Transperineal freehand multiparametric MRI fusion targeted biopsies under local anaesthesia for prostate cancer diagnosis: a multicentre prospective study of 1014 cases

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Original Article

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Transperineal freehand multiparametric MRI fusion targeted biopsies under local anaesthesia for prostate cancer diagnosis: a multicentre prospective study of 1014 cases

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Objective

To assess the outcomes of multiparametric magnetic resonance imaging (mpMRI) transperineal targeted fusion biopsy (TPFBx) under local anaesthesia.

Patients and Methods

We prospectively screened 1327 patients with a positive mpMRI undergoing TPFBx (targeted cores and systematic cores) under local anaesthesia, at two tertiary referral institutions, between September 2016 and May 2019, for inclusion in the present study. Primary outcomes were detection of clinically significant prostate cancer (csPCa) defined as (1) International Society of Urological Pathologists (ISUP) grade >1 or ISUP grade 1 with >50% involvement of prostate cancer (PCa) in a single core or in >2 cores (D1) and (2) ISUP grade >1 PCa (D2). Secondary outcomes were: assessment of peri-procedural pain (numerical rating scale [NRS]) and procedure timings; erectile (International Index of Erectile Function) and urinary (International Prostate Symptom Score) function changes; and complications. We also investigated the value of systematic sampling and concordance with radical prostatectomy (RP).

Results

A total of 1014 patients were included, of whom csPCa was diagnosed in 39.4% (n = 400). The procedure was tolerable (NRS pain score 3.1 ± 2.3), with no impact on erectile (P = 0.45) or urinary (P = 0.58) function, and a low rate of complications (Clavien–Dindo grades 1 or 2, n = 8; grade >2, n = 0). No post-biopsy sepsis was recorded. Twenty-two men (95% confidence interval [CI] 17–29) needed to undergo additional systematic biopsy to diagnose one csPCa missed by targeted biopsies (D1). ISUP grade concordance of biopsies with RP was as follows: k = 0.40 (95% CI 0.31–0.49) for targeted cores alone and k = 0.65 (95% CI 0.57–0.72; P < 0.05) overall.

Conclusions

The use of TPFBx under local anaesthesia yielded good csPCa detection and was feasible, quick, well tolerated and safe. Infectious risk was negligible. Addition of systematic to targeted cores may not be needed in all men, although it improves csPCa detection and concordance with RP.

Keywords

prostate cancer detection, transperineal MRI-guided fusion biopsy, local anaesthesia, procedural pain, complications, radical prostatectomy, #PCSM, #ProstateCancer, #urooncc

Introduction

The prostate cancer (PCa) diagnostic pathway has been recently revolutionized by multiparametric MRI (mpMRI) of the prostate, which currently represents the standard of care before prostate biopsies for men with cancer suspicion. In case of negative findings, patients can be either discharged or can undergo a systematic, blind biopsy of the prostate, depending on PCa risk. In case of a positive mpMRI, a targeted biopsy directed at the suspicious area is advised [1].

Nonetheless, there is still major debate about whether a prostate biopsy should be performed with a transperineal (TP) or transrectal (TR) approach. The debate dates as far back as the 1990s, and there are still no definitive conclusions in the current mpMRI targeted biopsy era. This uncertainty is of great significance, considering prostate biopsy is one of the most frequently performed urological procedures, with approximately two million men undergoing it each year in Europe and in the USA [2–4].

Those supporting the TR route argue that it provides superior deliverability in the outpatient setting, and superior patient tolerability in terms of pain, lower rates of urinary retention and shorter procedural timings compared with the TP route [5], whereas those supporting the TP route point to a reduction in the rate of infections, which constitutes a major supporting argument considering the dramatic increase in post-TR-biopsy sepsis rates in recent decades [6,7]. The TP route is also reported to provide greater accessibility to certain areas of the prostate, potentially resulting in higher PCa detection rates [5,8].

The potential advantages of one technique other the other have never been confirmed and/or investigated in a robust randomized controlled trial (RCT) and thus remain theoretical, but recent series proved the feasibility of TP biopsy in an outpatient setting, confirming an absence of significant infectious risks. These studies were mainly retrospective, however, potentially missing complications. Furthermore, they often included a limited number of patients [9–11], were performed at single institutions using different techniques [9–13] or did not evaluate important aspects, including pain and/or impact on erectile and urinary function [9–11]. Stefanova et al. [12] reported only pain outcomes for more than 1000 non-MRI-targeted biopsies.

