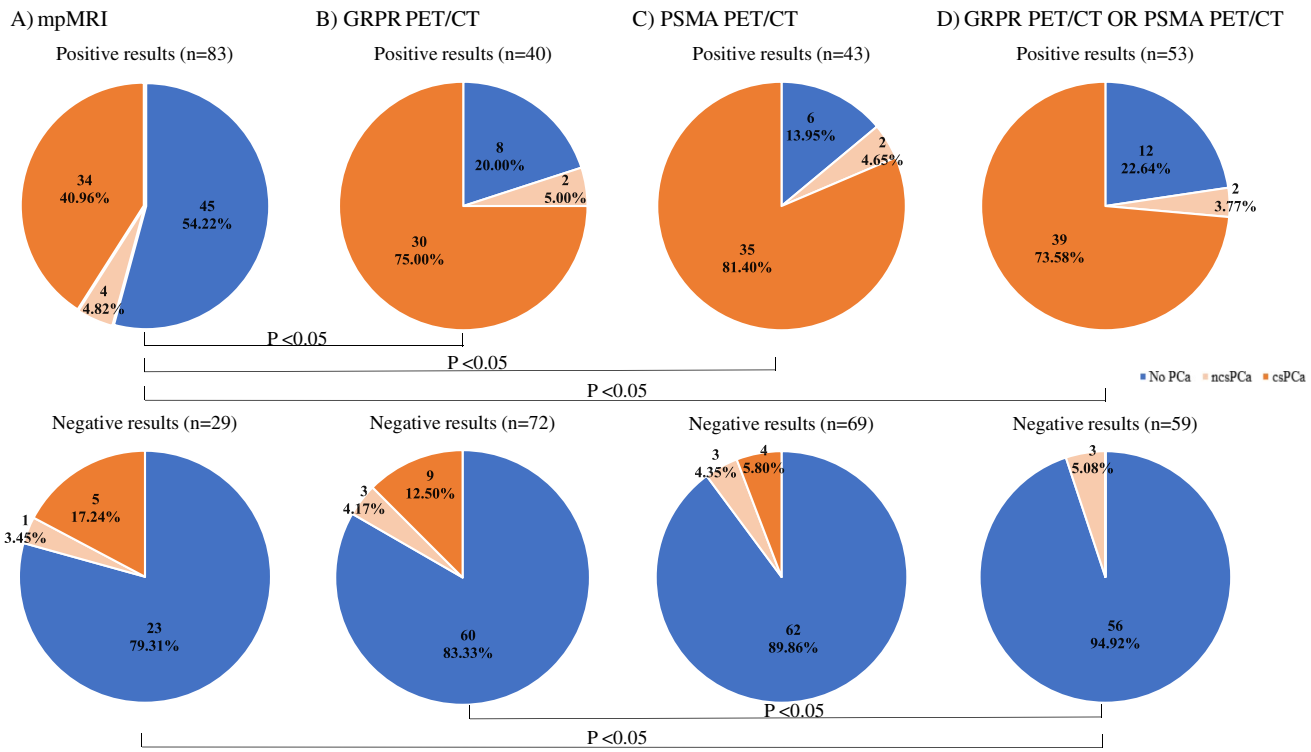

Fig. 3 Imaging performance of mpMRI, ^{68} Ga-GRPR PET/CT, ^{68} Ga-PSMA PET/CT, and dual-tracer PET/CT in diagnosing PCa. mpMRI, multi-parametric magnetic resonance imaging; PSMA, prostate-specific membrane antigen; GRPR, gastrin-releasing peptide receptor; PET/CT, positron emission tomography/computed tomography. PCa, prostate cancer; csPCa, clinically significant prostate cancers; ncsPCa, nonclinically significant prostate cancers

Table 2 Detection rate, omission diagnostic rate, and biopsy core analysis of different biopsy strategies

