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Original Article

Transitioning from transrectal to transperineal prostate biopsy using a freehand cognitive approach

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Objectives

To report a single-centre experience of a complete transition from transrectal (TR) to transperineal (TP) prostate biopsy under local anaesthesia using a freehand cognitive coaxial approach and without use of antibiotic prophylaxis.

Patients and Methods

Analysis was performed of a prospective database of patients undergoing prostate biopsy performed by four surgeons between 1 June 2018 and 31 May 2022. Outcomes of interest were complications, cancer detection rate, inter-operator reliability, and tolerability.

Results

Overall, 1915 patients underwent 2337 separate prostate biopsy sessions. Only 2.4% patients in the TP group received antibiotic prophylaxis, while 100% received antibiotics in the TR group. The complication rate was significantly lower in the TP group compared to the TR group (0.3% vs 5.0%, $P < 0.001$). In contrast to the TR group, there were no cases of urosepsis or admissions to intensive care in the TP group. The total cancer detection rate by TP biopsy was 70% and the overall pathology detection rate was 88.4%. There was no difference in cancer or pathology detection between operators. A stable level of cancer detection was reached early on for both Prostate Imaging-Reporting and Data System 4 and 5 lesions. All cases performed were performed successfully without need for early termination.

Conclusion

Implementing a complete transition from TR to TP biopsy can result in a significant reduction in complications and hospital re-admissions. A cognitive freehand coaxial technique is well tolerated by patients and achieves a high cancer detection rate.

Keywords

prostate biopsy, transrectal, transperineal, biopsy infections, biopsy complications, cognitive biopsies

Introduction

The risk of infection following transrectal (TR) biopsy of the prostate has been well documented [1,2]. This is of growing clinical relevance given the increasingly elderly population, as well as the number of individuals with a rising PSA who warrant prostate biopsy. There is a large burden on hospital resources associated with emergency re-admissions due to urosepsis following TR prostate biopsy. Furthermore, urosepsis carries a considerable mortality risk, which rises with age [3]. Antibiotic prophylaxis has been a traditional prerequisite; however, their use is being increasingly brought into question given that rates of antimicrobial resistance have increased as a result of widespread antibiotic usage across all areas of medicine. The European Association of Urology (EAU) guidelines strongly recommend against the use of fluoroquinolones in this setting [4]. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended choice according to the Norwegian Directorate of Health [5]. However, the local resistance rate for this particular antibiotic is 25%. The transperineal (TP) approach is an alternative that holds potential advantages including lower rates of post-procedural infection, although it is recognised that randomised studies are currently lacking [6,7]. Since 2022, the EAU guidelines have recommended adoption of the TP approach instead of TR biopsy despite the inherent logistical demands [4]. The latter are considerable, especially considering the aforementioned changes in patient

demographics and the high level of specialised knowledge required. To this end, novel strategies and practice patterns that allow for a simplified approach and high patient turnover are welcomed, especially when the diagnostic accuracy and complication profile are not compromised. One such approach is the cognitive freehand method and in 2019, we devised a simplified technique for performing TP prostate biopsies in this way. This was then implemented as our standard approach in 2020. This technique represents an alternative to software fusion methods.

The aim of this study was to report our approach to TP biopsy using a cognitive freehand method and its implementation, as well as evaluate outcomes including complications, cancer detection, and inter-operator reproducibility among others.

Patients and Methods

Patient Selection and Data Collection

Regional Ethics Committee approval (REK 2022-465 105-1) was gained, and all included patients provided consent. Analysis was performed of prospectively collected data on all patients undergoing outpatient prostate biopsy at Haukeland University Hospital, a tertiary referral centre in Western Norway between 1 June 2018 and 31 May 2022. Data collection was achieved using the UI-Path software package, which automatically reads data entered in the structured forms (Fig. S1) in a patient's electronic journal. All prostate biopsies were eligible including those performed in the primary setting or as part of active surveillance. These were performed by four consultant urologists.