The aim of the present study, therefore, was to perform a large multicentre prospective study to confirm the feasibility of freehand TP mpMRI targeted fusion biopsy (TPFBx) under local anaesthesia. We also evaluated the need to add systematic to targeted cores in a TP setting.

Patients and Methods

Study Outcomes

The primary outcome was the accuracy of TPFBx, demonstrated through clinically significant PCa (csPCa) detection. Secondary outcomes were evaluation of: pain; complications; need to add systematic cores to targeted cores for csPCa detection and, for those undergoing surgery, concordance with the final radical prostatectomy (RP) specimen; variation of urinary and erectile function; and procedural timings.

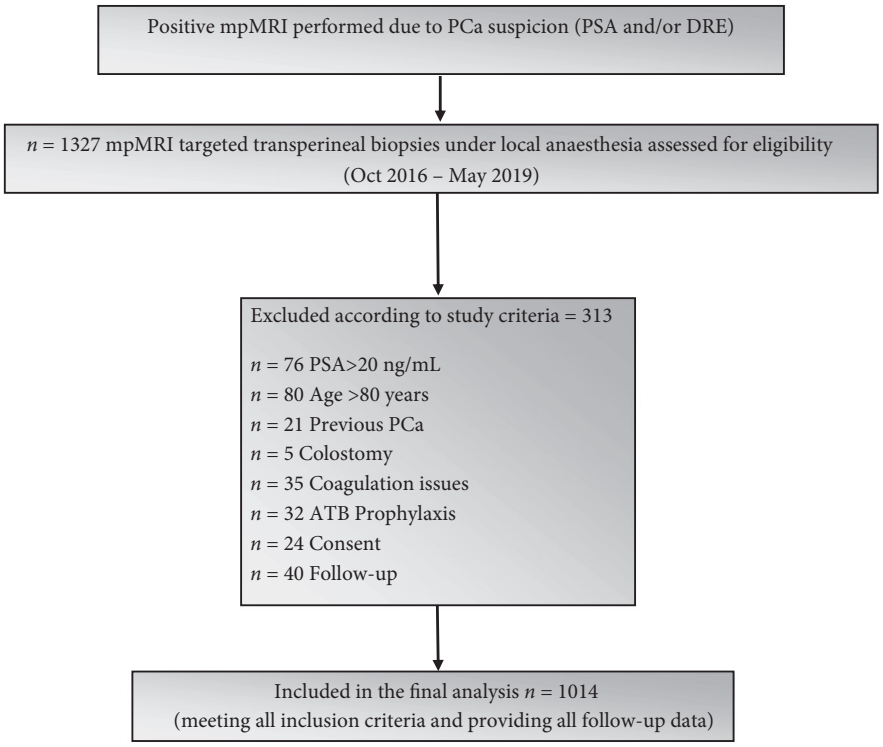
Study Cohort and Data Collection

Between September 2016 and May 2019 we prospectively screened 1327 consecutive patients undergoing TPFBx (targeted cores and systematic cores) at San Giovanni Battista Hospital, Turin, Italy and at Drum Tower Hospital, Nanjing, China for study eligibility. Indication to perform biopsy was a positive mpMRI (Prostate Imaging – Reporting and Data System [PI-RADS] version 2 score ≥3) performed owing to elevated PSA concentration and/or suspicious DRE. Exclusion criteria were as follows: PSA >20 ng/mL; age >80 years; previous PCa diagnosis; colostomy or rectal amputation; congenital coagulation alterations and/or non-interruption of anticoagulant therapy; absence of antibiotic prophylaxis; absence of consent for study participation; and absence of follow-up information. A study flow chart is presented in Fig. 1.

Data were collected before the procedure (baseline features), during the procedure (pain, peri-procedural complications and procedural timings), immediately after the procedure, before patient discharge (early-onset complications), and 40 days after the biopsy during the first clinical follow-up visit (pathology, complications and functional outcomes).

