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ORIGINAL ARTICLE

Diagnostic accuracy of multiparametric MRI- and microultrasound-targeted biopsy in biopsy-naïve patients with a PI-RADS 5 lesion: a single-institutional study

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Abstract

Purpose To evaluate the diagnostic accuracy of multiparametric magnetic resonance imaging (MRI)- and microultrasound (microUS)-guided targeted biopsy (TBx) in detecting prostate cancer (PCa) and clinically significant (cs) PCa among men with Prostate Imaging Reporting and Data System (PI-RADS 5) lesions and to compare this combined TBx (CTBx) strategy with CTBx plus systemic biopsy (SBx).

Methods One hundred and thirty-six biopsy-naïve patients with PI-RADS 5 lesion at multiparametric MRI undergoing CTBx plus SBx were retrospectively evaluated. Analysis of diagnostic performance of microUS-TBx, MRI-TBx, CTBx, SBx and combined CTBx plus SBx was performed. Cost (downgrade, upgrade and biopsy core) to effectiveness (detection rate) was compared.

Results CTBx achieved a comparable detection rate to CTBx plus SBx in diagnosis of PCa and csPCa (PCa: 78.7% [107/136] vs 79.4% [108/136]; csPCa: 67.6% [92/136] vs 67.6% [92/136]; $p > 0.05$) and outperformed SBx (PCa: 58.8% [80/136]; csPCa: 47.8% [65/136]; $p < 0.001$). Using CTB would have avoided 41.1% (56/136) unnecessary SBx, without missing any csPCa. The rate of any upgrading or csPCa upgrading was significantly higher by SBx than by CTBx [33/65 (50.8%) vs 17/65 (26.1%) and 20/65 (30.8%) vs 4/65 (6.15%), respectively, $p < 0.05$]. Considering csPCa detection rate, microUS showed high sensitivity and positive predictive value (94.6%, 87.9%, respectively), with lower specificity and negative predictive value (25.0% and 44.4%, respectively). At multivariable logistic regression models, positive microUS was identified as an independent predictor of csPCa ($p = 0.024$).

Conclusions A combined microUS/MRI-TBx approach could be the ideal imaging tool for characterizing primary disease in PI-RADS five patients, allowing SBx to be avoided.

Keywords Microultrasound · Multiparametric MRI · Prostate biopsy · Imaging · Diagnosis

Introduction

Multiparametric (mp) magnetic resonance imaging (MRI)- and MRI-targeted biopsies (TBx) increase the detection of clinically significant (cs) prostate cancer (PCa) while decreasing that of clinically insignificant (ci) PCa [1–5]. However, combining MRI-TBx with systematic biopsy (SBx) further improves csPCa diagnosis [6], with a lower risk of tumor upgrading at radical prostatectomy (RP) specimens [7]. Consequently, international guidelines are still recommending the use of both techniques for biopsy-naïve patients with suspicious of PCa [8, 9]. However, by this combined approach, more ciPCa is unnecessarily

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detected [2, 10], without drastically improving the detection rate of csPCa [2, 10], and yet resulting in higher rates of complications such as bleeding and infection [11]. These evidence raised questions about the need to perform SBx in patients with highly suspicious lesion at mpMRI, defined as Prostate Imaging Reporting and Data System (PI-RADS) 5 lesion [5]. Additional imaging techniques capable of identifying suspicious areas may further increase the diagnostic yield of mpMRI avoiding SBx in this subset of patients [12]. The use of microultrasound (microUS) enables to visualize potential targets in real time, while also adding MRI/ultrasound fusion targets [13]. Compared with SBx, microUS-TBx has been reported to decrease the detection of ciPCa [10, 14] while improving MRI-TBx detection rate of csPCa [15].

However, it remains unclear whether a combined targeted biopsy (CTBx) approach integrating mpMRI with microUS may avoid SBx in PI-RADS 5 patients. Therefore, the aim of this study was to evaluate the detection rate of PCa and csPCa by CTBx among men with PI-RADS 5 lesion at mpMRI and to assess the diagnostic yield of SBx in the same population.