Outcomes of Interest

Primary outcomes of interest were:

- Complications requiring hospital re-admissions within 30 days. These were graded according to the Clavien–Dindo Classification.
- Cancer detection measured in terms of total cancer detection rate (CDR), clinically significant CDR (CSCDR) and overall abnormal histopathology detection rate (OAPDR). The latter included cancer as well as other non-malignant histological changes such as atypical small acinar proliferation (ASAP)/prostatic intraepithelial neoplasia (PIN), inflammation, and atrophy.
- Inter-operator reproducibility determined by the differences in CDR, CSCDR and OAPDR between the four operators.

Secondary outcomes of interest were:

- Tolerability. Successful completion of TP biopsy under local anaesthesia (LA) was used as a surrogate for this.
- Efficiency as determined by biopsy turnover before and after transition to TP biopsy as the standard approach.

Data were also collected on baseline demographics including PSA, PSA density (PSAD), prostate volume, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and histological findings.

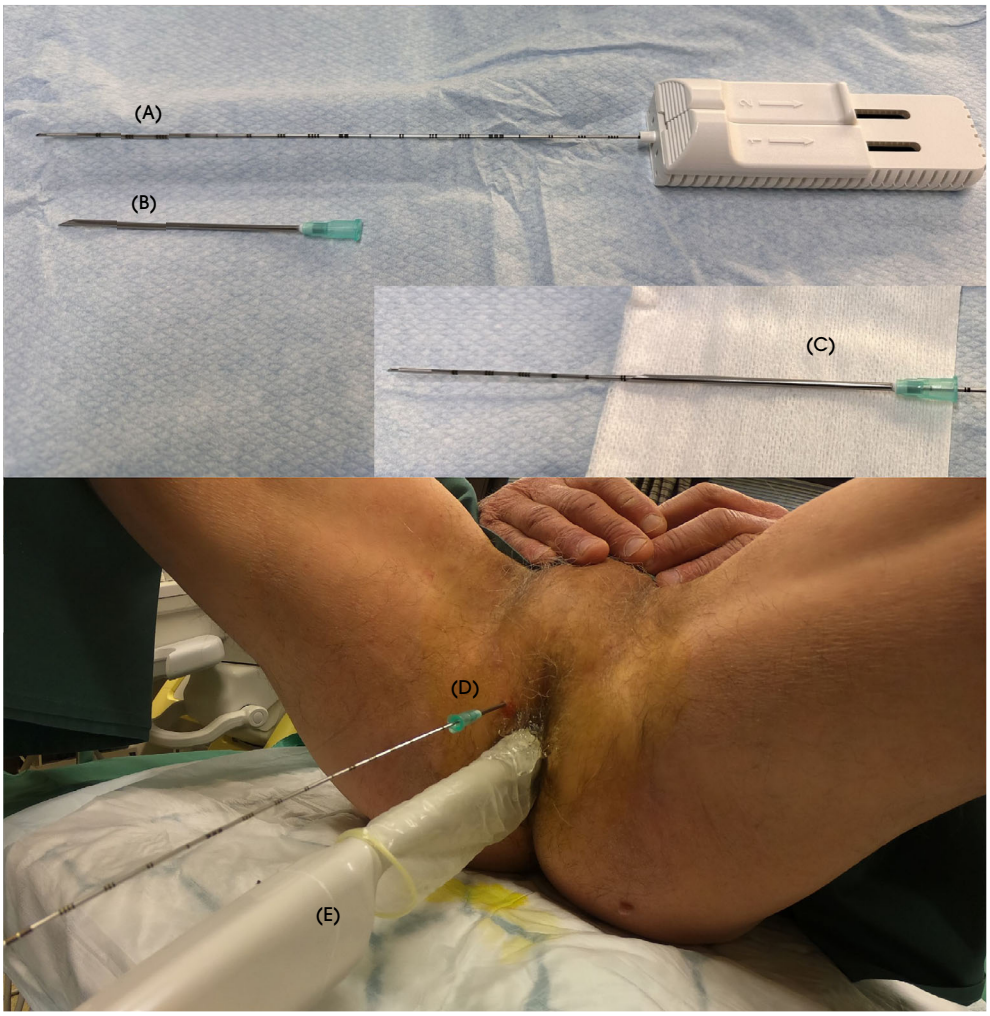
Patient Selection and Antibiotic Prophylaxis