Baseline features included detailed general and urological history and comorbidity status. Urinary and erectile function were assessed using the IPSS and the International Index of Erectile Function (IIEF-5), respectively. Peri-procedural pain was determined using a numerical rating scale (NRS) of 1–10 rather than a visual analogue scale as the investigators found it easier to ask the patients rather than get them to write the scores during each different stage of the procedure. Complications were graded according to Clavien–Dindo classification and reported according to the European Association of Urology guidelines on reporting urological complications. Clinically significant PCa (csPCa) was defined as: International Society of Urological Pathology (ISUP) grade >6 or ISUP grade 6 with >50% involvement of PCa in a single core or >2 cores (D1); or ISUP grade >1 (D2).

Fig. 1 Study flow chart, including number of patients excluded and reasons. Colostomy = colostomy not allowing biopsy and/or coagulation abnormalities; Coagulation = congenital coagulation pathologies or did not interrupt anticoagulants to undergo the procedure; ATB prophylaxis = did not perform the antibiotic. prophylaxis; Consent = did not provide written consent; Follow-up = did not provide follow-up data. mpMRI, multiparametric MRI; PCa, prostate cancer.



Biopsy Technique

All TPFBx procedures were carried out in an in-office setting using the same local anaesthesia technique (peri-prostatic block and s.c. injection) using 20 mL 1% lidocaine, by a total of 30 different operators. Table S1 details antibiotic prophylaxis and operator level of experience. Ultrasonography images and fusion of ultrasonography and mpMRI images were performed using the Esaote platform (Esaote MyLab Machine class C, NaviSuite 5.0; Esaote, Genova, IT, for the Italian patients, and Esaote Real Time Virtual Sonography, Hitachi Medical Corporation, Tokyo, Japan, for the Chinese patients). The TP technique has been previously described [13]. Briefly, after performing TPFBx (median [interquartile range] 2 [2–4] cores per target), a minimum of 10 systematic cores were taken in the posterior peripheral zone (in each lobe apex, mid, basal sectors at the lateral and paramedian aspects), with the skin being punctured each time a core was taken [13].

Multiparametric MRI Imaging and Pathology

We included both mpMRI procedures performed at the referral institution (n = 825) and those not (n = 189). The mpMRI protocol used at the two institutions has been previously described [14,15]. All mpMRI scans were scored using PI-RADS version 2 and lesions were localised using the sector map therein enclosed. Lesion and prostate size were calculated using the ellipsoid formula.

All biopsy and RP specimens, processed according to the Stanford protocol, were evaluated by two dedicated senior uro-pathologists with more than 10 years' experience in prostate pathology.

Statistical Analysis

Continuous variables satisfying the Shapiro–Wilk W test are expressed as mean ± SD, and otherwise (lesion size) as median, 1st quartile and 3rd quartile. The comparison used the non-parametric Mann–Whitney U-test (P values < 0.05 indicate statistically significant differences). Categorical variables are expressed as absolute numbers and/or percentages. Cohen's linearly weighted kappa was used to calculate the degree of agreement in classification over that expected by chance: k > 0.60 indicates substantial agreement.

Statistical analyses were performed using StatPlus: macLE version 5.9.92 (Analyst Soft, Walnut, CA, USA).

Ethics

The study was registered and approved by local ethics committees at San Giovanni Battista Hospital, Turin, Italy and Drum Tower Hospital, Nanjing, China.

Results

Baseline Features

Table 1 shows the baseline features of the 1014 included patients. The mean ± SD age and PSA level were 66.8 ± 7.4 years and 8.1 ± 4.1 ng/mL, respectively. A total of 1424 lesions were identified, the majority of which were scored as PI-RADS 4 (46.1%) and had a posterior location (59.3%). The mean ± SD mpMRI prostate and lesion volumes were 51.3 ± 25.9 and 0.5 ± 0.9 mL (median [interquartile range] 0.2 [0.07–0.46]), respectively. The mean ± SD number of cores taken was 15.3 ± 1.4. The majority of patients (84.4%) were biopsy-naïve.

Clinically Significant Prostate Cancer Detection

Table 2 shows the detection of PCa overall, according to clinical significance and stratified by PI-RADS score.