	Biopsy strategy								
	All	SB	mpMRI-TB	^{68}Ga-GRPR PET/CT-TB	^{68}Ga-PSMA PET/CT-TB	Dual-tracer PET/CT-TB (^{68}Ga-GRPR or ^{68}Ga-PSMA)	SB + mpMRI-TB	SB + ^{68}Ga-PSMA PET/CT-TB	SB + Dual-tracer PET/CT-TB (^{68}Ga-GRPR or ^{68}Ga-PSMA)
Biopsy performance, *n* (%)									
Negative imaging; no biopsy	NA	NA	29 (25.89)	72 (64.29)	69 (61.61)	59 (52.68)	29 (25.89)	69 (61.61)	59 (52.68)
Biopsy performed	112 (100)	112 (100)	83 (74.11)	40 (35.71)	43 (38.39)	53 (47.42)	83 (74.11)	43 (38.39)	53 (47.42)
Biopsy outcome, *n* (%)									
No PCa	68 (60.71)	73 (65.18)	53 (63.86)	18 (45.00)	13 (30.23)	18 (33.96)	46 (55.42)	6 (13.95)	12 (22.64)
PCa	44 (39.29)	39 (34.82)	30 (36.14)	22 (55.00)	30 (69.77)	35 (66.04)	37 (44.58)	37 (86.05)	41 (77.36)
csPCa (GG ≥ 2)	39 (34.82)	36 (32.14)	29 (34.94)	20 (50.00)	28 (65.17)	33 (62.26)	34 (40.96)	35 (81.40)	39 (73.58)
ncsPCa (GG = 1)	5 (4.46)	3 (2.68)	1 (1.21)	2 (5.00)	2 (4.66)	2 (3.77)	3 (3.61)	2 (4.65)	2 (3.77)
Missed diagnosis, *n* (%)									
PCa (*n* = 44)	NA	5 (11.36)	14 (31.82)	22 (50.00)	14 (31.82)	9 (20.45)	7 (15.91)	7 (15.91)	3 (6.82)
csPCa (GG ≥ 2) (*n* = 39)	NA	3 (7.69)	10 (25.64)	19 (48.72)	11 (28.21)	6 (15.38)	5 (12.82)	4 (10.26)	0 (0.00)
ncsPCa (GG = 1) (*n* = 5)	NA	2 (40.00)	4 (80.00)	3 (60.00)	3 (60.00)	3 (60.00)	2 (40.00)	3 (60.00)	3 (60.00)
Biopsy cores									
Total no. of cores	1957	1344	322	132	159	291	1318	675	927
Total no. of positive cores	352	161	73	50	70	120	226	221	275
Ratio positive/total cores (%)	17.99	11.98	22.67	37.88	44.03	41.24	17.15	32.74	29.67
Maximum tumor core involvement, *n* (%)									
< 10%	2 (4.55)	1 (2.56)	2 (6.67)	3 (13.64)	2 (6.67)	4 (11.43)	1 (2.70)	0 (0.00)	2 (4.88)
10–50%	14 (31.82)	12 (30.77)	9 (30.00)	4 (18.18)	9 (30.00)	7 (20.00)	16 (43.24)	7 (18.92)	10 (24.39)
> 50%	28 (63.64)	26 (66.67)	19 (63.33)	15 (68.18)	19 (63.33)	24 (68.57)	20 (54.05)	30 (81.08)	29 (70.73)

TB, targeted biopsy; *SB*, systematic biopsy; *mpMRI*, multi-parametric magnetic resonance imaging; *PSMA*, prostate-specific membrane antigen; *GRPR*, gastrin-releasing peptide receptor; *PET/CT*, positron emission tomography/computed tomography; *PCa*, prostate cancer; *csPCa*, clinically significant prostate cancers; *ncsPCa*, nonclinically significant prostate cancers; *GG*, grade group

higher PCa detection rate (41/53, 77.36%) when compared with SB, mpMRI-TB, ^{68}Ga-GRPR PET/CT-TB (22/40, 55.50%) and SB + mpMRI-TB (21/51, 41.18%) ($P < 0.05$). More detailed information is provided in Supplementary Table 4. Cross-tabulations of different biopsy strategies are provided in Supplementary Table 5.

The csPCa omission diagnostic rate of SB + dual-tracer PET/CT-TB (0.00%) was significantly lower than that of mpMRI-TB (25.64%), ^{68}Ga-GRPR PET/CT-TB (48.72%), ^{68}Ga-PSMA PET/CT-TB (28.21%), dual-tracer PET/CT-TB (15.38%), SB + mpMRI-TB (12.82%), and SB + ^{68}Ga-PSMA PET/CT-TB (10.26) ($P < 0.05$). No significant difference existed in PCa omission diagnostic rate between the SB (7.69%) and SB + dual-tracer PET/CT-TB ($P > 0.05$). More details about the comparison of csPCa omission diagnostic rate in different group were shown in Supplementary Table 6.

Patients in the SB group underwent the most biopsy cores with the lowest positive core ratio compared with other groups ($P < 0.005$). In four TB groups, mpMRI-TB had the

lowest positive core ratio ($P < 0.005$). Patients in the dual-tracer PET/CT-TB + SB groups underwent less biopsy cores with significantly higher positive core ratio when compared with SB + mpMRI-TB ($P < 0.005$) (Table 2).