In accordance with national guidelines, all patients planned for TR biopsy received two tablets of TMP-SMX 80/400 mg 1 h before the procedure [5]. During the transition from TR to TP biopsy, the first patients of the day were given antibiotic prophylaxis 1 h before the final choice of biopsy method was made. A 30-min period was scheduled prior to the start of every outpatient biopsy session so that the urologist could review all relevant imaging alongside a consultant radiologist with a subspecialisation in MRI. Most MRIs were performed on the day before the scheduled biopsy and therefore selection could not be determined further in advance. Each clinic appointment was allocated 30 min and up to 10 patient biopsy sessions were possible per day. In the early period of the transition, only patients with large Prostate Imaging-Reporting And Data System (PI-RADS) 4–5 lesions were selected for TP biopsy, while smaller lesions and patients with bilateral PI-RADS 3 lesions and a PSAD >0.2 ng/mL/mL still underwent TR biopsy (either targeted or 12-standard). By initially selecting TP biopsies in the patients with larger targets, the likelihood of missing the target was lower. For PI-RADS 3 lesions, TR biopsy was initially continued as the operators had more experience and therefore confidence with this approach. By 2021, antibiotic prophylaxis was not given routinely, and only patients with artificial heart valves were given prophylaxis (in the form of amoxicillin 2 g orally). TR biopsy was discontinued completely by February 2021, and since then only TP biopsy has been performed. Indications for biopsy include PI-RADS 4 and 5 lesions irrespective of PSAD, as well as PI-RADS 3 lesions and a PSAD >0.2 ng/mL/mL.

Description of the Technique

The TP technique is a simplified version of the Cambridge PROstate Biopsy devicE (CamPROBE)™ coaxial biopsy procedure [8]. The latter has not been available in Norway and therefore a modified approach was devised, which does not require the bespoke equipment. The technical approach used is similar to those described by the recent studies of both Wetterauer et al. [7] and Gorin et al. [9]. Off-the-shelf 14-G 80-mm large bore needles are used, which allows an 18-G biopsy needle to pass through (Fig. 1). The perineum is cleaned with chlorhexidine 5%, holding the sponges with

Fig. 1 Overview of equipment used for the TP approach: (**A**) 18-G TruCut disposable biopsy needle. (**B**) 14-G 80-mm large bore access needle. (**C**) Demonstration of biopsy needle passing through access needle. (**D**) TP approach without sterile drapes. (**E**) Longitudinal biplane ultrasound probe.