Applying D1 criteria, csPCa was diagnosed in 39.4% (n = 400) and non-csPCa in 4.4% (n = 45). The percentage of csPCa increased from 15.4% for PI-RADS 3 to 73.9% for PI-RADS 5. Considering those with csPCa defined as ISUP grade >1, the detection rate of csPCa decreased to 35.4% (n = 359) and the detection rate of non-csPCa increased to 8.4% (n = 86). The rate of csPCa increased from 12.6% for PI-RADS 3 to 70.3% for PI-RADS 5. No significant differences were noted in csPCa detection when comparing anterior vs posterior mpMRI lesions, either when considering mpMRI targeted biopsy alone or mpMRI targeted plus systematic biopsy (all $P > 0.1$).

Need for Systematic Cores in Addition to Targeted Cores for Clinically Significant Prostate Cancer Detection

Table 3 shows the diagnosis of csPCa and non-csPCa according both to different definitions and to the systematic or targeted strategy. By adding systematic to mpMRI targeted biopsies a significantly higher proportion of csPCa (+4.6%, 95% CI 3.5–6.1; $P < 0.001$) and non-csPCa (+2.3%, 95% CI 1.5–3.4; $P = 0.04$) was diagnosed according to the D1 criteria; that is, 22 patients (95% CI 17–29) needed to undergo additional systematic biopsy to diagnose one csPCa. If considering csPCa as ISUP grade >1 the number of patients needing additional mapping to diagnose one csPCa further increased to 27 (95% CI 19–36).

With both definitions of csPCa, 84.1% of patients had no benefit from addition of systematic cores.

Table 1 Baseline features.

Other factors possibly interfering with outcomes and/or complications	
Number of patients	1014
Age, years	66.8 ± 7.4
Race	
White	402 (39.6)
Black	3 (0.3)
Asiatic	609 (60.1)
PCa familiarity*, *n* (%)	74 (7.3)
PSA, ng/mL	8.1 ± 4.1
Suspicious DRE, *n* (%)	237 (23.4)
PSAD†, ng/mL/mL	0.2 ± 0.1
mpMRI prostate volume†, mL	51.3 ± 25.9
Number of lesions	1424
mpMRI lesion volume‡, mL	0.5 ± 0.9
PI-RADS§	
3	599 (42.1)
4	657 (46.1)
5	144 (10.1)
Number of target areas	
1	672 (66.3)
2	274 (27.0)
3	68 (6.7)
Number of cores taken	15.3 ± 1.4
Previous biopsies, *n* (%)	
No	856 (84.4)
1	106 (10.4)
≥ 2	52 (5.2)
Previous prostate surgery for BPH, *n* (%)	
No	972 (95.9)
Open adenomectomy	9 (0.9)
TURP	33 (3.2)
BPH treatment	
No, *n* (%)	748 (73.8)
α-blockers, *n* (%)	190 (18.7)
5-α-reductase-inhibitors, *n* (%)	21 (2.1)
Combined treatment, *n* (%)	45 (4.4)
Other, *n* (%)	10 (1.0)
Years of treatment	4.0 ± 3.8
Previous prostatitis, *n* (%)	96 (9.5)
ASA classification, *n* (%)	
1	306 (30.2)
2	673 (66.4)
3	32 (3.1)
4	3 (0.3)
ECOG performance status, *n* (%)	
0	318 (31.4)
1	361 (35.6)
2	327 (32.2)
3	6 (0.6)
4	2 (0.2)
Charlson comorbidity index¶	1.9 ± 1.2
BMI, kg/m²**	24.9 ± 3.0
Smoking status, *n* (%)	
Never	668 (65.9)
Current smoker	182 (18.0)
Former smoker	163 (16.1)
Diabetes, *n* (%)	123 (12.1)
Hypercholesterolaemia, *n* (%)	102 (10.1)
Hypertension, *n* (%)	395 (38.9)
Chronic drugs possibly interfering with complications, *n* (%)	
Antiplatelet agents	115 (11.3)
Anticoagulants	16 (1.6)
Immunosuppressors	13 (1.3)
Anxiolytic	27 (2.7)
Painkillers	10 (1.0)

