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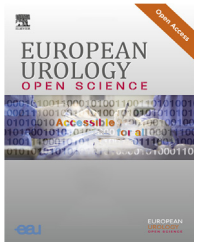

European Association of Urology

Prostate Cancer

A Propensity Score–matched Comparison of Micro-ultrasound–guided Transrectal and Magnetic Resonance Imaging/Transrectal Ultrasound Fusion-guided Transperineal Prostate Biopsies for Detection of Clinically Significant Prostate Cancer

Andrea Piccolini [a,b], *Pier Paolo Avolio* [a,b], *Cesare Saitta* [a,b], *Edoardo Beatrici* [a,b], *Stefano Moretto* [a,b], *Muhannad Aljoulani* [a,b], *Filippo Dagnino* [a,b], *Davide Maffei* [a,b], *Nicola Frego* [a,b], *Vittorio Fasulo* [a,b], *Marco Paciotti* [b], *Rodolfo Hurle* [b], *Alberto Saita* [b], *Massimo Lazzeri* [b], *Paolo Casale* [b], *Piergiuseppe Colombo* [a,c], *Miriam Cieri* [c], *Nicolò Maria Buffi* [a,b], *Giovanni Lughezzani* [a,b,*]

[a] *Department of Biomedical Sciences, Humanitas University, Milan, Italy;* [b] *Department of Urology, IRCCS Humanitas Research Hospital, Milan, Italy;* [c] *Department of Pathology, IRCCS Humanitas Research Hospital, Milan, Italy*

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Abstract

Background and objective: High-resolution micro-ultrasound (microUS) is an advanced imaging tool. Our objective was to determine whether systematic microUS use for transrectal biopsy (TRBx) improves the detection rate for clinically significant prostate cancer (csPCa) in comparison to transperineal biopsy (TPBx) performed with magnetic resonance imaging (MRI)/conventional transrectal ultrasound (TRUS) fusion software.

Methods: We retrospectively analyzed data for men who underwent prostate biopsies, including those on active surveillance (AS). TRBx was performed under microUS guidance, while MRI/TRUS fusion was consistently used to guide TPBx. Patients were matched according to propensity score matching (PSM). The primary endpoint was comparison of the csPCa detection rate with the two approaches. Secondary endpoints included predictors of csPCa (International Society of Urological Pathology grade group $\geq$2, assessed via multivariable logistic regression) and complication rates.

Key findings and limitations: Overall, 1423 patients were enrolled. After applying PSM we identified an analytical cohort of 1094 men, 582 in the TRBx group and 512 in the TPBx group. There was no significant difference in the csPCa detection rate between the TRBx (45%) and TPBx (51%) groups (p = 0.07). Complications occurred in nine of 1094 patients (1%). On adjusted multivariable analysis, TPBx had a similar csPCa detection rate to TRBx (adjusted odds ratio [aOR] 1.26; p = 0.09). Predictors of csPCa detection were a positive family history (aOR 1.68; 95% confidence interval [CI] 1.20–2.35; p = 0.002); age (aOR 1.04, 95% CI

* Corresponding author. Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy. Tel. +39 342 324 8136.
E-mail address: giovanni.lughezzani@hunimed.eu (G. Lughezzani).

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1.02–1.06; $p < 0.001$); positive digital rectal examination (aOR 2.35, 95% CI 1.70–3.25; $p < 0.001$); prostate-specific antigen density $\geq$0.15 ng/ml/cm^3 (aOR 3.23, 95% CI 2.47–4.23; $p < 0.001$); and a Prostate Imaging-Reporting and Data System score $\geq$3 (aOR 2.46; 95% CI 1.83–3.32; $p < 0.001$). Limitations include the retrospective nature of the study, the risk of underestimating the complication rate, and the heterogeneity of biopsy indications.