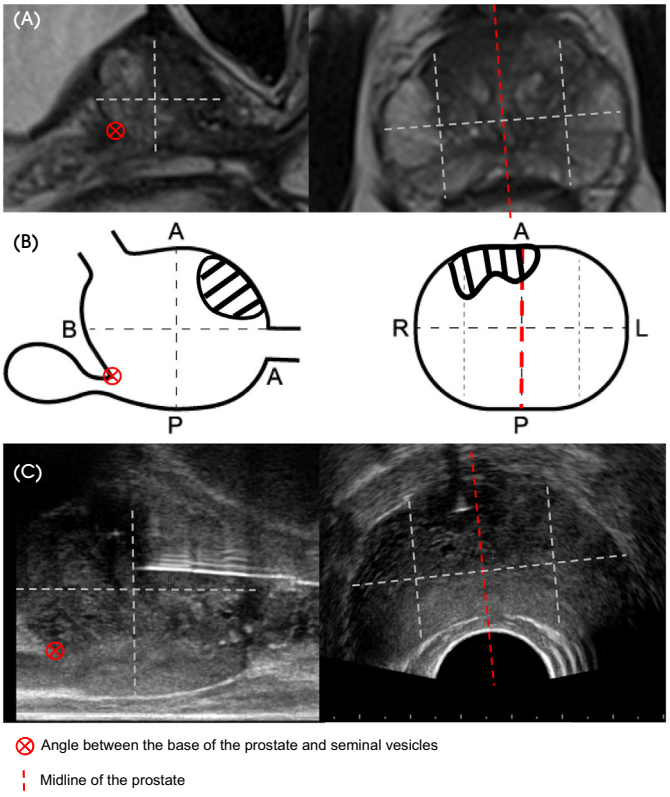


a sterile plastic tweezer to avoid direct contact. Sterile gloves or drapes are not used, and the patient holds the penis and scrotum away with a surgical towel. The skin is anaesthetised with 5 mL xylocaine 5% on each side as required and a further 10–15 mL is used as the large bore needle is advanced to the prostatic apex under ultrasound guidance. Care is taken that the biopsy needle only touches the inside of the 14-G access needle and the sterile field on the working table. A Hitachi Preirus™ ultrasound was used for all biopsies. A C41L47RP longitudinal biplane probe was used for all TP biopsies, while a EUP-V53W end-fire transducer was used for TR biopsies. Three biopsies are routinely taken from each visible MRI lesion and usually no more than two target lesions are biopsied per patient. Standard biopsies are also possible, as well as bilateral targeted biopsies. However, these require access needles on both sides of the perineal raphe.

Standardising the Approach to Cognitive TP Biopsies

From the latter part of 2021, an in-house prostate diagram (Fig. 2) was also implemented to aid the surgeon when locating the target lesion(s). A four-letter coordinate system (Left/Right, Apex/Base, Anterior/Posterior, Medial/Lateral) with 16 combinations helps locate the lesion in a grid that is easily transferable to the ultrasound image. This format was chosen to reflect the direction of the needle entering the prostate, where greater precision is needed in the axial view vs the sagittal view (the needle is 1 mm in diameter, but the biopsy throw length is 18–20 mm, i.e., a bigger margin of error in the sagittal view). During the above-mentioned imaging review between urologist and radiologist, the prostate diagram was annotated with target lesions. Primarily the axial MRI and ultrasound images are used as

Fig. 2 Example of freehand cognitive coaxial TP biopsy. (**A**) T2 MRI sagittal and axial images. (**B**) In-house prostate diagram with right apical anteromedial lesion. A, anterior; B, base; L, left; P, posterior; R, right. (**C**) TP biopsy with needle in the tumour.



these are the views that are most intuitive to both radiologists and clinicians, as well as being the most easy to reproduce between the two modalities. The distance from the midline to the centre of the target is measured and compared with the MRI measurement. A confirmatory measurement is made from the point at the angle between the base of the prostate and seminal vesicles, parallel to the rectal wall in the sagittal view. This point was chosen as it was easily found in both modalities.

Statistical Analyses

All analyses and graph plots were carried out using the R-4.2.2 build (R Foundation for Statistical Computing, Vienna, Austria). The Wilcoxon rank-sum test and Pearson's chi-square test were used to compare groups. The latter test was also used to investigate potential differences in inter-operator reproducibility of the TP method using results from operator 1 as reference after 50 and 100 consecutive biopsies. All statistics are given in the form of median and interquartile range (IQR) or *n* (%) unless otherwise specified. Tests were considered significant for $P < 0.05$.

