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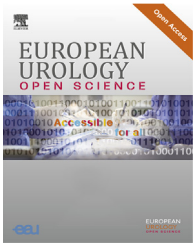

European Association of Urology

Trial Protocol

Clinical Trial Protocol for PERFECT: A Randomised Controlled Trial Comparing the Efficiency and Tolerance of Transperineal Fusion Versus Transrectal Imaging-targeted Prostate Biopsies (CCAFU-PR1 Study)

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Abstract

PERFECT is a multicentre randomised controlled clinical trial that evaluates the efficiency of fusion magnetic resonance imaging–targeted biopsies in the transperineal (TP) versus transrectal (TR) approach in terms of the detection of significant cancers. Our study builds on the hypothesis that the TP approach for prostate biopsies has at least the same diagnostic accuracy as the TR approach, with lower morbidity. Here, we describe the clinical protocol, study population, and primary and secondary outcomes.

1. Introduction and hypotheses

For decades, the transrectal (TR) route has been the recommended approach for prostate biopsies. However, for technical and anatomical reasons, this approach may be suboptimal to detect lesions located in the anterior and/or apical zone of the prostate [1]. In addition, this approach exposes patients to severe complications, driven mainly by febrile urinary infections [2–4]. Moreover, the use of fluoroquinolones, initially recommended as the preferred prophylaxis option, has now to be avoided for prostate biopsies in line with the European Commission final decision on drug safety.

For a few years, an alternative approach has been developed for performing biopsies: the transperineal (TP) route.

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Regarding the risks associated with a biopsy, the TP approach has the advantage of reducing significantly the occurrence of fever, rectal bleeding [4], and hospitalisations for sepsis [5]. A systematic review including 165 studies showed significantly different sepsis rates of 0.1% and 0.9% for TP and TR biopsies, respectively [6]. A population-based study demonstrated lower rates of sepsis and infection with a TP versus TR biopsy (0.31% vs 0.53%, $p \leq 0.001$) [7]. However, no definitive conclusion can be drawn regarding the overall rate of major complications. Indeed, although TR biopsies were associated with a higher burden of hospitalisation for urinary sepsis, TP biopsies were associated with higher rates of acute urinary retention [6]. Moreover, the observed differences have to be mitigated because of significant heterogeneity across countries and centres, in terms of biopsy strategy (systematic, magnetic resonance imaging [MRI] targeted, or both, and template), number of biopsy cores, and antibiotics prophylaxis. Recently, the NORAPP trial, which is a randomised noninferiority trial, compared sepsis or urinary tract infection rate after TP prostate biopsies in two groups: one received antibiotics and the other did not. This study showed no evidence of higher rates of infections when performing TP biopsies without antibiotic prophylaxis, with a number needed to treat to avoid infection of 137 [8].

The question of cancer detection equivalence between both routes remains open. While a literature review showed that both approaches had the same diagnostic accuracy [4], another study showed that the TP approach was associated with better detection of significant cancers in patients initially identified as having a low or a very low risk of cancer, probably due to improved sampling of the anterior and/or apical area [1]. A recent systematic review and meta-analysis comparing MRI-targeted TR biopsies with TP biopsies has suggested that the TP approach conferred higher sensitivity for the detection of clinically significant prostate cancer (PCa; 86% vs 73%) [9]. However, no high level of evidence exists, particularly in the era of MRI-targeted biopsies. Some studies suggested that both routes could be complementary according to the MRI lesion location, favouring TP for anterior and far apical zones, and TR for far lateral or basal lesions in the peripheral zone, paving the way of a more pragmatic approach in routine practice [10]. Indeed, the widespread use of TP biopsies may still be limited by logistical issues. Rai et al. [10] recently conducted a systematic review highlighting the paucity of good-quality evidence comparing MRI-targeted TP versus TR biopsies. No clear benefit was reported for TP in terms of overall and clinically significant PCa detection rate.

Thus, currently, despite an on-going movement to stop TR biopsies (“TREXIT”) [11], no formal proof of the superiority, or at least the noninferiority, of TP biopsies regarding clinically significant PCa detection on imaging-targeted biopsies has been provided, and the majority of urologists worldwide are still using the TR approach.

In this context, the PERFECT study aimed to compare both routes in terms of efficiency (detection of International Society of Urological Pathology [ISUP] grade ≥2 cancer) and safety for MRI-targeted cores through a randomised control study.

2. Design

2.1. Protocol overview

This is a multicentre randomised controlled clinical trial that evaluates the efficiency of fusion MRI-targeted biopsies in the TP versus TR approach in terms of the detection of significant cancers (ISUP grade ≥2). The study design is presented in Figure 1. Our study builds on the hypothesis that the TP approach for prostate biopsies has at least the same diagnostic accuracy as the TR approach, with lower morbidity.