Materials and methods

Study design and data source

This study is a subgroup analysis of a previously published experience. It was approved by our institution's ethical committee, and all participants provided informed consent for the clinical trial (ICH 003 v1.0 27/09/2017; study number 2004) [14]. A prospectively collected database of patients undergoing microUS-TBx was maintained since October 2017. Biopsies were offered to men suspected of having PCa based on digital rectal examination (DRE) and/or prostate-specific antigen (PSA) value. Among 835 procedures performed up to March 2022, 172 patients underwent PBx having PI-RADS 5 lesion at mpMRI. The inclusion criteria for this study were biopsy-naïve men with at least one PI-RADS 5 lesion at mpMRI, undergoing fusion PBx within 6 months of mpMRI. The exclusion criteria included: patients with a PI-RADS 5 lesion coexisting with another suspicious lesion, namely PI-RADS 3 or 4 lesions; patients with previous history of PBx; and patients enrolled in an active surveillance protocol (AS) (suppl. Figure 1).

mpMRI, microUS assessment and prostate biopsy procedure

All patients underwent mpMRI using 3.0-T scanners. When mpMRI was performed at different centers, images were routinely reviewed. Focal lesions on mpMRI were scored according to PI-RADS v 2.0 [16] or PI-RADS v 2.1 [17] from 2019. PSA value and prostate volume measured through mpMRI were recorded to obtain PSA density (PSAd). Prior to biopsy procedure, all patients were evaluated with the ExactVu system with an EV29 L 29 MHz side-fire transducer (Exact Imaging, Markham, Canada). The PRI-MUS grading system was used to assess the risk of PCa visualized under microUS and to locate targets in any prostatic region [18]. Local anesthesia using 1% lidocaine subcutaneously and at the junction of both seminal vesicles and the prostate was used for transperineal and transrectal procedures, with the addition of mild sedation under anesthesiologic control for the former. The urologist performing microUS was blinded to the mpMRI results. Each lesion with a PRI-MUS score of ≥ 3 was subjected to at least two TBxs. Subsequently, the urologist was unblinded to mpMRI results, and an mpMRI/microUS fusion TBx was performed obtaining at least two cores for each PI-RADS 5 lesion using the Biojet software. A transperineal approach was used in the case of lesions located at the level of the apex or in the anterior/transitional zone of the prostate, while a transrectal approach was preferred in the case of lesions located in the mid-portion or base of the prostate. In the case of topographically concordant lesions at microUS and mpMRI, targeted biopsies were obtained using both imaging modalities. Finally, each patient was subjected to a SBx.

Histopathological evaluation

Biopsies and prostatic specimens after RP were prepared and examined by a dedicated experienced uro-histopathologist according to the International Society of Urological Pathology (ISUP) 2014 recommendations [19]. For biopsy specimens, the number of positive cores, tumor percentages, length of cores and ISUP Grade Group (GG) were provided. CsPCa was defined as any ISUP GG ≥ 2 disease at biopsy specimens [19]. For histopathologic specimens, ISUP, as well as surgical margin, extracapsular extension, seminal vesicle invasion and lymph node invasion, was recorded.

Study endpoints

The primary endpoint was to compare the detection rate of PCa and csPCa through CTBx and CTBx plus SBx approach in men with PI-RADS 5 lesion.

The secondary endpoints were the following: to assess the diagnostic accuracy of microUS for detecting csPCa in this subset of individuals; to assess upgrading and downgrading of ISUP GG on RP specimens compared with CTBx and CTBx plus SBx; to assess how many PI-RADS 5 patients

could avoid SBx and the proportion of missed csPCa; and to assess the predictors of csPCa in PI-RADS 5 patients.

Statistical analysis

Descriptive statistics were used to present clinical, mpMRI and microUS characteristics. Continuous variables were presented as median (interquartile range) and categorical variables as numbers with percentages. The Mann–Whitney *U* test and Pearson Chi-square tests were applied to determine the statistical significance of differences in medians and proportions, respectively. Sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) of microUS were also determined. To compare the proportions of csPCa and ciPCa in both pathways, McNemar's tests were used. The frequency of avoided biopsies was determined as the number of negative tests divided by the total cohort. Multivariable logistic regression models (MLRMs) were fitted to determine the predictors of csPCa. The diagnostic accuracy of MLRM was reported as area under the receiver operator characteristic (ROC) curve. Statistical significance was set at $p < 0.05$. Statistical analysis was performed with STATA®16.1 (StataCorp, College Station, Texas).