Results

Patient Characteristics

Overall, 1915 patients underwent 2337 separate prostate biopsy sessions. There were 1088 patients who underwent TR biopsy and 1028 patients who underwent TP biopsy. The use of TR and TP per year is shown in Fig. S2. Some patients first underwent TR biopsies and later TP biopsies as they were part of an active surveillance programme. The median age was only slightly higher in the TP group compared with the TR group, but statistical significance was reached (66 vs 68 years, $P < 0.001$). There was no significant difference in the median (IQR) PSA level at 8 (6–12) ng/mL. However, the median prostate volume (43 vs 39 mL, $P < 0.001$) and PSAD (0.18 vs 0.21 ng/mL/mL) were higher in the TP group (Table 1). The ECOG PS scores were the same for both groups ($P = 0.5$). There were significantly more targeted biopsies in the TP group (38% vs 89%), mainly primary in both cases. There were only three patients with PI-RADS 1–2 findings who were biopsied in the TP group. There were also fewer PI-RADS 3 lesions biopsied in the TP group (31% vs 21%).

Complications and Antibiotic Prophylaxis

The complication rate was significantly lower in the TP group compared to the TR group (0.3% vs 5.0%, $P < 0.001$). In the latter group, all adverse events ($n = 54$) were hospital admissions due to urosepsis (Table 1). The complications in the TP group included two cases of combined urinary retention and infection, which were managed with a urinary catheter and oral antibiotics. One of these two had received antibiotics prior to the procedure. The third complication was haematuria and clot retention, which warranted catheterisation and bladder irrigation. The latter case had undergone 12 biopsies at their session, six biopsies per side via coaxial access. None of the three patients had urosepsis. Only 25 (2.4%) patients in the TP group had received antibiotic prophylaxis, while 100% had received antibiotics in the TR group. No patients were lost to follow up and no mortalities were recorded.

Cancer Detection and Inter-Operator Reproducibility

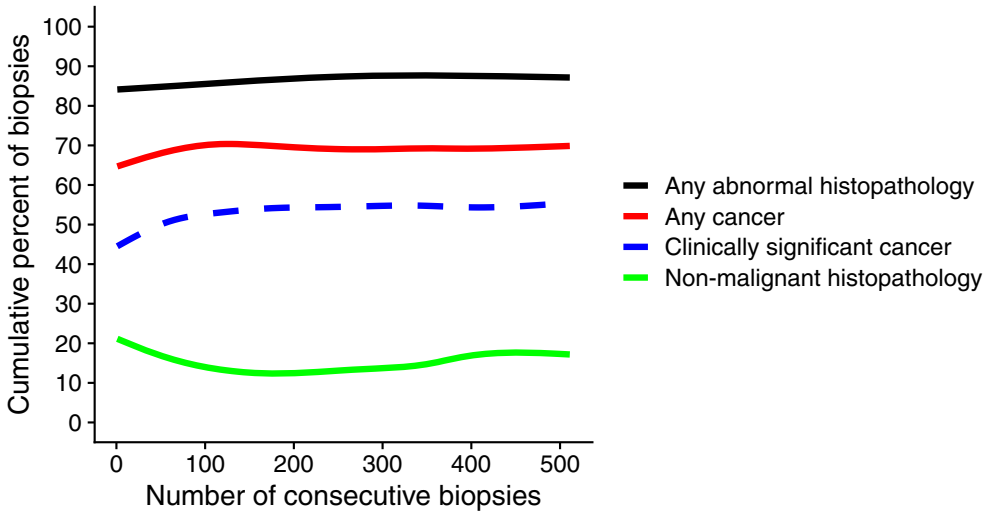
The total CDR by TP biopsy was 70% and the OAPDR was 88.4% (Fig. 3). In all, 75% of detected cancers by TP biopsy were clinically significant, defined as International Society of Urological Pathology (ISUP) Grade Group (GG) ≥2 (53% of all patients biopsied). The CDR/OAPDR categorised by MRI finding was 90/98% for PI-RAD 5, 70/88% for PI-RADS 4 and approximately 40/70% for PI-RADS 3 changes (Fig. S3). The greatest difference between cancer detection

Table 1 Summary of patient characteristics.