Comparison between biopsy samples and prostatectomy specimens

The rates of any upgrading or clinically significant upgrading (GG ≥ 2) in prostatectomy specimens were 41.67% and 38.89% for SB, 69.44% and 58.33% for mpMRI-TB, 77.78% and 69.44% for ^{68} Ga-GRPR PET/CT-TB, 61.11% and 52.78% for ^{68} Ga-PSMA PET/CT-TB, 50.00% and 41.67% for dual-tracer PET/CT-TB, 44.44% and 38.89% for SB + mpMRI-TB, 41.67% and 33.33% for 30.56% SB + ^{8} Ga-PSMA PET/CT-TB, and22.22% for SB + dual-tracer PET/CT-TB, respectively. No biopsy samples were downgraded to clinically insignificant downgrading (GG = 1) compared with prostatectomy specimens. The rates of any downgrading in prostatectomy specimens were 13.89% for SB; 8.33% for mpMRI-TB; 5.56% for ^{68} Ga-GRPR PET/CT-TB; 13.89% for ^{68} Ga-PSMA PET/CT-TB; 19.44% for dual-tracer PET/CT-TB, SB + mpMRI-TB, and SB + ^{8} Ga-PSMA PET/CT-TB; and 25.00% for SB + dual-tracer PET/CT-TB ($P > 0.05$) (Supplementary Table 7). The cross-tabulations between biopsy and prostatectomy specimens are provided in Supplementary Table 8.

Recommended prostate biopsy protocol

Considering all above results, we propose a biopsy protocol for suspicious PCa patients with early stage. We recommend such patients to undergo dual-tracer PET/CT (GRPR + PSMA) firstly. Active surveillance might be a good choice for suspicious patients with both negative dual-tracer PET/CT results, because 52.67% (59/112) patients could avoid biopsy in this way. Our findings support that SB + dual-tracer PET/CT-TB simultaneously might be a beneficial choice in suspicious patient with anyone positive results of dual-tracer PET/CT for preventing misdiagnosis of PCa, and patients with both negative combined biopsy results were recommended active surveillance (Fig. 4).

Discussion

PCa has the second highest incidence rate of malignancy worldwide but is characterized by considerable diagnostic uncertainty, especially in the early stage [7]. Most PCa patients are diagnosed at advanced stages, leading to limited treatment options and dissatisfactory prognosis [2, 42, 43]. Therefore, it is necessary to explore a sensitive and effective method for diagnosing PCa. In our study, SB + dual-tracer PSMA PET/CT-TB may be the best biopsy strategy because of its increased certainty and decreased cost.

In the last few years, studies have proved the superiority of mpMRI in diagnosing PCa and avoiding unnecessary biopsy [6–8, 10, 11]. Therefore, mpMRI was recommended as the best imaging technique in PCa diagnosis [4]. However, PI-RADS score, which was used for assessing suspicious lesion in prostate mpMRI, was prone to subjective evaluation among different radiologists, thereby increasing the diagnostic uncertainty of mpMRI-TB [13]. In our study, inter-reader variability existed in PI-RADS score and lesion location in 28 (33.73%) patients.