*ASA, American Society of Anesthesiology; BMI, body mass index; EGOG, Eastern Cooperative Oncology Group; mpMRI, multiparametric MRI; PCa, prostate cancer; PSAD, PSA density. BPH combined treatment = 5-α-reductase-inhibitors and α-blockers. Data are mean ± SD, unless otherwise indicated. *PCa familiarity has been defined according to a first degree relative with PCa diagnosis. †Missing in n = 26 men. ‡Missing in n = 24 mp-MRI lesions. §Missing for n = 24. ¶Missing for n = 1. **Missing for n = 9.*

Table 2 Prostate cancer detection overall and stratified by PI-RADS score.

	n (%)	PI-RADS 3	PI-RADS 4	PI-RADS 5
Number of patients	1014	358	500	138
Overall PCa	445 (43.9)	72 (20.1)	253 (50.6)	108 (78.2)
Non-csPCa	45 (4.4)	17 (4.7)	22 (4.4)	6 (4.3)
csPCa+	400 (39.4)	55 (15.4)	231 (46.2)	102 (73.9)
csPCa by definition				
GS ≥7	359 (35.4)	45 (12.6)	207 (41.4)	97 (70.3)
≥3 positive cores	26 (2.6)	7 (1.9)	14 (2.8)	3 (2.2)
≥50% of extension	15 (1.5)	3 (0.8)	10 (2.0)	2 (1.4)

Histological Concordance with Radical Prostatectomy

Overall, 188 patients underwent RP within the study period. Results are shown in Table S2. ISUP concordance of targeted biopsies alone with RP was 44.1% ($k = 0.34$, 95% CI 0.27–0.42) if including PCa missed by targeted biopsies and 49.7% ($k = 0.40$, 95% CI 0.31–0.49) if including only PCa identified by targeted biopsies, and significantly increased to 68.1% ($k = 0.65$, 95% CI 0.57–0.72; $P < 0.05$) when adding systematic cores.

Peri-procedural and Functional Outcomes

The procedure time was relatively short, with mean procedure time being 15.9 ± 4.9 min (systematic cores sampling 4.1 ± 1.7 min), and the procedure was tolerable, with mean NRS peri-procedural pain being low (local anaesthesia 3.9 ± 2.1; prostate sampling 3.1 ± 2.3). Thirteen patients (1.3%) did not complete the procedure due to pain and were re-scheduled for TP biopsy under general anaesthesia.

Baseline urinary (IPSS 9.9 ± 7.8) and erectile function (IIEF-5 10.4 ± 8.6) were unchanged 40 days after the procedure (IPSS 10.1 ± 7.7, $P = 0.58$, Δ IPSS 0.7 ± 1.9; IIEF-5 10.2 ± 8.6, $P = 0.45$, Δ IIEF-5 0.6 ± 1.8).

Complications

Complications are shown in Table 4. No major complications occurred (Clavien–Dindo grade >2, $n = 0$). The most frequent collateral event was haematuria (58.1%), followed by haematospermia (22.2%), both usually resolving without treatment within 10 and 20 days, respectively.

Acute urinary retention, vasovagal reactions and bleeding were rare events, occurring in <2% of patients. Fever in the 40 days following the procedure occurred in 0.7% (seven patients, two of whom did not require any antibiotic treatment). No cases of sepsis were recorded.

Discussion

To our knowledge, this is the largest multicentre study to prospectively evaluate TPFBx under local anaesthesia.

Overall, TP sampling performed using an mpMRI targeted fusion freehand technique proved feasible and safe in an in-office setting using local anaesthesia. Several aspects of this biopsy technique deserve additional comment.

First, TPFBx yields good csPCa detection. The in-office setting may be argued to have a theoretically negative influence on csPCa detection. Patient movement is not infrequent under local anaesthesia and does not occur under general anaesthesia. Furthermore, patient pain under local anaesthesia may increase movement. Nonetheless, our results are in line with recently published series that suggest there are no major differences in csPCa detection under local anaesthesia [16,17]. No relevant differences exist between cognitive and software-based fusion, although the latter may be more precise in terms of millimetres [18]. Similarly, compared with general anaesthesia, the local anaesthesia setting may slightly decrease targeting precision, but this probably does not result in relevant differences when taking multiple cores from the identified mpMRI lesion. Also, no major impact of operator level of experience was noted.