Variable	Patient characteristics			
	Overall, *N* = 2116	TR, *N* = 1088	TP, *N* = 1028	*P*†
Age, years, median (IQR)	67 (62, 71)	66 (61, 70)	68 (63, 72)	<0.001
ECOG PS, *n* (%)				
0	2014 (95)	1039 (95)	975 (95)	0.5
1+	102 (4.8)	49 (4.5)	53 (5.2)	
PSA level, ng/mL, median (IQR)	8 (6, 12)	8 (6, 12)	8 (6, 12)	0.5
Pre-biopsy MRI, *n* (%)	2015 (95)	1027 (94)	988 (96)	0.064
PI-RADS, *n* (%)				
1–2	69 (3.3)	66 (6.1)	3 (0.3)	<0.001
3	549 (26)	336 (31)	213 (21)	
4–5	1498 (71)	686 (63)	812 (79)	
Indication for biopsy, *n* (%)				
Primary	1634 (77)	807 (74)	827 (80)	<0.001
Surveillance	482 (23)	281 (26)	201 (20)	
TRUS volume, mL, median (IQR)	40 (29, 56)	43 (31, 60)	39 (28, 53)	<0.001
PSAD, ng/mL/mL, median (IQR)	0.20 (0.12, 0.32)	0.18 (0.11, 0.30)	0.21 (0.14, 0.34)	<0.001
Biopsy method, *n* (%)				
Systematic biopsy	785 (37)	672 (62)	113 (11)	<0.001
Targeted biopsy	1331 (63)	416 (38)	915 (89)	
Total no. biopsies, median (IQR)	4.0 (3.0, 12.0)	12.0 (4.0, 12.0)	3.0 (3.0, 4.0)	<0.001
Grade group (GG), *n* (%)				
Benign	697 (33)	385 (35)	312 (30)	0.022
GG1	376 (18)	205 (19)	171 (17)	
GG2	550 (26)	253 (23)	297 (29)	
GG3	219 (10)	105 (9.7)	114 (11)	
GG4	107 (5.1)	56 (5.1)	51 (5.0)	
GG5	167 (7.9)	84 (7.7)	83 (8.1)	
Pre-biopsy antibiotics, *n* (%)	1113 (53)	1088 (100)	25 (2.4)	<0.001
Post-biopsy complication, *n* (%)	57 (2.7)	54 (5.0)	3 (0.3)	<0.001
Clavien–Dindo classification, *n* (%)				
0	2059 (97.3)	1034 (95)	1025 (99.7)	<0.001
II	55 (2.6)	52 (4.8)	3 (0.3)	
IV4a	2 (<0.1)	2 (0.2)	0 (0)	

†*Wilcoxon rank-sum test; Pearson's chi-squared test.*

Fig. 3 Cumulative detection rates for overall abnormal histopathology (black line), any cancer (red line), clinically significant cancer (GG ≥2) (dotted blue line) and non-malignant histopathological findings (green line). The latter includes mostly inflammation and atrophy, but also <5% ASAP/PIN.



and OAPDR was seen in the PI-RADS 3 group, where 43% of the lesions detected were found to be pathology other than cancer. Cancer was found in only 30% of the biopsied PI-RADS 3 lesions. There was no difference in cancer or overall pathology detection between the four operators after 50 procedures ($P > 0.6$) (Fig. S3).

Tolerability

All TP biopsy procedures performed under LA (n = 1027) were completed successfully and none were terminated early. To this end, no periprocedural complications were recorded. In the whole study sample, one case underwent planned TP biopsy under general anaesthesia due to anorectal stricture associated with inflammatory bowel disease.

Efficiency

In 2018, 30 × TR biopsy cases were performed per month while in 2022, 65 × TP biopsies were undertaken per month. This was achieved by maximising the utilisation of the biopsy sessions and avoiding them being used for other purposes. Transitioning from TR to TP biopsies has not therefore limited productivity nor impeded case turnover. The current set up allows for 10 patients per day, 2 days a week.