Conclusions and clinical implications: TRBx using microUS alone showed a comparable csPCa detection rate to TPBx guided by MRI/TRUS fusion software. Given the better visualization and real-time detection of suspicious zones with microUS, the potential for improvement in the csPCa detection rate with greater integration of microUS in the TPBx setting warrants further investigation.

Patient summary: We compared the ability of two different prostate biopsy approaches to detect clinically significant prostate cancer. We found that transrectal biopsy guided by micro-ultrasound had similar detection rates to transperineal biopsy guided by a combination of magnetic resonance imaging and conventional ultrasound. More research is needed to confirm the potential of micro-ultrasound for transperineal biopsy.

1. Introduction

The traditional method for diagnosis of prostate cancer (PCa) involves prostate-specific antigen (PSA) screening and transrectal ultrasound (TRUS)-guided biopsy [1,2]. However, this strategy can result in overdiagnosis of clinically insignificant PCa and underdiagnosis of clinically significant PCa (csPCa) [3]. The widespread adoption of multiparametric magnetic resonance imaging (mpMRI)-guided biopsy has increased the csPCa detection rate over conventional systematic biopsy [4,5]. However, the effectiveness of MRI-targeted biopsy is hindered by limitations in MRI/TRUS fusion strategies. At the same time, mpMRI may overlook clinically significant lesions: despite negative mpMRI results, up to 35% of patients may still harbor PCa [6].

The 2023 European Association of Urology (EAU) guidelines included micro-ultrasound (microUS) as a novel imaging modality for csPCa detection. With an operating frequency of 29 MHz, in contrast to 6–12 MHz for conventional TRUS, microUS provides efficient spatial resolution (up to 70 μm) and better visualization [7]. MicroUS can guide prostate biopsies and facilitate real-time detection of potentially cancerous regions, and thus reduces the need for MRI/TRUS fusion when targeting mpMRI-visible lesions. Furthermore, microUS/mpMRI image fusion appears to improve cancer detection rates in comparison to MRI/TRUS fusion [8]. Nonetheless, mpMRI provides functional details such as diffusion-weighted imaging and dynamic contrast-enhanced sequences [9].

Besides the different strategies available, prostate biopsy complications represent a significant public health challenge [10]. A recent meta-analysis found no significant association between the biopsy approach and the csPCa detection rate when considering all biopsy indications [11]. Current microUS hardware supports both transrectal biopsy (TRBx) and transperineal biopsy (TPBx) with FusionVu™ mpMRI/microUS image fusion software [12]. Our objective was to determine whether systematic use of microUS for TRBx improves the csPCa detection rate in comparison to TPBx with mpMRI/TRUS fusion software.

2. Materials and methods

2.1. Study population

We conducted a retrospective analysis of data for men who underwent prostate biopsy at our tertiary care center from October 2017 to May 2023. Our study included men, irrespective of biopsy history, aged between 40 and 75 yr who had total PSA <20 ng/ml and presented with clinical suspicion of PCa because of elevated PSA, positive digital rectal examination (DRE) findings (evidence of cT1 or cT2 disease), or mpMRI examination (1.5-T scanner equipped with an endorectal coil or 3.0-T scanner) revealing at least one suspicious lesion with a Prostate Imaging-Reporting and Data System (PI-RADS) score $\geq$3. Patients on active surveillance (AS) were also included. In our cohort, patients on AS had PCa of International Society of Urological Pathology grade group (GG) 1–2, clinical stage $\leq$cT2b, PSA $\leq$20 ng/ml, and PSA density $\leq$0.20 ng/ml/cm^3 at the time of diagnosis. Patients with PCa incidentally discovered during prostate resection for benign pathology were also included [13]. The exclusion criteria were total PSA >20 ng/ml (six patients) and prior treatments such as radiation therapy (two patients), focal therapy (four patients), or androgen deprivation therapy (three patients). We also excluded 56 men (10%) men in the TPBx group who underwent microUS-guided TPBx from the analysis.