2.2. Study population and setting

Six hospitals are involved in this multicentre study. The study aims to recruit 270 men. Adult prostate biopsy–naïve male patients with prostate-specific antigen (PSA) ≤20 ng/ml, multiparametric magnetic resonance imaging (mpMRI) with a lesion scored 4–5 on Prostate Imaging Reporting and Data System (PI-RADS), and a negative urine culture are eligible for inclusion. PI-RADS 3 lesions are excluded due to the lower detection rate of clinically significant PCa [12]. The inclusion and exclusion criteria are listed in Table 1.

This study was authorised and approved ethically by the Ile-de-France VII Ethics Committee on October 29, 2021 (ID-RCB: 2021-A01793-38). The study is prospectively registered in the US National Library of Medicine Trial Registry (NCT number: NCT05069584). This prospective randomised clinical trial is funded by “GCS Ramsay Santé pour l’Enseignement et la Recherche”.

2.3. Assessment of baseline characteristics

Standard patient characteristics will be collected during the diagnostic work-up, including family history of PCa, general medical history, initial serum PSA test, and clinical tumour stage assessed by digital rectal examination and mpMRI and urine culture. All radiological reporting will be performed by local dedicated radiologists. Reporting will be done according to the PI-RADS v2 guidelines [13].

2.4. Patient inclusion

Men are eligible for inclusion if they are biopsy naïve, eligible for a prostate biopsy, are with a PSA value of <20 ng/ml, have an mpMRI finding of at least one PI-RADS 4–5 lesion, have a negative urine culture, and accept to participate in the study. Informed consent will be obtained from all individuals participating in the study.

2.5. Randomisation and blinding

After study inclusion, patients will receive an appointment to undergo a prostate biopsy. Patients will be given the choice between local and general anaesthesia. If general anaesthesia is chosen, patients will receive an appointment with the anaesthesia team. Questionnaires on quality of life (QoL), and urinary and sexual functions (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life questionnaire for cancer [QLQ-C30], EORTC