Discussion

Key Findings

In this study of >2000 prostate biopsy sessions, the findings reveal that abandoning a TR approach in favour of an exclusively TP method resulted in a significant reduction in complications despite antibiotic prophylaxis being discontinued. Furthermore, implementing a cognitive freehand coaxial technique delivered reproducible results between four operators. To our knowledge, this study has the one of the highest proportions of targeted biopsy using this cognitive freehand coaxial technique. In comparison, other studies with similar sample sizes mostly use a software fusion approach [10,11].

Implementation

In this study, patients were slightly older in the TP group, reflecting the gradual shift in patient demographics. The PROstate MRI Imaging Study (PROMIS) study elegantly showed that MRI does not overlook significant cancers by using TP mapping biopsy as the reference. [12]. When the PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION) trial showed that an alternative pathway using targeted biopsy alone was superior to standardised biopsies [13], a successful transition to targeted biopsy could be safely made without compromising diagnostic quality. Only 11% of patients underwent standard biopsies after a template biopsy scheme and this was performed when the PSAD exceeded 0.15–0.2 ng/mL/mL in diffuse PI-RADS 3 lesions. Due to the variability in prostate volume estimation, it is arguably more practical to apply a threshold nearer to 0.2 ng/mL/mL in order to avoid overdiagnosis. The optimal cut-off value for PSAD without MRI has been shown to be 0.18 ng/mL/mL, which has a sensitivity and specificity of 77% and 69%, respectively [14]. This is a stricter value with a higher specificity and lower sensitivity compared to studies using 0.15 ng/mL/mL as their cut off value [15,16].

Advantages of Freehand Cognitive Biopsy

Given this is a coaxial freehand technique, there are no restrictions regarding prostate size or lesion location. With the use of software-fusion equipment and where the biopsy needle is fixed to the ultrasound probe, there is a risk of hitting the inferior pubic ramus/bony pelvis when targeting anterior tumours in large prostates. There is the added advantage of being able to biopsy and insert gold markers in local recurrences after previous prostatectomy, as there is no reliance on elastic or rigid fusion based on a computer-generated wireframe representation of the prostate. There has to date been no studies showing a clear benefit of software fusion over cognitive fusion in terms of CDR [17–20]. With increasing skill and experience using the freehand approach, and without a reliance on imaging software, it is also possible to identify and biopsy larger lesions in patients when MRI is contraindicated.

Complications and Antibiotic Use

The EAU guidelines state that there is growing evidence that antibiotic prophylaxis may not be required for TP biopsy [4]. In this study there was a significant reduction in infection from 5.0% to 0.3%, despite giving prophylaxis to only 2.4% of TP biopsy patients. This is in line with findings from the only randomised multicentre study evaluating the necessity of antibiotic prophylaxis [21]. The technique in that study required perforating the perineum with every biopsy, resulting in more trauma, and may explain a slightly higher rate of adverse reactions of 0.6%. A coaxial approach is less traumatic to the perineum, and this may help explain why the complication rate is lower in our study and others reporting outcomes with the coaxial approach [7]. We would therefore argue that there is enough evidence to suggest a change in the EAU guidelines to include that antibiotic prophylaxis can be safely omitted if prostate biopsies are performed using the TP approach, especially if the coaxial technique is employed.

Cancer Detection Rate

The CDRs recorded in this study (40%, 70% and 90% for PI-RADS score 3, 4 and 5, respectively) are similar to studies evaluating targeted biopsy, which range from 26% to 45% for PI-RADS 3, 62–69% for PI-RADS 4 and 84–94% for PI-RADS 5 lesions [7,13,21,22]. Specifically, the PRECISION trial had an overall CDR of ~65% overall (118 cancers detected ranging from GG1–5 out of 181 patients biopsied), where

CDR (GG1–5) was 34% for PI-RADS 3, 69% for PI-RADS 4 and 94% for PI-RADS 5 [13]. The results are also higher than those reported in older targeted TR biopsy studies comparing targeted and systematic biopsies [23,24]. To this end, cognitive fusion can offer a safe alternative to software fusion. Several studies have used a similar technique to gain access to the prostate, but these studies included mainly standardised biopsies with a mean number of cores in the range of 15 to 24 and not mainly cognitive fusion biopsies [25–27].