Results

Baseline characteristics

Of 136 men included, 108/136 (79.4%) were diagnosed as PCa and 92/136 (67.6%) as csPCa. Most of the patients underwent transrectal PBx procedure, 104/136 (76.5). Patients with PRI-MUS ≥ 3 had higher median PSAd (0.20 vs 0.13 ng/ml^2; $p = 0.027$), higher positive DRE rates (67% vs 18%; $p = 0.002$), greater diameter of mpMRI lesion (20 mm vs 17 mm; $p = 0.002$), higher proportion of PCa (99% vs 9%; $p < 0.001$), higher proportion of csPCa (87% vs 5%; $p = 0.009$) and higher ISUP group value ($p < 0.001$) than those with PRI-MUS 1–2. The baseline characteristics of the patients are summarized in Table 1.

microUS imaging and biopsy results

MicroUS identified lesions in 117/136 (86.0%) patients, with 85/117 (72.6%) having PRI-MUS score of 5. Concordant lesions between mpMRI and microUS were found in 107/136 (78.7%) patients. A concordance between PRI-MUS 5 and PI-RADS 5 score was observed in 78/107 (72.9%) cases. Conversely, in 29 (27.1%) patients, the lesion score was upgraded from a lower PRI-MUS to a PI-RADS 5 score. Finally, a similar csPCa detection rate between microUS-TBx and MRI-TBx was observed in patients with topographically discordant lesions. A detailed stratification of patients according to PRI-MUS finding and concordance lesions with mpMRI are reported in supplementary suppl. table 1.

Among patients with a negative microUS examination, 9/19 (47.4%) did harbor PCa and 5/19 (26.3%) harbored csPCa. Among patients with at least 1 PRI-MUS ≥ 3 lesion, 99/117 (84.6%) patients were diagnosed with PCa and 87/117 (74.4%) with csPCa. Complete results of ciPCa and csPCa detection stratified according to PRI-MUS are depicted in suppl. Figure 2.

Considering csPCa detection rate, microUS showed high SE and PPV (94.6%, 87.9%, respectively), while SP and NPV were lower (25.0%, 44.4%, respectively). A detailed comparison of diagnostic accuracy of microUS for both PCa and csPCa detection is reported in suppl. table 2.

The distribution of the detection rate for PCa and csPCa between CTBx, SBx, MRI-TBx, mircoUS-TBx and combined CTBx/SBx is illustrated in Fig. 1a. Using CTBx/SBx as reference standard, CTBx had a similar detection rate for PCa (78.7% [107/136]) and csPCa (67.6% [92/136]) compared with CTBx/SBx (PCa, 79.4% [108/136]; csPCa, 67.6% [92/136]; *p* values 0.3173). CTBx resulted in a higher overall detection rate for PCa and csPCa than did by SBx (PCa, 58.8% [80/136]; csPCa, 47.8% [65/136]; *p* values < 0.001).

Overall, CTBx detected 99.1% (107/108) PCa and 100% (92/92) csPCa, while SBx missed 25.2% (27/107) PCa and 29.3% (27/92) csPCa. In paired comparison matrix (Fig. 1b), CTBx redetected 28/136 (20.6%) additional PCa lesions and 27/136 (19.8%) additional csPCa lesions against SBx. On the contrary, SBx redetected only 1/136 (0.73%) new PCa lesions and no new csPCa lesions against TBx. Regarding ISUP GG upgrading at biopsy specimens, CTBx was responsible for upgrading of events in 37/136 (27.2%) patients against SBx (yellow-shaded area in Fig. 1b), while SBx was responsible for upgrading of events in 4/136 (2.94%) patients against TBx (blue-shaded area in Fig. 2b). Considering the effects of three different biopsy approaches on the reduction of biopsy cores, CTBx had lower number of biopsy cores (median 4; range 3–5) compared with SBx (median 12; range 10–12) and combined CTBx plus SBx (median 15; range 14–16) ($p < 0.001$). Thus, a total of 344 SBx cores could have been avoided in 136 men. If the optimized strategy is used, men with PI-RADS 5 undergoing CTBx can achieve an excellent PCa detection rate (99.1% [107/108]), at lower costs (median biopsy core, 4) compared with CTBx/SBx.