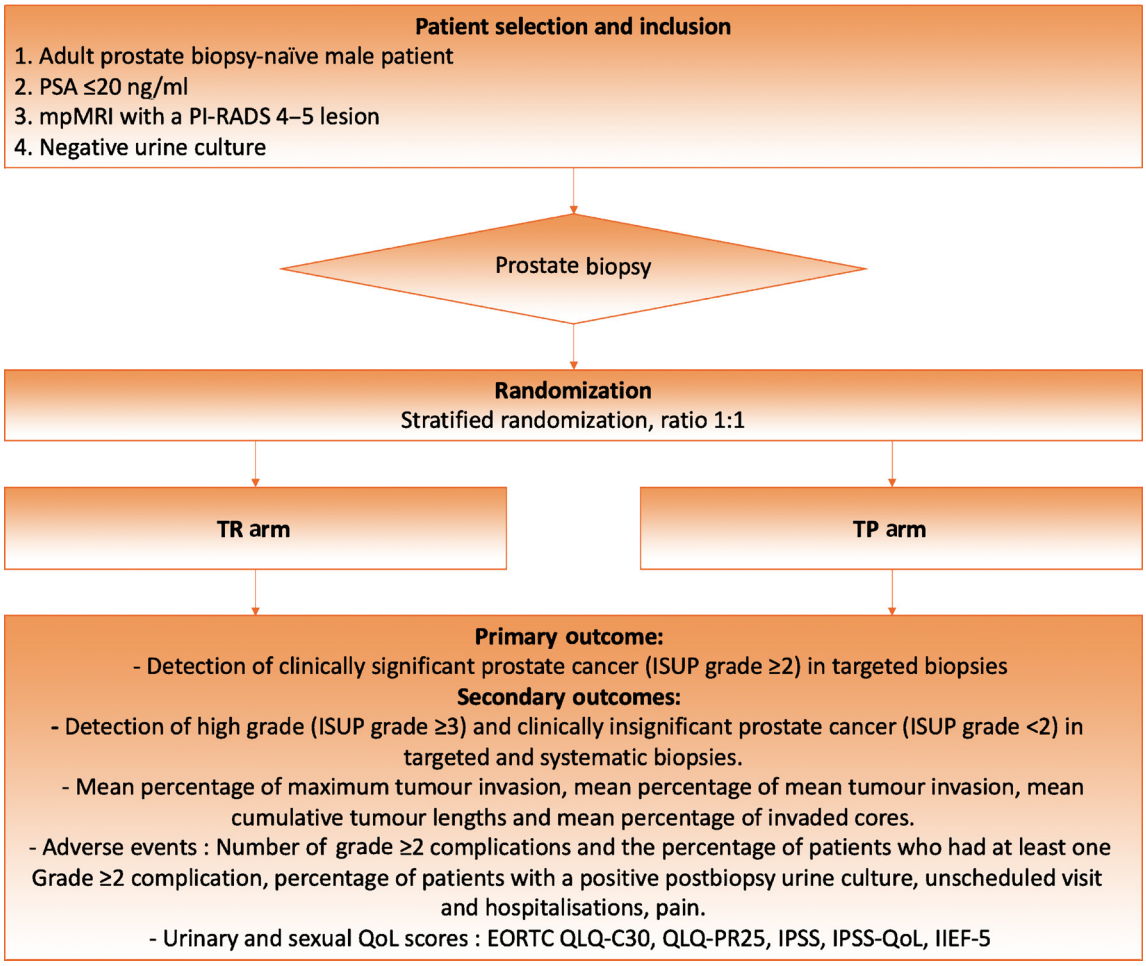

Fig. 1 – Study flowchart. EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire for cancer; IIEF-5 = International Index Erectile Function; IPSS = International Prostatic Symptom Score; IPSS-QoL = International Prostate Symptom Score Quality of Life index; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire for prostate cancer; QoL = quality of life; TP = transperineal; TR = transrectal.

Table 1 – Inclusion and exclusion criteria for participation in the PERFECT study

Inclusion criteria	Exclusion criteria
Age ≥18 yr	History of prior prostate biopsy
Three-sequence mpMRI with at least one PI-RADS 4–5 lesion	≥cT3a prostate cancer
Patients eligible for TR and TP prostate biopsies (targeted and systematic)	Negative MRI, or lesion(s) with PI-RADS score <4
Negative prebiopsy urine culture	Positive urine culture
PSA ≤20 ng/ml	Active therapeutic anticoagulation or untreated haemostasis disorder
Patients able to understand the study-related information, to answer questionnaires in French, to read the instructions, and those who expressed consent to participate in the study	Inability to place the transrectal ultrasound transducer
	Perineal skin disease preventing from perineal access

mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TP = transperineal; TR = transrectal.

Quality of Life questionnaire for prostate cancer [QLQ-PR25], International Prostatic Symptom Score [IPSS], IPSS Quality of Life index [IPSS-QoL], and International Index Erectile Function [IIEF-5]) will be given to patients, and these must be returned filled to the physician on the appointment day.

On the appointment day, the patient will be randomised between the two groups using stratified block randomisation, with each participating hospital, anaesthesia type, and lesion localisation as a stratum. The randomisation will be done by an online interactive procedure (Interactive Web Response System—IWRS). In the control group (arm A), all patients will undergo a TR prostate biopsy. In the intervention group (arm B), all patients will undergo a TP prostate biopsy. There will be no blinding for either the patient or the treating physician.

Table 2 – Mandatory pathology report information

Core characteristics	Tumour characteristics
Number of targeted biopsies	ISUP grade determined on targeted biopsies
Number of systematic biopsies	ISUP grade determined on systematic biopsies
Length of targeted core biopsies	Tumour length on each core (on targeted biopsies)
Length of systematic core biopsies	Tumour length on each core (on targeted biopsies)
	Percentage of tumour invasion on each core (on targeted biopsies)
	Percentage of tumour invasion on each core (on systematic biopsies)
	Number of invaded and noninvaded targeted biopsies
	Number of invaded and noninvaded systematic biopsies

ISUP = International Society of Urological Pathology.

2.6. Procedure

All targeted biopsies will be performed using fusion software. The type of fusion software must be specified: brand, model, version, etc. The biopsy will be performed as recommended by the European Association of Urology guidelines for PCa [14]. For the targeted biopsies, three cores per PI-RADS score of 4 or 5 lesion will be taken, for a maximum of two lesions. Concerning the systematic biopsies, it is advised to obtain six cores per lobe according to the usual diagram for the TR approach and five cores per lobe in the peripheral zone according to the Michigan Urological Surgery Improvement Collaborative (MUSIC) template for the TP approach. The duration of the procedure must be noted.

2.7. Surveillance

Immediately after the biopsy, the patient will remain under surveillance for 1–2 h, where the pain will be assessed with a pain visual analogue scale and the patient will be checked for adverse effects. On discharge, the patient will be given a notebook to note down any complications (bleeding, fever, pain, etc.) and their severity from day 1 (D1) to D15–21. The patient will have an appointment with his physician between D15 and D21 for the assessment of QoL, and urinary and sexual functions (EORTC QLQ-C30, QLQ-PR25, IPSS, IPSS-QoL, and IIEF-5), with a urine culture done 3–5 d before.