The CDR between TR and TP groups was the same, but it should be noted that 38% of TR biopsies included targeted biopsy. Thus, we would not expect to see the same reduction of low-grade prostate cancer as earlier studies have shown [13].

By standardising the approach to cognitive biopsy, we have shown this technique to be both reliable and reproducible. The method is operator independent, where the CDR and the OAPDR are high and stable for all four urologists, even after just 50 procedures for PI-RADS 4 and 5 lesions. The variability of PI-RADS 3 lesions is more likely due to differences in evaluation of the MRI and PSA/PSAD/prostate volume. This reflects the selection bias of the institution, not the procedure itself.

Another important finding is that lesions identified on MRI may not be cancerous, which supports the advantage that radiology only shows you a shadow of the truth. An interesting aspect of this is the large disparity between the OAPDR and CDR seen in PI-RADS 3 lesions, where ~30% of lesions were non-malignant. In these patients, the apparent diffusion coefficient (ADC) is generally higher, and changes are more diffuse. We are therefore confident that the number of false negative biopsies is low, but this warrants further study.

Strengths and Limitations

Our study is strengthened by a large patient cohort, which includes both TR and TP patients, as well as data collected in a prospective format. Had all patients undergone concurrent systematic biopsies, this would have provided a more accurate evaluation of the CDR associated with target biopsy approach. Given the sample combined patients undergoing different approaches, the data are heterogeneous. While it was a single-centre study, it was not a single-surgeon series, which is in contrast to similar series that have been previously published. Although no patient-reported outcome measure was used to assess patient experience of the procedure under LA, the 99% successful completion rate supports its tolerability. The main limitation was the lack of a control group to help determine the rate of false-negative findings. Initially, highly suspicious findings were re-biopsied where histology was benign on the initial TP biopsy. However, given repeat biopsy with a TR approach confirmed benign findings in all cases and given the OAPDR in the PI-RADS 5 group was high, this practice was discontinued. Whole-gland therapy is the standard of care at our centre and partial gland therapy is not currently offered. This does leave the potential for overtreatment and future studies on treatments such as focal ablation will serve to aid in addressing this important question.

Conclusion

Implementing a complete transition from TR to TP biopsy can result in a significant reduction of complications. Adoption of a cognitive freehand coaxial technique allows for a well-tolerated procedure that achieves a high CDR, which is reproducible between operators.

Disclosure of Interests

Alfred Honoré reports personal fees from Bayer Norway and Intuitive Surgical, outside of the submitted work. No other interests to disclose.

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Abbreviations: ASAP, atypical small acinar proliferation; CDR, cancer detection rate; CSCDR, clinically significant detection rate; EAU, European Association of Urology; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GG, Grade Group; IQR, interquartile range; LA, local anaesthesia; OAPDR, overall abnormal histopathology detection rate; PIN, prostatic intraepithelial neoplasia; PI-RADS, Prostate Imaging-Reporting And Data System; PRECISION, PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not?; PSAD, PSA density; TMP-SMX, trimethoprim-sulfamethoxazole; TP, transperineal; TR, transrectal.

Supporting Information

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

Fig. S1. Example of data registration form with dummy patient.

Fig. S2. Number of biopsies performed by type over time, by year.

Fig. S3. Black lines denotes cumulative detection rates for overall abnormal histopathology (OAPDR) and cancers (CDR) for all patients (A, B). C–H shows OAPDR and CDR for PI-RADS 5, 4 and 3, respectively.