Of 27/136 (19.8%) csPCa cases missed by SBx, 23/136 (16.9%) csPCa cases were detected by both microUS- and MRI-targeted biopsies. The remaining four cases of csPCa

Table 1 Baseline characteristics of the overall population and after stratification according to PRI-MUS score at microultrasound

		Total *N* = 136	PRI-MUS 1–2 *N* = 19	PRI-MUS ≥ 3 *N* = 117	*p* value
Age, median (IQR)	years	68.5 (60.5–74.0)	68 (59–73)	69 (61–74)	0.64
Body max index, median (IQR)	Kg/m^2	25.6 (24.3–27.8)	25.6 (24.6–27.5)	25.56 (24.3–27.8)	0.85
PCa familiarity, no (%)	No	104 (76.5)	16 (84.2)	88 (75.2)	0.39
	Yes	32 (23.5)	3 (15.8)	29 (24.8)	
Total PSA, median (IQR)	ng/mL	8.75 (6.35–13.0)	6.7 (5.6–12)	9.1 (6.6–13.4)	0.15
Prostate volume, median (IQR)	mL	45 (35.0–65.5)	55 (40–65)	45 (33–66)	0.094
PSAd, median (IQR)	ng/mL/mL	0.19 (0.12–0.29)	0.13 (0.10–0.18)	0.20 (0.12–0.31)	**0.027**
PSAd cut-off, no (%)	< 0.15 ng/mL/mL	50 (36.8)	10 (52.6)	40 (34.2)	0.12
	≥ 0.15 ng/mL/mL	86 (63.2)	9 (47.4)	77 (65.8)	
Digital rectal examination, no (%)	No	85 (62.5)	18 (94.7)	67 (57.3)	**0.002**
	Yes	51 (37.5)	1 (5.30)	50 (42.7)	
Systematic cores, median (IQR)		12 (10–12)	12 (10–12)	12 (10–12)	0.43
Target cores, median (IQR)		4 (3–5)	3 (2–5)	4 (3–5)	0.20
Total cores, median (IQR)		15 (14–16)	15 (14–16)	15 (14–16)	0.94
Length of lesion at mpMRI, median (IQR)		20 (17–23)	17 (15–18.5)	20 (18–24)	**0.002**
Prostate cancer, no (%)	No	28 (20.6)	10 (52.6)	18 (15.4)	**< 0.001**
	Yes	108 (79.4)	9 (47.4)	99 (84.6)	
Clinically significant Prostate Cancer, no (%)	No	16 (14.8)	4 (44.0)	12 (12.0)	**0.009**
	Yes	92 (85.2)	5 (56.0)	87 (88.0)	
ISUP grade group, no (%)	Negative	28 (20.6)	10 (52.6)	18 (15.4)	**< 0.001**
	1	16 (11.8)	4 (21.1)	12 (10.3)	
	2	25 (18.4)	3 (15.8)	22 (18.8)	
	3	26 (19.1)	2 (10.5)	24 (20.5)	
	4	18 (13.2)	0 (0.0)	18 (15.4)	
	5	23 (16.9)	0 (0.0)	23 (19.7)	
Radical prostatectomy, *n* (%)	No	65 (60.2)			

All values are reported as median and interquartile range

The ANOVA test was used to compare categorical variables, while the Mann–Whitney *U* test was used to compare continuous variables

ANOVA analysis of variance, *IQR* interquartile range, *mpMRI* multiparametric magnetic resonance imaging, *PRI-MUS* prostate risk identification using microultrasound, *PSA* prostate-specific antigen, *PSAd* PSA density