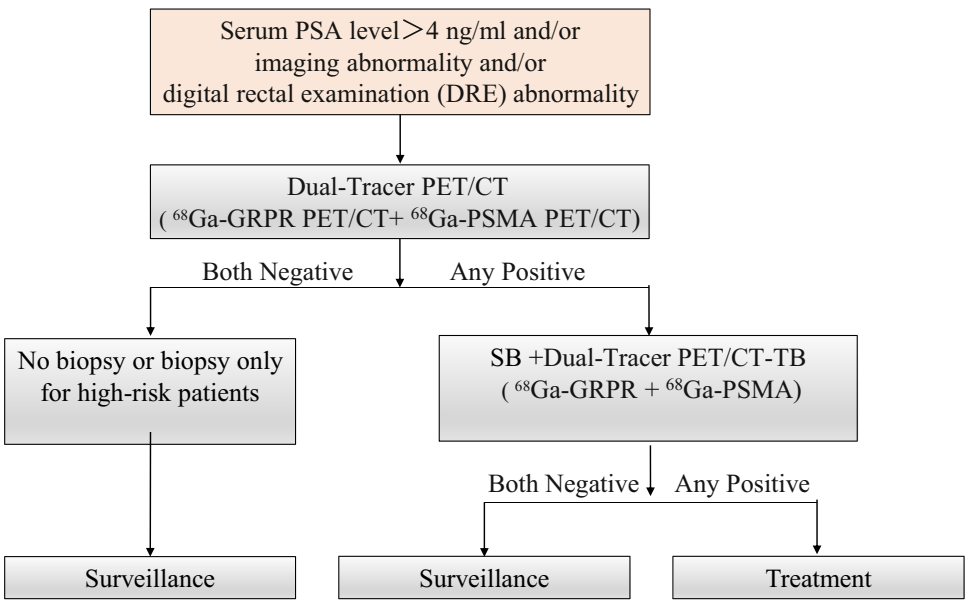

Fig. 4 Flowchart of the recommended prostate biopsy protocol. PSMA, prostate-specific membrane antigen; GRPR, gastrin-releasing peptide receptor; PET/CT, positron emission tomography/computed tomography; TB, targeted biopsy; SB, systematic biopsy

PMSA and GRPR, used as dual tracers of PET/CT, have been proven to significantly improve diagnostic sensitivity of PCa [44]. Moreover, the objectivity and accuracy of PET/CT interpretation can compensate for the uncertainty and subjectivity of prostate mpMRI. Recent studies demonstrated that ^{68} Ga-PSMA PET/CT is a promising prostate imaging tool, and it could improve the detection of csPCa when combined with mpMRI [45, 46].Other studies proved the capability and superiority of ^{68} Ga-PSMA PET/CT in detecting csPCa, especially in PCa relapsed patients and patients with high clinical suspicion of PCa, negative biopsy history, and negative mpMRI or with mpMRI contraindications [14, 15, 47–49]. Moreover, studies proved that ^{68} Ga-PSMA PET/CT or ^{68} Ga-PSMA PET/MRI may have an incremental advantage in primarily diagnosing PCa, providing superior accuracy in staging localized PCa, and making treatment decision along the whole spectrum of PCa compared with mpMRI [18, 50–53]. A clinical study identified the diagnostic value of ^{68} Ga-PSMA PET/CT-TB in csPCa [25], while another prospective randomized study proved that PET/CT-TB improves the detection rate of csPCa when compared with TRUS-SB, especially in patients with a PSA level of 4.0–20.0 ng/mL [26]. The study correlated findings on whole gland pathological samples with ^{68} Ga-PSMA PET/CT supported its use in prostate biopsy and primary diagnosis setting [49]. However, there is no prospective study comparing the efficiency of mpMRI-TB and ^{68} Ga-PSMA PET/CT-TB directly. Moreover, no clinical study has proven the efficiency of GRPR PET/CT in prostate TB.

Our study has several advantages. First, the detection rate and efficiency of ^{68} Ga-PSMA PET/CT-TB and mpMRI-TB were compared directly. The detection rate of ^{68} Ga-PSMA PET/CT-TB in our study was 58.62%, which is similar to that reported earlier [25, 26]. The detection rate of mpMRI-TB in our study was 33.33%, which was lower than the detection rate reported in a previous study [7]. The reason for this difference might be the low PCa incidence rate in China [54], the Chinese patients' lack of PCa knowledge, and the enrolled men with low PSA, which usually indicated PCa at an early stage. Our study identified that ^{68} Ga-PSMA PET/CT-TB achieved a significantly higher PCa detection rate and twice positive core ratio than mpMRI-TB. Moreover, nearly half of the study population who underwent mpMRI-TB could avoid biopsy in the ^{68} Ga-PSMA PET/CT-TB group with nonsignificant omission diagnostic rate. The above results indicate that ^{68} Ga-PSMA PET/CT-TB may be a more effective biopsy strategy than mpMRI-TB. Second, there is only theoretical foundation of GRPR as a tracer of PET/CT in diagnosing PCa without clinical practice [30, 32]. Our study proved that GRPR as an imaging marker for PET/CT-TB was not effective as expected. However, GRPR and PSMA, as dual tracers of PET/CT, were recommended to screen suspicious PCa patients for avoiding unnecessary biopsy in this study. Third, we performed SB in all of the enrolled patients for avoiding PCa omission. The results showed that the combined biopsy could reduce the omission rate significantly, which is consistent with previous findings [7, 9]. Although SB + dual-tracer PET/CT-TB had no significantly difference with SB in the omission diagnostic rate and cost more 56.92 dollar and 324.33 dollar each man than SB and mpMRI-TB (+ SB) group, respectively, dual-tracer PET/CT-TB plus SB achieved a significantly higher PCa detection rate, thus avoiding 52.67% of unnecessary biopsy without the omission of csPCa. From the perspective of PCa detection rate and csPCa omission diagnostic rate, SB + dual-tracer PET/CT-TB might be a better biopsy strategy compared with that with other biopsy methods. In addition, we evaluated the accuracy of each biopsy strategy by comparing biopsy samples with prostatectomy specimens. This study possibly achieved the most detailed and comprehensive comparison toward determining the best biopsy method to accurately diagnose PCa.