Second, the need to add systematic cores to targeted ones using the TP route is questionable as 22–27 patients need to undergo systematic cores to diagnose a single csPCa not detected by targeted biopsy; moreover, in the vast majority of the cases of our series, csPCa missed by targeted cores and diagnosed at systematic mapping are not classed as high-risk cancer. As observed in TR biopsy studies, addition of systematic cores also results in increased detection of non-csPCa, although our proportions are slightly lower compared to other reports [19,20].

The decision of whether or not to perform systematic sampling should also be based on other factors. Considering only pathological costs, the cost is estimated to be approximately $7–$10 per prostatic core; avoiding systematic sampling would save approximately $100 per procedure [21] and would have an important impact on healthcare costs worldwide [2–4].

By contrast, given the low complication rates and pain levels and the need for approximately 5 additional minutes to perform systematic sampling after targeting mpMRI-suspicious areas, addition of systematic cores may not result

Table 3 Diagnosis of clinically significant and non-clinically significant prostate cancer according to different definitions (A and B) and to the systematic (rows) or targeted (columns) strategy.

Table 3A. CSPCa if ISUP>6 or ISUP 6 with >50% involvement of PCa in a single core or >2 cores

			Target							
			No Pca	nCSPCa	CSPCa					
		ISUP	0	1	1	2	3	4	5	
Systematic	No Pca	0	569 (56.1)	12 (1.2)	6 (0.6)	33 (3.2)	24 (2.4)	7 (0.7)	0 (0.0)	651 (64.2)
	nCSPCa	1	23 (2.3)	10 (1.0)	13 (1.3)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	48 (4.8)
	CSPCa	1	8 (0.8)	0 (0.0)	14 (1.4)	3 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	26 (2.6)
		2	25 (2.4)	0 (0.0)	27 (2.6)	74 (7.3)	16 (1.6)	2 (0.2)	1 (0.1)	145 (14.2)
		3	8 (0.8)	0 (0.0)	13 (1.3)	19 (1.9)	37 (3.6)	2 (0.2)	1 (0.1)	80 (7.9)
		4	5 (0.5)	0 (0.0)	3 (0.3)	7 (0.7)	13 (1.3)	23 (2.2)	0 (0.0)	51 (5.0)
		5	1 (0.1)	0 (0.0)	2 (0.2)	1 (0.1)	2 (0.2)	4 (0.4)	3 (0.3)	13 (1.3)
			639 (63.0)	22 (2.2)	78 (7.7)	138 (13.6)	93 (9.2)	39 (3.8)	5 (0.5)	1014 (100.0)

% (95% CI)	Summary	ADDING SYSTEMATIC CORES
4.6% (95% CI 3.5 -6.1)	Systematic biopsy diagnosing a csPCa missed by Target biopsy	NET BENEFIT
1.2% (95% CI 0.7 -2.1)	Systematic biopsy not diagnosing a nCSPCa found by Target biopsy	NO BENEFIT
9% (95% CI 7.4 -10.9)	Systematic biopsy increasing ISUP of Target biopsy	POTENTIAL BENEFIT
72% (95% CI 69.2 -74.7)	Systematic biopsy not chaging ISUP or diagnosis	NO BENEFIT
2.6% (95% CI 1.7 -3.7)	Systematic biopsy finding lower ISUP compared to Target biopsy	NO BENEFIT
2.3% (95% CI 1.5 -3.4)	Systematic biopsy diagnosing a ncsPCa missed by Target biopsy	WORSE
8.3% (95% CI 6.8 -10.2)	CSPCa identified by target biopsy only	NO BENEFIT

