

# Prostate biopsy in patients without rectal access: a systematic review and proportional meta-analysis

Konstantinos Kotrotsios, Konstantinos Douroumis, Panagiotis Katsikatsos, Evangelos Fragkiadis, Dionysios Mitropoulos

First Urologic Clinic of Athens University, Laiko General Hospital, Athens, Greece

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## Corresponding author

Konstantinos Kotrotsios  
First Urologic Clinic of  
Athens University,  
Laiko General Hospital  
Agiou Thoma 17,  
Athens 115 27, Greece  
kotrwtiosk@gmail.com

**Introduction** Historically, the anal canal plays a substantial role in both screening and diagnosis of prostate cancer with digital rectal examination (DRE) and transrectal ultrasound (TRUS) guided biopsy, respectively. However, in patients with a prior history of abdominoperineal resection the transrectal route towards the prostate capsule cannot be utilized and thus alternative approaches have to be employed. The aim of this systematic review and proportional meta-analysis is to evaluate the available alternative prostate biopsy techniques in patients without rectal access.

**Material and methods** The systematic literature review was performed using MEDLINE, Scopus, EMBASE, and the CENTRAL register for randomized controlled trials (RCTs). The following search algorithm was used: “resection of rectum” OR “abdominoperineal resection” OR “without rectal access” AND “prostate biopsy” (PROSPERO 2023 CRD42023459080).

**Results** A total of 21 studies and 203 patients were included in this systematic review and meta-analysis, while 6 different prostate biopsy techniques were detected in the current literature. The transperineal approach under transperineal US (TPUS) and the transgluteal approach guided by computed tomography (CT) were associated with 0.74 [0.48; 0.94] and 0.70 [0.49; 0.89] pooled diagnostic yield estimates as well as 0.01 [0.00; 0.01] and 0 [0.00; 0.01] pooled complication rate estimates. The performance of multiparametric magnetic resonance imaging (mpMRI) prior to transgluteal CT-guided prostate biopsy seemed to significantly affect the biopsy result ( $p = 0.0002$ ).

**Conclusions** Based on current data, the TPUS-guided prostate biopsy has the highest pooled diagnostic yield estimate. However, this conclusion is based on poor evidence and more reliable and well-organized studies are needed to thoroughly explore this problem.

**Key Words:** prostate ↔ biopsy ↔ prostate cancer ↔ transperineal ↔ ultrasound

## INTRODUCTION

Prostate cancer is the second most common malignancy detected in men with virtually one million new cases reported every year. In fact, prostate cancer accounts for 10.0% of new malignancies diagnosed annually in males and is responsible for 300,000 deaths every year [1, 2]. Some well-established risk factors associated with prostate cancer are age, with almost 75.0% of men above 80 years displaying some kind of latent disease, family history, African-American race and certain

genetic factors, for instance, *BRCA1* and *BRCA2* mutations [3–7].

The fact that prostate cancer incurs a substantial incidence and mortality burden of that magnitude poses an invincible need for a well-coordinated screening program [8]. Although there are no consensus guidelines for prostate cancer screening most of the experts' recommendations incorporate prostate-specific antigen (PSA) measurement as the initial screening tool [8–11]. In addition to PSA, digital rectal examination (DRE) can be utilized to aid screening and can potentially increase the intrinsically

low specificity of PSA, especially when it is performed by an experienced clinician [12].

After shared-decision making, a reasonable step for a patient with adequate life expectancy and abnormal findings in screening tests is prostate biopsy [13]. Historically, transrectal ultrasound (TRUS) guided biopsy has been the mainstay of obtaining prostate specimens from patients with increased suspicion of prostate cancer [14]. Its cancer detection rates (CDRs) have been reported to be as high as 37.5% in patients with elevated PSA levels, while the introduction of a novel prostate imaging technique, more specifically the multiparametric magnetic resonance imaging (mpMRI), in combination with TRUS has increased the detection of clinically important lesions [15, 16].

From the aforementioned data, it has been demonstrated that the anatomical proximity between the prostate and the rectum is a feature of high significance regarding both the screening and the diagnosis of prostate cancer. The abdominoperineal resection (APR) is the cornerstone of surgical treatment in cases of rectal cancer, ulcerative colitis and familial polyposis [17]. During this procedure, the rectum along with the mesorectum, the anus, perineal soft tissue and pelvic floor musculature are resected [18].

Considering that the detection of synchronous and metachronous prostate and rectal cancers is highly prevalent, the screening and diagnosis of prostate cancer after APR are a common diagnostic challenge for healthcare providers [19].