However, there are several limitations in our study. First, we performed this pilot study at one institution, which may limit its generalizability. Second, different biopsy methods were performed in a fixed order, so the front biopsy method may have affected the results of the latter because of the bleeding and swelling of the glands. Third, not all PCa patients underwent RP, which might create a selection bias in the prostatectomy cohort. The feasibility of undergoing pre-biopsy mpMRI and PET/CT needs further evaluation. Fourth, the high standard of PET/CT brings restriction to its wide use as a routine imaging examination.

In conclusion, ^{68} Ga-PSMA PET/CT-TB achieved a high detection rate for csPCa and avoided unnecessary biopsies significantly, but it showed a significant omission of csPCa in this study. However, dual-tracer (GRPR + PSMA) PET/CT might be a useful method to screen patients for avoiding the unnecessary biopsy. Moreover, dual-tracer PET/CT-TB plus SB achieved significantly higher PCa detection rate without the omission of csPCa compared with mpMRI-TB and mpMRI-TB + SB in this study, which might be a more effective and promising strategy for diagnosing PCa.

Abbreviations *TB*: Targeted biopsy; *SB*: Systematic biopsy; *mpMRI*: Multi-parametric magnetic resonance imaging; *PSMA*: Prostate-specific membrane antigen; *GRPR*: Gastrin-releasing peptide receptor; *PET/CT*: Positron emission tomography/computed tomography; *GG*: Grade group; *PCa*: Prostate cancer; *csPCa*: Clinically significant prostate cancers; *ncsPCa*: Nonclinically significant prostate cancers; *RP*: Radical prostatectomy

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-021-05636-1.

Acknowledgements We thank everyone who provided support for this study. We thank the support from the Key Research and Development Program of Hunan Province (2021SK2014), the National Natural

Science Foundation of China (91859207), the National Natural Science Foundation of China (81800590, 81902858, 81902606), and the Natural Science Foundation of Hunan Province (2020JJ5882, 2020JJ5949, 2020JJ5891).

Funding This investigation was sponsored by the Key Research and Development Program of Hunan Province (2021SK2014), the National Natural Science Foundation of China (91859207), the National Natural Science Foundation of China (81800590, 81902858, 81902606), and the Natural Science Foundation of Hunan Province (2020JJ5882, 2020JJ5949, 2020JJ5891).

Data availability The individual participant data study protocol, statistical analysis plan, analytical code text, tables, figure, and appendices will all be available. Data will be available between 9 and 36 months after the article publication. All related data is available for analyses that achieve the aims of the approved proposal. Requests for data should be directed by email to Yi Cai. Data requestors will need to sign a data access agreement first to obtain data.

Declarations

Ethics 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. The study was approved by the local ethic committee (201909253).

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

Conflict of interest The authors declare no competing interests.