2.2. Biopsy procedure

MicroUS was consistently used for TRBx, while an MRI/TRUS fusion system (Biojet; D&K Technologies GmbH, Barum, Germany) was consistently used for TPBx. All patients,

regardless of biopsy approach, underwent mpMRI before biopsy. The urologist performing the microUS assessment was blinded to the MRI results. All suspicious lesions with a Prostate Risk Identification Using Micro-Ultrasound (PRIMUS) score ≥3 were targeted. In the TPBx setting, mpMRI/TRUS fusion biopsy was performed for all lesions with a PI-RADS score ≥3; in cases with negative mpMRI results, only systematic biopsy was performed. All biopsies were performed by two urologists with expertise in microUS; both clinicians used a TRBx or TPBx approach, depending on the location of the lesions. Both TRBx and TPBx targeted strategies were complemented by systematic randomized biopsies, consisting of at least six cores in the repeat biopsy setting and at least 12 cores in the initial biopsy setting, in accordance with the EAU guidelines [1]. All patients received prophylactic antibiotic therapy with fosfomycin.

2.3. Statistical analysis

The primary endpoint was the csPCa detection rate on targeted/systematic biopsy with microUS-guided TRBx versus MRI/TRUS fusion-guided TPBx. Secondary endpoints were predictors of clinically significant PCa (defined as any GG ≥2 disease in biopsy specimens [14]) and the complication rates for the two approaches. Patients were routinely contacted 3–4 wk after their procedure, and any complications that occurred during this time were reported by the attending physician on an electronic form and subsequently recorded in our database. Data are reported in accordance with the guidelines for reporting of statistics for clinical research in urology [15]. Statistical analysis was conducted according to the parameter distribution as determined via a Shapiro-Wilk test for normality. Results for continuous variables are reported as the mean and standard deviation for those following a normal distribution, or the median with interquartile range (IQR) for variables with a non-normal distribution. To address variations in demographic and tumor characteristics, we applied propensity score matching (PSM) for comparison of the TRBx and TPBx groups. PSM was performed within a caliper width of 0.0001, considering relevant covariates such as age at diagnosis, DRE results, PI-RADS scores, and detection of extraprostatic extension on MRI. The propensity scores were calculated using an extensive multivariable logistic regression model with nearest-neighbor matching algorithm at a 1:1 ratio. We then assessed differences in preoperative variables between the groups, both before and after PSM was applied. Continuous variables were analyzed using a paired *t* test for normally distributed variables, and a Wilcoxon rank-sum test for variables that were not normally distributed. For categorical variables, the Pearson χ^2 test was applied, or Fisher's exact test with Yates correction when appropriate. All statistical tests were two-sided at an α level of 0.05. Analyses were performed using Stata 18/SE software (StataCorp, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

Overall, 1423 patients underwent prostate biopsy. After applying PSM, we selected a matched cohort of 1094 men, 582 in the TRBx group and 512 in the TPBx group. Baseline characteristics of the matched cohort stratified by biopsy approach are reported in Table 1. After PSM, the TRBx and TPBx groups were well balanced for all the covariates included (biopsy history, age, positive DRE and side, total PSA, PSA density, lesion site, and prostate volume). Complications occurred in nine of 1094 patients (1%), comprising three cases with acute urinary retention and one with fever in the TRBx group, and three cases with acute urinary retention, one with fever, and one with bleeding in the TPBx group.

3.2. Biopsy results

There was no significant difference in the csPCa detection rate between the matched TRBx (45%) and TPBx (51%) groups (p = 0.07, Table 2). In addition, TRBx and TPBx resulted in comparable csPCa detection rates when stratified by lesion site (anterior/transitional or posterior/peripheral zone; p = 0.08, Table 3).