2.8. Pathology results

The elements that must appear on the pathology report are summarised in Table 2.

3. Statistics

According to Rouvière et al. [15], the detection rate of TR targeted biopsies in patients with a Likert score of $\geq$3 is 32.3%. The PERFECT study includes patients whose PI-RADS score is 4 or 5. We, therefore, expect a higher percentage of detection of significant cancers. According to the experience at the investigating centre, this percentage is estimated at 55%. The investigating centre also evaluates the percentage of detection of significant cancers on TP targeted biopsies at 70% [9]. With an alpha risk of 2.5% and a power of 90%, and considering a noninferiority margin of 5%, it would take 122 patients per group, or 244 patients in total, to demonstrate the noninferiority of the TP approach. Accounting for 10% dropouts and/or missing data, it will be necessary to include 270 patients (135 per arm).

Analyses of primary and secondary outcomes will be performed according to the intention-to-treat principle. For the primary outcome, we will compare the percentage of significant cancers in targeted biopsies in the two arms. The one-sided 97.5% confidence interval (CI) will be calculated by the Wald method and compared with the noninferiority limit as well. If the upper limit of the 97.5% CI is lower than the noninferiority limit, then the noninferiority of the TP approach will be demonstrated in the per-protocol population. A chi-square test will also be performed to compare the detection percentages.

Secondary outcomes are other efficiency criteria and tolerance. Percentages of high-grade (ISUP grade $\geq$3) and non-significant (ISUP grade <2) cancers will be compared between the two groups (TP vs TR) by a chi-square test, and also for targeted and systematic biopsies. The mean percentage of maximum tumour invasion, mean percentage of mean tumour invasion, mean cumulative tumour length, and mean percentage of invaded cores will be compared between the groups (TP vs TR) by Student *t* test, and also for targeted and systematic biopsies.

Tolerance between the two arms will be evaluated by the total number of grade $\geq$2 complications and the percentage of patients who had at least one grade $\geq$2 complication using a Fisher test, the number of days of rectal bleeding and/or haematuria and/or haemospermia during follow-up using a Student *t* test, the percentage of patients with a positive postbiopsy urine culture and the identified bacteria using a Fisher test, the number of unscheduled visits (emergency and consultation) and the percentage of patients who had at least one unscheduled visit between the biopsy and the scheduled appointment, and the number of unplanned hospitalisations using a Fisher test. Changes in QoL scores, urinary and sexual functions, and pain during follow-up will be analysed by using a mixed model for repeated measures.

In patients subsequently treated by radical prostatectomy, we will compare the percentage of ISUP upgrading on targeted biopsies and that on systematic biopsies between the groups (TP vs TR) using a chi-square test.

A statistical analysis will be performed using SAS (Statistical Analysis Software 9.4; SAS Institute Inc., Cary, NC, USA).

4. Discussion

The past years have witnessed a revolution in the diagnostic strategy for PCa. Many published studies have highlighted the key role of mpMRI before a biopsy in the diagnosis of significant PCa [15–17]. In addition, the traditional TR approach has been called into question, not only because of the supposed increased risk of infection [18,19], but also because mpMRI has made possible the detection of anterior lesions, more accurately detected with the TP approach

[20]. Therefore, the TP approach has been presented as the emerging standard for prostate biopsies [14].

Given a similar risk of general complications reported in previous studies [19] and the relatively low rate of isolated anterior significant PCa [21], we may question whether the TP approach should be used solely for PCa diagnosis, or if the approach should be tailored based on cancer location, prostate anatomy, or other factors that our study will try to identify. A prespecified stratification by lesion location (anterior vs peripheral) and type of anaesthesia is planned.

Moreover, the PERFECT trial will allow the prospective collection of patient-reported QoL and symptoms in order to assess the impact of biopsy route and template using validated questionnaires.

Lastly, we hope that the results of our study could raise a debating point: the usefulness of performing systematic biopsies.

***Author contributions*:** Guillaume Ploussard 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: Ploussard.
Acquisition of data: Barret, Renard-Penna, Salin, Pradère, Rozet, Beauval, Malavaud, Colin, Rouprêt.
Analysis and interpretation of data: Ploussard.
Drafting of the manuscript: Touzani.
Critical revision of the manuscript for important intellectual content: Fiard, Ploussard.
Statistical analysis: Ploussard.
Obtaining funding: Ploussard.
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Supervision: Giannarini, Rouprêt, Ploussard.
Other: None.

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***Ethics statement*:** This study was authorised and approved ethically by the Ile-de-France VII Ethics Committee on October 29, 2021 (ID-RCB: 2021-A01793-38).

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