Disclaimer The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: a cancer journal for clinicians. 2020;70.https://doi.org/10.3322/caac.21590.
2. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med. 2016;375:1415–24. https://doi.org/10.1056/NEJMoa1606220.
3. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. N Engl J Med. 2018;379:2319–29. https://doi.org/10.1056/NEJMoa1807801.
4. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. European urology. 2021;79:263–82. https://doi.org/10.1016/j.eururo.2020.09.046.
5. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline part I. J Urol. 2021;205:14–21. https://doi.org/10.1097/JU.0000000000001375.
6. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet (London, England). 2017;389:815–22. https://doi.org/10.1016/S0140-6736(16)32401-1.
7. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med. 2020;382:917–28. https://doi.org/10.1056/NEJMoa1910038.
8. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, et al. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naive: the Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) study. JAMA Surg. 2019;154:811–8. https://doi.org/10.1001/jamasurg.2019.1734.
9. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol. 2019;20:100–9. https://doi.org/10.1016/s1470-2045(18)30569-2.
10. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol. 2015;68:438–50. https://doi.org/10.1016/j.eururo.2014.11.037.
11. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol. 2019;75:570–8. https://doi.org/10.1016/j.eururo.2018.11.023.
12. Panebianco V, Barchetti G, Simone G, Del Monte M, Ciardi A, Grompone MD, et al. Negative multiparametric magnetic resonance imaging for prostate cancer: what's next? Eur Urol. 2018;74:48–54. https://doi.org/10.1016/j.eururo.2018.03.007.
13. Sonn GA, Fan RE, Ghanouni P, Wang NN, Brooks JD, Loening AM, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. Eur Urol Focus. 2019;5:592–9. https://doi.org/10.1016/j.euf.2017.11.010.
14. Lopci E, Guazzoni G, Lazzeri M. Ga Prostate-specific membrane antigen PET/CT for primary diagnosis of prostate cancer: complementary or alternative to multiparametric MR imaging. Radiology. 2018;287:725–6. https://doi.org/10.1148/radiol.2017172607.
15. Lopci E, Lughezzani G, Castello A, Colombo P, Casale P, Saita A, et al. PSMA-PET and micro-ultrasound potential in the diagnostic pathway of prostate cancer. Clin Transl Oncol. 2021;23:172–8. https://doi.org/10.1007/s12094-020-02384-w.
16. Lopci E, Saita A, Lazzeri M, Lughezzani G, Colombo P, Buffi NM, et al. Ga-PSMA positron emission tomography/computerized tomography for primary diagnosis of prostate cancer in men with contraindications to or negative multiparametric magnetic resonance imaging: a prospective observational study. J Urol. 2018;200. https://doi.org/10.1016/j.juro.2018.01.079.
17. Paschalis A, Sheehan B, Riisnaes R, Rodrigues DN, Gurel B, Bertan C, et al. Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. Eur Urol. 2019;76:469–78. https://doi.org/10.1016/j.eururo.2019.06.030.
18. Mapelli P, Ghezzo S, Samanes Gajate AM, Preza E, Brembilla G, Cucchiara V, et al. Preliminary results of an ongoing prospective clinical trial on the use of 68Ga-PSMA and 68Ga-DOTA-RM2 PET/MRI in staging of high-risk prostate cancer patients. Diagnostics. 2021;11. https://doi.org/10.3390/diagnostics11112068.