Table 1 – Patient characteristics at baseline stratified according to the biopsy approach after propensity score matching

Parameter [a]	Transrectal biopsy (n = 582)	Transperineal biopsy (n = 512)	p value
Age (yr)	64 (58–71)	65 (59–70)	0.7
Active surveillance, *n* (%)			0.04
No	536 (92)	453 (88)	
Yes	46 (8)	59 (12)	
DRE findings, *n* (%)			0.3
Negative	439 (75)	372 (73)	
Positive	143 (25)	140 (27)	
Side positive on DRE, *n* (%)			0.2
Right	57 (10)	66 (13)	
Left	43 (7)	57 (11)	
Bilateral	9 (2)	4 (1)	
Data missing	473 (81)	385 (75)	
Family history, *n* (%)			0.7
Positive	107 (18)	103 (20)	
Negative	475 (82)	409 (80)	
Total PSA (ng/ml)	6.6 (5–9)	6.7 (5–9)	0.8
PSA density, *n* (%)			0.6
<0.15 ng/ml/cm^3	334 (57)	286 (56)	
≥0.15 ng/ml/cm^3	248 (43)	226 (44)	
Lesion location, *n* (%)			<0.001
Apex	155 (27)	152 (30)	
Base	69 (12)	88 (17)	
Margin	107 (18)	109 (21)	
Anterior	15 (3)	7 (1)	
Transitional zone	154 (27)	66 (13)	
Negative	82 (13)	90 (18)	
Prostate volume (cm^3)	50.0 (37.9–70.0)	50.0 (35.0–68.0)	0.2
Previous biopsy, *n* (%)			0.2
No	418 (72)	385 (75)	
Yes	164 (28)	127 (25)	
Number of targeted cores	4 (3–6)	3 (2–4)	<0.001
Total number of cores	14 (12–16)	14 (12–15)	0.08
Complications, *n* (%)			0.6
No	578 (99)	507 (99)	
Yes	4 (1)	5 (1)	

DRE = digital rectal examination; PSA = prostate-specific antigen.
[a] Results for continuous variables are presented as median (interquartile range).

3.3. Predictors of csPCa

Adjusted multivariable analysis for the PSM cohort revealed that microUS-guided TRBx had similar ability to detect csPCa to MRI/TRUS fusion-guided TPBx, with TPBx showing a higher adjusted odds ratio (aOR) for csPCa detection without reaching statistical significance (aOR 1.26; $p = 0.09$). Predictors of csPCa detection included positive family history (aOR 1.68, 95% confidence interval [CI] 1.20–2.35; $p = 0.002$), age (aOR 1.04, 95% CI 1.02–1.06; $p < 0.001$), positive DRE (aOR 2.35, 95% CI 1.70–3.25; $p < 0.001$), PSA density $\geq$0.15 ng/ml/cm^3 (aOR 3.23, 95% CI 2.47–4.23; $p < 0.001$), and PI-RADS $\geq$3 lesions (aOR 2.46, 95% CI 1.83–3.32; $p < 0.001$). The results are presented in Table 4.

4. Discussion

In our study, microUS-guided TRBx and MRI/TRUS-guided TPBx resulted in similar csPCa detection rates (45% vs 51%) in our PSM cohort, with no significant difference. Multivariable analysis also revealed that TPBx had similar odds of detecting csPCa compared to TR. There is a lack of uniformity among guideline recommendations for prostate biopsy. The EAU guidelines support the TPBx approach, emphasizing lower rates of infection and sepsis [1]. Conversely, the American Urological Association supports both approaches given the lack of prospective randomized controlled trials (RCTs) on the risk of infection [16]. However, TPBx is gaining in popularity because of its higher PCa detection rate in the anterior and apical zones, lower sepsis rates, and a lower risk of rectal bleeding [17]. No RCT has yet examined the impact of the access route on the csPCa detection rate using microUS/mpMRI fusion. A recent single-center retrospective analysis showed comparable csPCa diagnostic performance with microUS/mpMRI fusion for TRBx and TPBx [17]. Consistent with these findings, our results demonstrated a nonsignificant difference in csPCa detection rates between the two approaches in our matched cohort. The similar csPCa detection rate after adjustment for clinical covariates suggests the importance of patient selection when deciding between TRBx and TPBx [18]. In agreement with our results, the prospective PERFECT RCT showed that tailoring biopsy procedures according to lesion location could improve csPCa detection. In this trial comparing csPCa detection rates after prebiopsy mpMRI between image-guided TRBx and TPBx, the overall PCa detection rates were similar [19,20].