Bold values indicate $p < 0.05$

were diagnosed on microUS-targeted ($n = 3$; 2.21%) and MRI-targeted ($n = 1$; 0.73%) biopsies only. Of 6/136 (4.41%) ciPCa identified by CTB, 4/136 (2.94%) were detected by both microUS- and MRI-targeted biopsies. The remaining two cases of ciPCa were diagnosed on MRI-TBx. Using CTBx would have resulted in avoiding 56/136 (41.1%) unnecessary biopsies, without missing any csPCa. Full comparative results between microUS and MRI-TBx are provided in suppl. Figure 3. At MLRMs, positive microUS was identified as independent predictors of csPCa, as shown in suppl. table 3. The accuracy of a model including PRI-MUS score, PSAd cut-off, age, body mass index, length of lesion at mpMRI and digital rectal examination was 0.79 (95% CI 0.78–0.92) (suppl. Figure 4).

Comparison between biopsy and prostatectomy results

A total 65 patients underwent RP at our institutions and therefore had RP pathology/histology report available. Bilateral csPCa, pathological stage pT2c or greater and nodal metastases (N1) were identified in (15/65) 23.1%, (58/65) 89.2% and (18/65) 27.7%, respectively. In RP specimens, GS upgrading was observed in 16/65 (24.6%) patients and 4/65 (6.15%) of them occurred in biopsied ciPCa lesions. Compared with CTBx, the rates of any upgrading or csPCa upgrading were significantly higher by SBx than those by CTBx, respectively, 33/65 (50.8%) vs 17/65 (26.1%) and 20/65 (30.8%) vs 4/65 (6.15%) (Fig. 1c), $p < 0.001$.