Table 3B. CSPCa if ISUP>1

			Target						
			No Pca	nCSPCa	CSPCa				
		ISUP	0	1	2	3	4	5	
Systematic	No Pca	0	569 (56.1)	18 (1.8)	33 (3.2)	24 (2.4)	7 (0.7)	0 (0.0)	651 (64.2)
	nCSPCa	1	31 (3.1)	37 (3.7)	4 (0.4)	1 (0.1)	1 (0.1)	0 (0.0)	74 (7.4)
	CSPCa	2	25 (2.4)	27 (2.6)	74 (7.3)	16 (1.6)	2 (0.2)	1 (0.1)	145 (14.2)
		3	8 (0.8)	13 (1.3)	19 (1.9)	37 (3.6)	2 (0.2)	1 (0.1)	80 (7.9)
		4	5 (0.5)	3 (0.3)	7 (0.7)	13 (1.3)	23 (2.2)	0 (0.0)	51 (5.0)
		5	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)	4 (0.4)	3 (0.3)	13 (1.3)
			639 (63.0)	100 (9.9)	138 (13.6)	93 (9.2)	39 (3.8)	5 (0.5)	1014 (100.0)

% (95% CI)	Summary	ADDING SYSTEMATIC CORES
8.3% (95% CI 6.7 -10.1)	Systematic biopsy diagnosing a csPCa missed by Target biopsy	NET BENEFIT
1.8% (95% CI 1.1 -2.8)	Systematic biopsy not diagnosing a nCSPCa found by Target biopsy	NO BENEFIT
4.5% (95% CI 3.4 -6)	Systematic biopsy increasing ISUP of Target biopsy	POTENTIAL BENEFIT
73.2% (95% CI 70.5 -75.9)	Systematic biopsy not chaging ISUP or diagnosis	NO BENEFIT
2.2% (95% CI 1.4 -3.3)	Systematic biopsy finding lower ISUP compared to Target biopsy	NO BENEFIT
3.1% (95% CI 2.2 -4.3)	Systematic biopsy diagnosing a ncsPCa missed by Target biopsy	WORSE
6.9% (95% CI 5.5 -8.6)	CSPCa identified by target biopsy only	NO BENEFIT

Table 4 Peri- and post-procedural complications.

Number of patients Complications	1014
Acute urinary retention, *n* (%)	17 (1.7)
Vasovagal reaction, *n* (%)	18 (1.8)
Haematuria*	589 (58.1)
Mean ± SD duration, days	9.6 ± 7.2
Haematospermia*, *n* (%)	225 (22.2)
Mean ± SD duration, days	18 ± 11.9
Perineal bleeding*, *n* (%)	12 (1.2)
Rectal bleeding*, *n* (%)	3 (0.3)
Fever*, *n* (%)	7 (0.7)
Requiring antibiotic treatment, *n* (%)	5 (0.5)
Not requiring antibiotic treatment, *n* (%)	2 (0.2)
UTI*, *n* (%)	1 (0.1)
Clavien–Dindo classification, *n* (%)	
0	1006 (99.2)
1	7 (0.7)
2	1 (0.1)

*Missing in *n* = 6.

in large benefits in terms of morbidity, and certainly not in terms of infection rates. Nonetheless, our study design does not allow a definite conclusion to be drawn as we did not randomize patients to either undergo or not undergo systematic sampling.

For patients diagnosed with csPCa by targeted cores, addition of systematic sampling improved ISUP grade only in a small proportion of patients; however, when using RP specimen as the meter of comparison, concordance significantly improved, as recently found by others [22]. In our view, if envisaging whole-gland treatment options only, targeting the mpMRI-suspicious areas may be sufficient. By contrast, systematic cores may be added if considering focal therapy because of the need to exclude mpMRI-invisible csPCa in prostate zones that need to be preserved or to reduce upgrading risk. Given the low benefit with regard to csPCa detection, systematic sampling may also be considered in a second timeframe, with re-biopsy performed only for candidates for organ-preserving strategies after a first-line targeted biopsy alone.

Third, the procedure was tolerable, with a low mean NRS score and only a small minority of patients being unable to complete the procedure. As previously reported, pain is higher during local anaesthesia and then decreases when the biopsy is being performed [10,11]. Recently, pain was evaluated in a large cohort of patients undergoing TP biopsy under local anaesthesia [12]. However, that study did not include mpMRI targeted biopsies, which, because of images overlap time and the addition of targeted sampling, usually last longer than standard biopsies.. These factors are potential causes for the higher degree of pain reported during the biopsy when performing a TPFBx. Nonetheless, our findings largely support the fact that pain does not affect the feasibility of TP biopsy, even in an mpMRI targeted biopsy context.