Although mpMRI/TRUS fusion enhances the PCa detection rate during biopsy, it involves additional costs, time, and technical expertise in comparison to traditional TRUS-guided biopsy [21]. The current microUS system offers real-time orientation tracking and allows longitudinal comparison of lesions and mpMRI image fusion. While interobserver agreement and the learning curve for PRI-MUS scoring are still under investigation, preliminary data suggest that satisfactory sensitivity can be achieved within the first 20–40 cases, with satisfactory specificity requiring 40–90 cases [8]. On the basis of the results for our TRBx cohort, integration of microUS devices into MRI-targeted TPBx protocols could offer enhanced precision in targeting suspicious lesions identified by both imaging modalities.

Challenges such as limited availability, costs, the need for radiological expertise, and the complexity of the procedure have hindered widespread adoption of mpMRI, so several studies have investigated the diagnostic accuracy of microUS in comparison to mpMRI for csPCa detection [22]. Our previous study demonstrated high sensitivity (94%) but limited specificity (28%) for microUS in detecting csPCa. Multiple articles from 2019 to 2022 highlighted similarities in csPCa detection rates between mpMRI and microUS for biopsy guidance. Results from a prospective study of 194 patients suggested that microUS may have a comparable csPCa detection rate to mpMRI [23]. Another study involving 320 patients confirmed the potential of microUS, showing comparable csPCa detection rates [24]. A multicenter prospective registry trial compared the sensitivity and specificity of mpMRI and microUS: the device demonstrated noninferiority to mpMRI and superiority in sensitivity and negative predictive value [25]. A subsequent study and two meta-analyses supported the noninferiority of microUS targeted biopsy non-inferiority to mpMRI in detecting csPCa [9,26,27]. Moreover, according to a 2023 report, microUS is a valuable tool for identifying the presence of csPCa in patients with persistent clinical suspicion despite previous negative mpMRI findings [28].

Table 2 – csPCa detection rate with transrectal versus transperineal biopsy propensity score matching

csPCa	Patients, *n* (%) Transrectal biopsy	Transperineal biopsy	*p* value
No	318 (55)	249 (49)	0.07
Yes	264 (45)	263 (51)	

csPCa = clinically significant prostate cancer.

Table 3 – csPCa detection rate with transrectal versus transperineal biopsy according to lesion site

	csPCa detected, *n* (%)		*p* value
	Transrectal biopsy	Transperineal biopsy	
Anterior/transitional zone	89 (15)	107 (21)	0.08
Posterior/peripheral zone	175 (30)	154 (30)	

csPCa = clinically significant prostate cancer.

Table 4 – Multivariable logistic regression analysis of potential predictors of clinically significant prostate cancer after propensity score matching

Predictor	Odds ratio (95% CI)	*p* value
Transperineal biopsy (vs transrectal)	1.26 (0.96–1.64)	0.09
Family history (vs no history)	1.68 (1.20–2.35)	0.002
Age	1.04 (1.02–1.06)	<0.001
Positive DRE (vs negative)	2.35 (1.70–3.25)	<0.001
PSA density $\geq$0.15 ng/ml/cm^2 (vs <0.15)	3.23 (2.47–4.23)	<0.001
Anterior lesions	1.31 (0.97–1.75)	0.08
PI-RADS score $\geq$3	2.46 (1.83–3.32)	<0.001
Previous biopsies (vs biopsy-naïve)	0.76 (0.56–1.04)	0.09

CI = confidence interval; DRE = digital rectal examination; PSAD = prostate-specific antigen; PI-RADS = Prostate Imaging-Reporting and Data System.