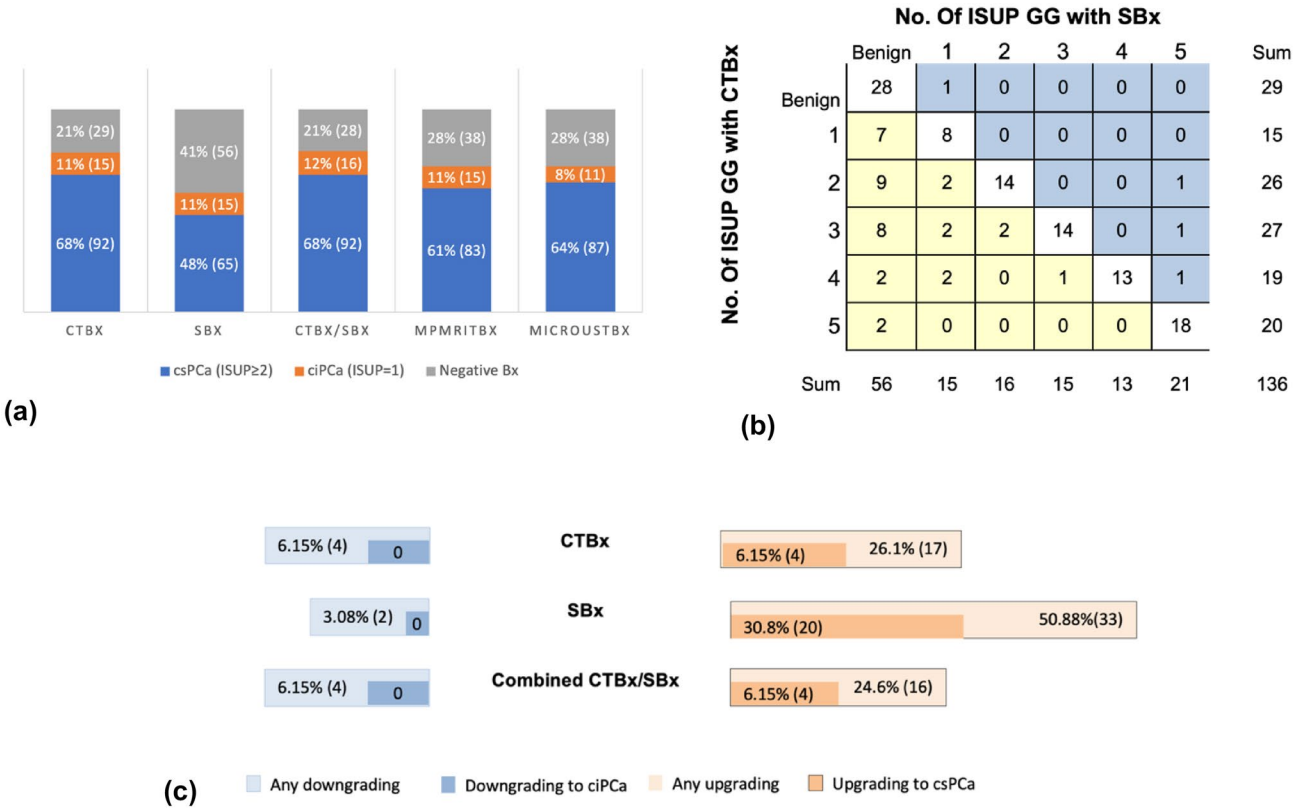

Fig. 1 Pairwise comparison of detection rates for PCa between CTBx, SBx and combined CTBx + SBx. **a** Shown are the percentage (detection rate) and number of cancers detected by CTBx, SBx and CTBx + SBx, MRI-TBx and microUS-TBx stratified according to biopsy results (negative, ISUP 1, ISUP ≥ 2). **b** Shown is the cross-tabulation of ISUP GG detected by CTBx and SBx. The areas shaded in yellow indicate the men who were upgraded to higher ISUP GG by CTBx against SBx, and the areas shaded in blue indicate the men who were upgraded to higher ISUP GG by SBx against CTBx. **c** Among the 65 men who underwent radical prostatectomy, shown are the numbers and percentages of those in whom the ISUP GG of PCa was downgraded or upgraded after whole-mount histopathological analysis of surgical specimens according to the biopsy methods. *PCa* prostate cancer, *csPCa* clinically significant PCa, *ciPCa* clinically insignificant PCa, *SBx* systematic biopsy, *CTBx* combined targeted biopsy, *MRI-TBx* multiparametric magnetic resonance imaging TBx, *microUS-TBx* microultrasound TBx, *GG* grade group, *ISUP* International Society Urological Pathology

Discussion

To the best of our knowledge, this is the largest published series analyzing the impact of two different imaging-guided TBxs among biopsy-naïve patients presenting PI-RADS 5 lesion. According to our results, performing prebiopsy mpMRI and microUS seems a valuable strategy to avoid SBx without compromising csPCa detection rate in this subset of patients. These findings confirm the usefulness of integrating microUS and mpMRI to rule out csPCa in this specific population [15, 20, 21]. In our study cohort, CTBx detected 99.1% PCa and 100% csPCa. Adding SBx to CTBx in those patients did not improve the detection rate of csPCa, while it increased the number of biopsy cores, which could lead to increased post-biopsy complications [11, 22]. Our results are consistent with those of several studies showing that microUS improves the accuracy of mpMRI [14, 23, 24]. Thus, Socarras et al. reported that microUS-TBx detected 11% additional cancers undetected by both MRI-TBx and SBx[25]. Similarly, Ghai et al. demonstrated that a CTBx approach led to the detection of csPCa in 38 of 94 men, whereas no other cases of csPCa were identified by adding SBx [15]. Aligned with this study, we demonstrate that microUS-TBx added 2.21% csPCa to MRI-TBx, with CTBx redetecting 20.6% additional PCa lesions and 19.8% additional csPCa lesions against SBx. Besides, the literature reports many valuable options to improve MRI-TBx accuracy [13]. Among radiological tools, prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) may be helpful in localizing cancer within the prostate [26, 27]. However, compared with PSMA-PET, microUS is a non-invasive, rapidly available and economic tool [15]. Moreover, before recommending the introduction of PSMA-PET-TBx into the diagnostic pathway of PCa, future studies evaluating its cost-effectiveness are