19. Budäus L, Leyh-Bannurah S-R, Salomon G, Michl U, Heinzer H, Huland H, et al. Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol. 2016;69:393–6. https://doi.org/10.1016/j.eururo.2015.06.010.
20. Sheikhbahaei S, Afshar-Oromieh A, Eiber M, Solnes LB, Javadi MS, Ross AE, et al. Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging. Eur J Nucl Med Mol Imaging. 2017;44:2117–36. https://doi.org/10.1007/s00259-017-3780-7.
21. Donato P, Roberts MJ, Morton A, Kyle S, Coughlin G, Esler R, et al. Improved specificity with (68)Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. Eur J Nucl Med Mol Imaging. 2019;46:20–30. https://doi.org/10.1007/s00259-018-4160-7.
22. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol. 2016;70:829–36. https://doi.org/10.1016/j.eururo.2015.12.053.
23. Wang B, Gao J, Zhang Q, Fu Y, Liu G, Shi J, et al. Diagnostic value of (68)Ga-PSMA PET/CT for detection of phosphatase and tensin homolog expression in prostate cancer: a pilot study. J Nucl Med. 2020;61:873–80. https://doi.org/10.2967/jnumed.119.236059.
24. Zhang Q, Zang S, Zhang C, Fu Y, Lv X, Zhang Q, et al. Comparison of Ga-PSMA-11 PET-CT with mpMRI for preoperative lymph node staging in patients with intermediate to high-risk prostate cancer. J Transl Med. 2017;15:230. https://doi.org/10.1186/s12967-017-1333-2.
25. Liu C, Liu T, Zhang Z, Zhang N, Du P, Yang Y, et al. Ga-PSMA PET/CT combined with PET/ultrasound-guided prostate biopsy can diagnose clinically significant prostate cancer in men with previous negative biopsy results. J Nucl Med. 2020;61:1314–9. https://doi.org/10.2967/jnumed.119.235333.
26. Zhang L-L, Li W-C, Xu Z, Jiang N, Zang S-M, Xu L-W, et al. Ga-PSMA PET/CT targeted biopsy for the diagnosis of clinically significant prostate cancer compared with transrectal ultrasound guided biopsy: a prospective randomized single-centre study. Eur J Nucl Med Mol Imaging. 2021;48:483–92. https://doi.org/10.1007/s00259-020-04863-2.
27. Lopci E, Colombo P, Lazzeri M. Mismatched imaging findings of prostate cancer diagnosis: 68 Ga-PSMA PET/CT vs mpMRI. Nucl Med Mol Imaging. 2021;55:199–202. https://doi.org/10.1007/s13139-021-00701-x.
28. Lopci E, Lughezzani G, Castello A, Saita A, Colombo P, Hurle R, et al. Prospective evaluation of Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography in primary prostate cancer diagnosis. Eur Urol Focus. 2021;7:764–71. https://doi.org/10.1016/j.euf.2020.03.004.
29. Uprimny C, Kroiss AS, Decristoforo C, Fritz J, von Guggenberg E, Kendler D, et al. Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. Eur J Nucl Med Mol Imaging. 2017;44:941–9. https://doi.org/10.1007/s00259-017-3631-6.
30. Mansi R, Fleischmann A, Mäcke HR, Reubi JC. Targeting GRPR in urological cancers–from basic research to clinical application. Nat Rev Urol. 2013;10:235–44. https://doi.org/10.1038/nrurol.2013.42.
31. Wieser G, Mansi R, Grosu AL, Schultze-Seemann W, Dumont-Walter RA, Meyer PT, et al. Positron emission tomography (PET) imaging of prostate cancer with a gastrin releasing peptide receptor antagonist–from mice to men. Theranostics. 2014;4:412–9. https://doi.org/10.7150/thno.7324.
32. Zhang J, Niu G, Fan X, Lang L, Hou G, Chen L, et al. PET using a GRPR antagonist Ga-RM26 in healthy volunteers and prostate cancer patients. J Nucl Med. 2018;59:922–8. https://doi.org/10.2967/jnumed.117.198929.
33. Touijer KA, Michaud L, Alvarez HAV, Gopalan A, Kossatz S, Gonen M, et al. Prospective study of the radiolabeled GRPR antagonist BAY86-7548 for positron emission tomography/computed tomography imaging of newly diagnosed prostate cancer. Eur Urol Oncol. 2019;2:166–73. https://doi.org/10.1016/j.euo.2018.08.011.
34. Epstein JI, Feng Z, Trock BJ, Pierorazio PM. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol. 2012;61:1019–24. https://doi.org/10.1016/j.eururo.2012.01.050.
35. Bittner N, Merrick GS, Butler WM, Bennett A, Galbreath RW. Incidence and pathological features of prostate cancer detected on transperineal template guided mapping biopsy after negative transrectal ultrasound guided biopsy. J Urol. 2013;190:509–14. https://doi.org/10.1016/j.juro.2013.02.021.
36. Walz J, Graefen M, Chun FKH, Erbersdobler A, Haese A, Steuber T, et al. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. Eur Urol. 2006;50:498–505.
37. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, Prostate imaging reporting and data system version 2.1, et al. update of prostate imaging reporting and data system version 2. Eur Urol. 2019;2019(76):340–51. https://doi.org/10.1016/j.eururo.2019.02.033.
38. Lv Z, Jiang H, Hu X, Yang C, Chand H, Tang C, et al. Efficacy and safety of periprostatic nerve block combined with perineal subcutaneous anaesthesia and intrarectal lidocaine gel in transrectal ultrasound guided transperineal prostate biopsy: a prospective randomised controlled trial. Prostate Cancer Prostatic Dis. 2020;23:74–80. https://doi.org/10.1038/s41391-019-0155-0.
39. Mai Z, Zhou Z, Yan W, Xiao Y, Zhou Y, Liang Z, et al. The transverse and vertical distribution of prostate cancer in biopsy and radical prostatectomy specimens. BMC Cancer. 2018;18:1205. https://doi.org/10.1186/s12885-018-5124-9.
40. Bjurlin MA, Carter HB, Schellhammer P, Cookson MS, Gomella LG, Troyer D, et al. Optimization of initial prostate biopsy in clinical practice: sampling, labeling and specimen processing. J Urol. 2013;189:2039–46. https://doi.org/10.1016/j.juro.2013.02.072.
41. van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol. 2020;44:e87-e99. https://doi.org/10.1097/PAS.0000000000001497.
42. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33:272–7. https://doi.org/10.1200/JCO.2014.55.1192.
43. Tosoian JJ, Mamawala M, Epstein JI, Landis P, Wolf S, Trock BJ, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol. 2015;33:3379–85. https://doi.org/10.1200/JCO.2015.62.5764.
44. Eder M, Schäfer M, Bauder-Wüst U, Haberkorn U, Eisenhut M, Kopka K. Preclinical evaluation of a bispecific low-molecular heterodimer targeting both PSMA and GRPR for improved PET imaging and therapy of prostate cancer. Prostate. 2014;74:659–68. https://doi.org/10.1002/pros.22784.
45. Kesch C, Vinsensia M, Radtke JP, Schlemmer HP, Heller M, Ellert E, et al. Intraindividual comparison of F-PSMA-1007 PET/CT, multiparametric MRI, and radical prostatectomy specimens in