Our study confirms a low risk of infection regardless of the biopsy approach, in line with results reported by Mian et al [10] for a prospective RCT involving 351 patients, of whom underwent TRBx and 367 underwent TPBx. According to a composite measure, an infectious complication event occurred in nine patients (2.6%) in the TRBx group and ten (2.7%) in the TPBx group, with no septic event, confirming clinical safety for both procedures. In our study, complications occurred in nine of 1094 patients (1%), with four in the TRBx group and five in the TPBx group. A recent study [29] and a previous meta-analysis [30] on the role of periprocedural prophylactic antibiotics for TPBx indicated that avoidance of routine antibiotic use carries a very low risk of side effects, although there is still a need to determine when a subset of men might benefit from antibiotic prophylaxis. Optimization of patient selection could be key to reducing the risk of infection: in our cohort, patients with a larger prostate preferably underwent TPBx to reduce the risk of infection and urinary retention. It is important to note that every patient in our cohort received antibiotic prophylaxis before biopsy, regardless of the access route.

Given the recognized advantages of microUS over conventional TRUS, such as the better visualization and real-time detection of suspicious zones, and the use of TRUS in our TPBx cohort, adoption of microUS for TPBx to improve the csPCa detection rate warrants additional investigation. Further studies with a larger sample size and systematic integration of devices supporting microUS in TPBx are needed. OPTIMUM RCT is assessing the potential of microUS as a standalone alternative to both mpMRI and conventional TRUS fusion, with a focus on csPCa detection rates for microUS versus microUS/mpMRI fusion versus conventional US/mpMRI fusion for targeted biopsies [31]. Findings from the trial will provide valuable insights into whether microUS should be considered a substitute for or an adjunct to systematic and mpMRI-targeted biopsy procedures.

Considering the evidence discussed, the procedural costs of TPBx [12], and recent data supporting the safety of both biopsy procedures, our study results confirm the utility of microUS as an aid when performing TRBx to limit logistics and nonconsumable support costs in urological centers where TRBx is still routinely performed.

Our study has some limitations. First, this was a retrospective study susceptible to selection bias. We mitigated this limitation via accurate PSM to obtain an appropriately matched cohort of patients; however, it is important to consider that the biopsy approach depends on multiple clinical characteristics and the surgeon's preference. Our complication rates are likely to be underestimated because of the focus on complications reported by patients 3–4 wk after their procedure. Lastly, the study is limited by heterogeneity in biopsy indications.

While we await more robust evidence from studies designed to compare microUS against the standard of care in more homogeneous and larger cohorts, the current findings may stimulate interest in this technology, demonstrating its apparent effectiveness and utility for both TRBx and TPBx. Large-scale studies are needed to validate the utility of microUS and refine its role in PCa diagnosis.

5. Conclusions

Our study suggests that TRBx using microUS alone offers similar ability to detect csPCa as TPBx using MRI/TRUS fusion with conventional transrectal ultrasound. Given the better visualization and real-time detection of suspicious zones with microUS, the potential for improvement in the csPCa detection rate with increasing integration of microUS in the TPBx setting warrants further investigation.

Author contributions: Giovanni Lughezzani had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Piccolini, Avolio, Lughezzani.
Acquisition of data: Piccolini, Saitta, Beatrici, Moretto, Aljoulani, Dagnino, Maffei, Fasulo, Frego.
Analysis and interpretation of data: Saitta, Avolio, Piccolini.
Drafting of the manuscript: Piccolini.
Critical revision of the manuscript for important intellectual content: Avolio, Lughezzani, Buffi, Paciotti, Hurle, Saita, Lazzeri, Casale.
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