warranted [26]. Furthermore, a growing body of evidence is focusing on the combination of MRI-TBx with PCa risk calculators to improve TBx diagnostic accuracy [28]. For instance, Tafuri et al. in a retrospective study of patients in different biopsy settings showed that SBx added a negligible value to MRI-TBx among men with PI-RADS 5 and PSAd > 0.15 ng/ml^2 [11]. However, if SBx was not performed, 4% of csPCa would be missed, whereas in our case series CTBx achieved 100% csPca detection. In addition, 45% of these patients presented csPCa in the contralateral biopsy sample, which could have been detected by adding another imaging test, such as microUS. Thus, we believe that CBTx approach is a better strategy, adding different anatomic and pathological information provided by the real-time microUS examination. Indeed, in our population a total of 344 SBx cores could have been avoided in 136 men, without decreasing the detection rate of csPCa. Therefore, avoiding SBx could improve cost-effectiveness and patients' satisfaction, reducing discomfort, adverse events and complications [11]. Additionally, in line with previous studies [15], we report that among men undergoing RP, CTBx results in fewer upgrade events compared with SBx (50.8% and 26.1%, respectively), with lower upgrade to ISUP GG ≥ 2 than SBx alone (6.15%, vs 30.8%, respectively). Interestingly, our ISUP GG ≥ 2 upgrade rate is even lower than that of MRI-TBx alone [7, 11]. Performing CTBx also led to a high ciPCa detection rate. However, as suggested by previous studies, ISUP GG 1 cancers that are visible on mpMRI have a higher risk of adverse pathological findings at RP specimens and a higher risk of progressing than mpMRI-negative, especially among this relatively young age group [5, 29]. Finally, the literature shows more audacious papers that even suggest skipping prostate biopsy before RP, in a well-defined PCa population. For instance, a recent retrospective case series showed that, in patients with a high suspicion of PCa at mpMRI and PSMA-PET, avoiding PBx before RP could be a valid option [30]. However, as the false-positive rate of both tools seems high, this practice cannot be recommended as a standard procedure at this time. Our intent is to improve mpMRI findings by the real-time microUS examination and avoid SBx, not to avoid TBx at all. This study has several limitations. Firstly, it is a retrospective study. However, the data were prospectively collected, and this represents one of the largest series evaluating PI-RADS 5 patients. Secondly, all biopsies were performed by two urologists with large experience performing MRI-TBx in a tertiary center, raising concern about generalizability to non-tertiary centers. Thirdly, although the urologists were blinded to lesion locations on mpMRI, an observer bias may be present because all patients included in the current study had suspicious lesions on mpMRI. Including only these patients makes it impossible to assess the diagnostic accuracy of mpMRI and to provide a comparison of the accuracy of the two diagnostic tools, leading to results that may be misleading. In addition, high prostate volume and tumor localization may affect results, as anterior or transitional lesions may be missed or misinterpreted by microUS. Finally, the number of SBx and TBx cores that were taken per patient was not standardized, possibly leading to an underestimation of csPCa in patients with fewer biopsy cores.

Conclusions

In conclusion, our results highlight the potential of a combined microUS/mpMRI approach as the ideal imaging tool for characterizing primary disease. This approach might reduce over detection, overtreatment and undertreatment, thus improving oncologic outcomes, quality of life and cost-efficiency for the population. Performing TBx guided by microUS and mpMRI findings could avoid SBx in PI-RADS 5 patients. Future research should further evaluate this promising strategy in terms of decision making and cost-effectiveness.

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Author contributions PPA was involved in protocol/project development, data analysis and manuscript—writing/editing. VF was involved in data collection or management and data analysis. RS-S and NMB were involved in manuscript—writing/editing. DM, NF and MP were involved in data collection or management. ML, AS, RH, GG and PC contributed to protocol/project development. GL contributed to protocol/project development and involved in manuscript—writing/editing.

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Data availability Not Available.

Declarations

Conflict of interest Giovanni Lughezzani certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties or patent filed, received or pending), are the following: nothing to disclose.

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

consent for the clinical trial (ICH 003 v1.0 27/09/2017; study number 2004).

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