Taking into account the prevailing occurrence of rectal cancer beyond the age of 50, which is the same age category with men of high risk for prostate cancer, a prostate cancer screening by measuring PSA levels before undergoing APR has been suggested [20, 21]. In case of elevated levels of PSA after APR, several methods have been proposed in order to acquire sufficient prostate tissue to reliably establish a diagnosis [22].

The aim of this study is to perform a systematic review of the current literature with respect to management of a patient without rectal access and elevated conjecture regarding the presence of prostate cancer and to provide through a pooled proportional meta-analysis and insight on the most effective and safe prostate biopsy technique in these untypical patients.

## MATERIAL AND METHODS

A literature search was performed (9<sup>th</sup> of June 2023) using the MEDLINE, the CENTRAL, the EMBASE and the SCOPUS databases (PROSPERO 2023

CRD42023459080). The following terms were used in the search text fields; “resection of rectum” OR “abdominoperineal resection” OR “without rectal access” AND “prostate biopsy”.

Published observational and interventional studies describing prostate biopsy techniques in patients without rectal access and evaluating its efficiency were included. Reviews, letters, commentaries and articles whose texts were not available in English were excluded.

The abstracts of all articles were screened and the full texts of all the relevant articles were examined for possible inclusion by 2 separate reviewers. Subsequent to the initial study, selection was the citation searching of the already included studies. Upon the conclusion of the compilation of studies a risk of bias assessment was performed utilizing the 2013 National Heart, Lung and Blood Institute (NHLBI) quality assessment tool and the Risk Of Bias In Non-randomized Studies – of Exposures (ROBINS-E) of the Cochrane group for case series and observational cohort studies, respectively [23, 24].

Efficiency of the prostate biopsy technique used was identified as the primary outcome because it ensures the feasibility of the method, while complications rate was the secondary outcome because it is associated with direct harm to the patients. The sample size and the number of patients with positive prostate biopsy were used to pool the diagnostic yield of each biopsy technique. A random-effects model was assumed using the DerSimonian-Laird approach with Freeman-Tukey double arcsine transformed proportion at 95.0% CI.

## RESULTS

A flow diagram of the selection procedure is presented in Figure 1. We initially identified 754 papers and after removal of duplicates, 647 were considered eligible for title-abstract based screening. Subsequently, 33 articles were selected for full text screening, 15 of them were excluded due to the reasons presented in Figure 1, while 17 of them met the inclusion criteria and were finally included. Furthermore, references of the included studies along with articles published by high impact journals were hand-searched and 4 additional articles that were lost from the initial search were also included. A summary of the included studies' characteristics along with some of their most important results is presented in order to provide a brief outlook on the available data before their more thorough review (Table 1).

A total of 203 patients were included in this systematic review and meta-analysis and 6 different pros-

tate biopsy techniques were detected in the current literature; transperineal approach with cognitive guidance by intravenous urogram (IVU) and ultrasound (US), transgluteal approach guided by computed tomography (CT), transperineal approach under concurrent transperineal US (TPUS), transperineal approach under concurrent transurethral US, transperineal approach under fluoroscopy guidance and transperineal approach during mpMRI and transabdominal ultrasound fusion.

The first case of prostate biopsy in a patient without rectal access was described by Schapira [26] in 1982. In this case the prostate was approached transperineally with the patient in lithotomy position, while the lesion was targeted cognitively based on the findings of an IVU and a sonogram that both were previously performed. The histological examination revealed fragments of prostatic adenocarcinoma.

The transperineal route and the advancement of the needle to the prostate capsule under transperineal ultrasound guidance was the procedure of choice in 8 studies [27–34]. In pooled estimates, overall diagnostic yield of this technique was 0.74 [0.48; 0.94] (Figure 2). After moderator analysis, for age, PSA level and pre-biopsy mpMRI performance, it emerged that none of these moderators significantly affected the diagnostic yield of the technique ( $p = 0.2997$ ,  $p = 0.9891$ ,  $p = 0.3368$ , re-

spectively). Regarding the safety of the technique, the complication rate in pooled estimates is as high as 0.01 [0.00; 0.18].

A novel approach to the prostate, which was introduced by Krauss et al. [35] in 1993, utilizes CT imaging as a guide and the gluteal region as the needle inserting point all the way to the prostatic gland.

This technique was described by 7 studies [35–41]. In pooled estimates, its overall diagnostic yield was 0.70 [0.49; 0.89] (Figure 3). The primary pooled proportional analysis was followed by moderator analysis for age, PSA level and pre-biopsy mpMRI performance. It was concluded that pre-biopsy mpMRI was the sole moderator significantly affecting the outcome ( $p = 0.0002$ ). Only 4 complication events were observed throughout these 7 studies leading to a pooled estimate of 0.00 [0.00; 0.01].