patients with primary prostate cancer: a retrospective, proof-of-concept study. J Nucl Med. 2017;58:1805–10. https://doi.org/10.2967/jnumed.116.189233.
46. Scheltema MJ, Chang JI, Stricker PD, van Leeuwen PJ, Nguyen QA, Ho B, et al. Diagnostic accuracy of Ga-prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) and multiparametric (mp)MRI to detect intermediate-grade intra-prostatic prostate cancer using whole-mount pathology: impact of the addition of Ga-PSMA PET to mpMRI. BJU Int. 2019;124(Suppl 1):42–9. https://doi.org/10.1111/bju.14794.
47. Donato P, Roberts MJ, Morton A, Kyle S, Coughlin G, Esler R, et al. Improved specificity with Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. Eur J Nucl Med Mol Imaging. 2019;46:20–30. https://doi.org/10.1007/s00259-018-4160-7.
48. Hoffmann MA, Miederer M, Wieler HJ, Ruf C, Jakobs FM, Schreckenberger M. Diagnostic performance of Gallium-PSMA-11 PET/CT to detect significant prostate cancer and comparison with FEC PET/CT. Oncotarget. 2017;8:111073–83. https://doi.org/10.18632/oncotarget.22441.
49. Rüschoff JH, Ferraro DA, Muehlematter UJ, Laudicella R, Hermanns T, Rodewald A-K, et al. What's behind Ga-PSMA-11 uptake in primary prostate cancer PET? Investigation of histopathological parameters and immunohistochemical PSMA expression patterns. Eur J Nucl Med Mol Imaging. 2021;48:4042–53. https://doi.org/10.1007/s00259-021-05501-1.
50. Lazzeri M, Chiti A. PSMA PET-CT: the winner takes it all. Eur J Nucl Med Mol Imaging. 2021;48:3760–1. https://doi.org/10.1007/s00259-021-05534-6.
51. Bodar YJL, Jansen BHE, van der Voorn JP, Zwezerijnen GJC, Meijer D, Nieuwenhuijzen JA, et al. Detection of prostate cancer with F-DCFPyL PET/CT compared to final histopathology of radical prostatectomy specimens: is PSMA-targeted biopsy feasible? The DeTeCT trial. World J Urol. 2020. https://doi.org/10.1007/s00345-020-03490-8.
52. Donato P, Morton A, Yaxley J, Ranasinghe S, Teloken PE, Kyle S, et al. Ga-PSMA PET/CT better characterises localised prostate cancer after MRI and transperineal prostate biopsy: is Ga-PSMA PET/CT guided biopsy the future? Eur J Nucl Med Mol Imaging. 2020;47:1843–51. https://doi.org/10.1007/s00259-019-04620-0.
53. Sawicki LM, Kirchner J, Buddensieck C, Antke C, Ullrich T, Schimmöller L, et al. Prospective comparison of whole-body MRI and Ga-PSMA PET/CT for the detection of biochemical recurrence of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging. 2019;46:1542–50. https://doi.org/10.1007/s00259-019-04308-5.
54. Zhao J, Liu J, Sun G, Zhang M, Chen J, Shen P, et al. The prognostic value of the proportion and architectural patterns of intraductal carcinoma of the prostate in patients with de novo metastatic prostate cancer. J Urol. 2019;201:759–68. https://doi.org/10.1016/j.juro.2018.10.016.

Authors and Affiliations

Dong-Xu Qiu[1] · Jian Li[2] · Jin-Wei Zhang[3] · Min-Feng Chen[1] · Xiao-Mei Gao[4] · Yong-Xiang Tang[2] · Ye Zhang[5] · Xiao-Ping Yi[3] · Hong-ling Yin[4] · Yu Gan[1] · Gui-Lin Wang[1] · Xiong-Bing Zu[1] · Shuo Hu[2] · Yi Cai[1]

✉ Shuo Hu
cai-yi@csu.edu.cn; hushuo2018@163.com

✉ Yi Cai
cai-yi@csu.edu.cn; hushuo2018@163.com

[1] Department of Urology, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, People's Republic of China

[2] Department of PET Center, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, People's Republic of China

[3] Department of Radiology, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, People's Republic of China

[4] Department of Pathology, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, People's Republic of China

[5] Department of Oncology, NHC Key Laboratory of Cancer Proteomics, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, People's Republic of China