Fourth, in line with previous studies, we observed no impact on erectile and urinary function. Peri-prostatic nerve block and oedema of neurovascular bundles and on the sampled areas are possible mechanisms behind the alteration of erectile and voiding function. Nonetheless, this does not translate into any relevant changes 40 days after the procedure [2,3]. Similarly, urinary retention was a rare event. Although it may occur, taking up to 20 TP cores under local anaesthesia, urinary retention is negligible and comparable to that observed after the TR approach [2,3]. A urinary retention rate of up to 24% has been reported in TP series [2,3]. This is far higher than that observed in the present study and others [2,3,11,23]. One reason for these differences is that several series used a template mapping technique, where up to 100 cores are taken in large prostates. Extensive sampling probably increases prostate oedema compared to other biopsy schemes, thus translating to clinically meaningful differences in terms of urinary retention. Also, general anaesthesia is an important precipitating factor for urinary retention and could explain higher retention rates [12].

Fifth, complications were negligible, mainly consisting of self-resolving haematuria, haematospermia and bleeding. In this context, we confirmed the infection rate of almost zero of recent single-centre studies [12,24]. Several groups suggested upfront antibiotic augmentation [7,25], even using carbapenem-based prophylaxis [26,27], to face the alarming worldwide increase of post-procedural sepsis following TR biopsies [3–6]. Given the global warnings on antibiotic overuse, the TP biopsy infection rate should be regarded as a major reason to prefer the TP over the TR approach.

The present study has some limitations. The absence of randomization including a TR approach is important. However, the need to perform RCTs to prove TP superiority in terms of infections is questionable given the absence of sepsis events and the very low rate of fever and UTI. Similarly, non-inferiority compared to the TR route in terms of acute urinary retention, other complications and erectile and urinary function changes probably does not need to be proven through randomization as it is not likely to have any clinical relevance.

Multicentre RCTs are, however, urgently awaited to assess pain, despite this being low using the TP route, and, more importantly, the potential advantages in terms of csPCa detection.

Other limitations include the relatively high number of different operators performing the procedure. It is likely that, if performed by experienced operators only, results would have even improved. In our view, the use of multiple operators, together with the multicentre nature of the study, rather than being a limitation, strengthens our results in terms of reproducibility. Similarly, inclusion of different mpMRI protocols and a minority of mpMRI procedures

performed outside the referral centres, enhance the generalizability of our results. Concordance with RP may appear to be suboptimal. However, if using similar categories without differentiating between Gleason score 3 + 4 and 4 + 3 (ISUP concordance), the results of the present technique (targeted and systematic cores) appear at least not to be inferior to previously published data using TP template mapping stepper-based techniques under general anaesthesia [28]. Prospective and ideally randomized comparisons of stepper-based vs freehand techniques are also needed to further explore the potential advantages of different TP approaches [29].

In conclusion, TPFBx under local anaesthesia is feasible and safe. The procedure yields good csPCa detection, requires a relatively short procedure time, has good tolerability, with overall low pain levels, low complication rates, including negligible risk of infections, and no impact on erectile and urinary function. In this context, the addition of systematic to targeted cores may not be needed and should be tailored according to the accepted rate of missed csPCa, costs, complications and treatment options availability.

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Conflict of Interests

All authors have nothing to disclose.

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Abbreviations: csPCa, clinically significant prostate cancer; IIEF-5, International Index of Erectile Function; ISUP, International Society of Urological Pathologists; mpMRI, multiparametric MRI; PCa, prostate cancer; PI-RADS, Prostate Imaging – Reporting and Data System; RCT, randomized controlled trial; RP, radical prostatectomy; TPFBx, targeted transperineal fusion biopsy; TP, transperineal; TR, transrectal.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Antibiotic Prophylaxis and Operators. Number of operators who performed prostate biopsies is stratified by experience (number of previous transperineal biopsies being performed before study initiation). On univariate analysis, operators' experience did not influence csPCa detection ($P = 0.12$).

Table S2. A) Concordance of Targeted + Systematic Biopsy with RP; B) Concordance of positive Targeted Biopsy with RP; C) Concordance of all Targeted Biopsy with RP.