Transurethral ultrasound was the imaging technique of choice regarding needle guidance in 6 cases described by Kirby et al. [42] and Seaman et al. [43]. The first author published a case report of a patient with a previous abdominoperineal resection and a significantly elevated PSA level (>30 ng/ml). This patient had undergone two prior prostate biopsies with the third attempt being performed by placing the patient in lithotomy position and under mild sedation inserting an ultrasound transducer into the prostatic urethra with the help of a flexible cystoscope. Perineal prostatic biopsies were then obtained

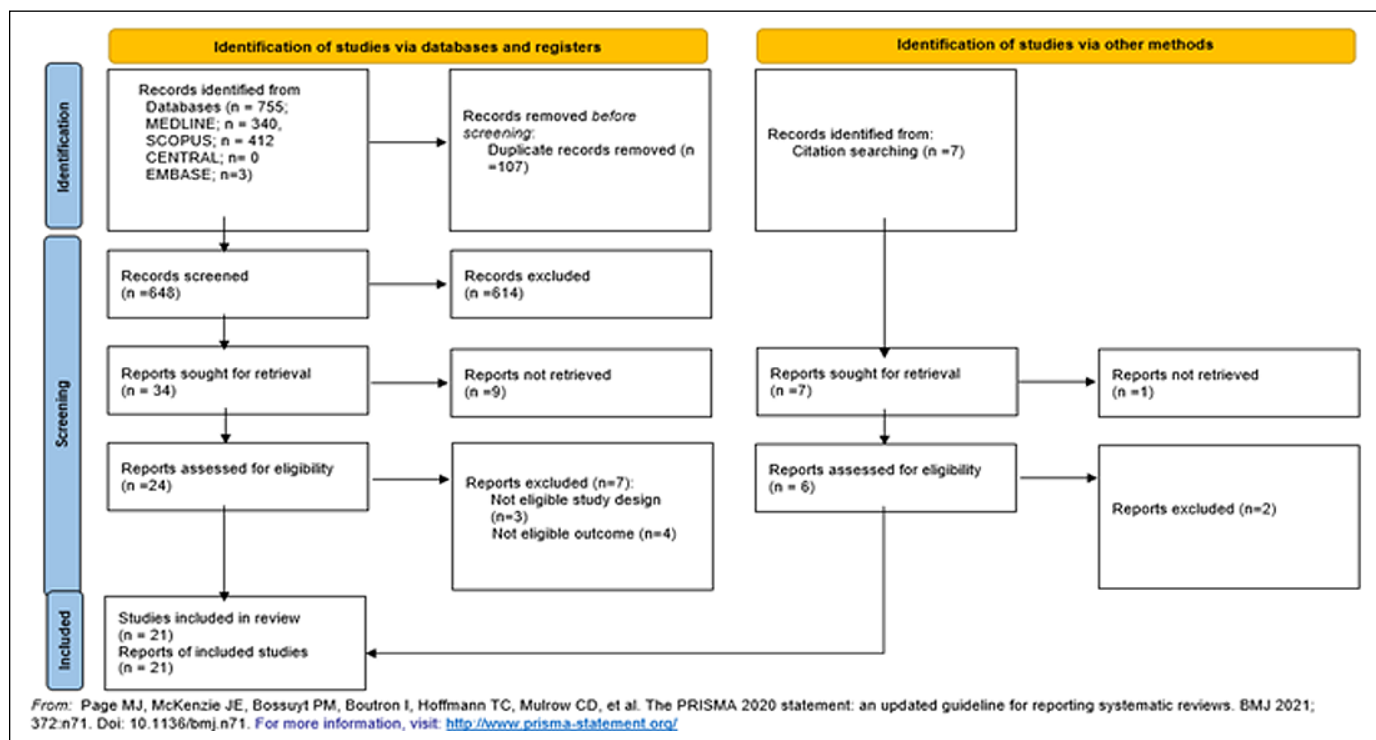


Figure 1. PRISMA flow diagram summarizes the selection process [25].

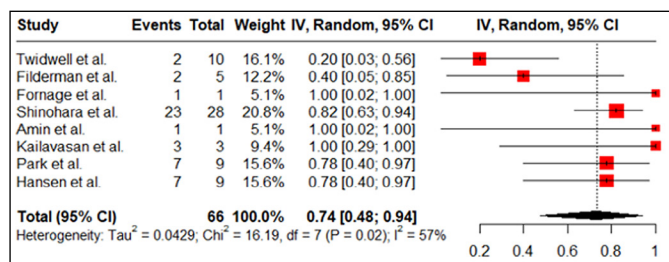
while circumferential real-time ultrasonic images were acquired. The histologic specimens originating mainly from the posterior prostate confirmed the presence of benign prostatic gland tissue. This particular technique was applied by Seaman et al. [43] in 5 patients without rectal access and lead to the diagnosis of prostate cancer in 3 of them. Instead of cognitively combining prior mpMRI and real-time ultrasound images, De Vulder et al. [44] described the first case of a patient with a history of abdominoperineal resection and rising PSA who

underwent mpMRI-US fusion biopsy. MRI images were pre-imported into the ultrasound system and a region of interest, meaning the area suspected of being malignant, was identified. A transabdominal ultrasound approach was necessary in order to begin the fusion with the cranial and caudal most aspects of the pubic symphysis being the primary fusion points. Then, the ultrasound probe was placed to the perineum and prostate biopsies were obtained free hand establishing a Gleason 8 prostatic adenocarcinoma.

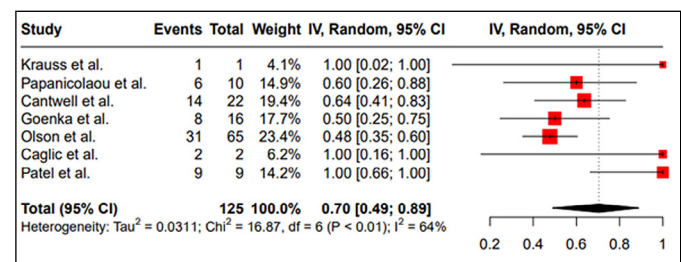
**Table 1.** Basic characteristics of the studies

Author	Publication (year)	Study design	Mean PSA (ng/ml)	Prostate approach	Guidance	PCa cases, Mean GS
Schapira [26]	1982	Case report	NA	Transperineal	Cognitive IVU, US guided	n = 1, NA
Krauss et al. [35]	1993	Case report	13.5	Transgluteal	CT	n = 1, NA
Twidwell et al. [27]	1993	Case series	6.5	Transperineal	US	n = 2, NA
Filderman et al. [28]	1994	Case series	16.5	Transperineal	US	n = 2, NA
Fornage et al. [29]	1995	Case report	17.0	Transperineal	US	n = 1, combined 8
Kirby et al. [42]	1995	Case report	>30.0	Intraluminal	Transurethral US	n = 0
Seaman et al. [43]	1996	Case series	13.5	Transperineal	Transurethral US	n = 3, NA
Papanicolaou et al. [36]	1996	Case series	34	Transgluteal	CT	n = 6, NA
D'Amico et al. [45]	2000	Case report	43.5	Transperineal	Cognitive mpMRI MRI guided	n = 1, 6 (3 + 3)
Shinohara et al. [31]	2003	Case series	22	Transperineal	US	n = 23, 6.6
Cantwell et al. [37]	2008	Retrospective study	11.1	Transgluteal	CT	n = 14, 7.4
Goenka et al. [38]	2015	Retrospective study	11.4	Transgluteal	CT	n = 8, combined 8
Caglic et al. [40]	2016	Case report	14.2	Transgluteal	Cognitive mpMRI, CT guided	n = 2, 7.5
Hansen et al. [34]	2016	Case series	14.5	Transperineal	Cognitive mpMRI, US guided	n = 7, 8
Olson et al. [39]	2016	Retrospective study	7.8	Transgluteal	CT	n = 31, 7
Amin et al. [30]	2020	Case report	NA	Transperineal	US	n = 1, 7
Merrick et al. [46]	2020	Case report	8.84	Transperineal	CT planned, fluoroscopy guided	n = 1, 9
Kailavasan et al. [32]	2021	Case series	9.4	Transperineal	Cognitive mpMRI, US guided	n = 3, 7
Patel et al. [41]	2021	Retrospective study	14.1	Transgluteal	Cognitive mpMRI, CT guided	n = 9, 7
De Vulder et al. [44]	2021	Case report	NA	Transperineal	MRI-transperineal US fusion	n = 1, 8
Park et al. [33]	2023	Retrospective study	22.6	Transperineal	Cognitive mpMRI, US guided	n = 7, 7.5

CT – computed tomography, GS – Gleason score, IVU – intravenous urogram; mpMRI – multiparametric magnetic resonance imaging; US – ultrasound; PCa – prostate cancer; PSA – prostate-specific antigen



**Figure 2.** Forest plot transperineal ultrasound-guided prostate biopsy.



**Figure 3.** Forest plot transgluteal computed tomography prostate biopsy.



The 2 last prostate biopsy protocols have only been described once. The first one refers to a patient with prior proctocolectomy due to ulcerative colitis and increasing values of PSA. Firstly, the patient underwent a prostate MRI in order to identify regions highly suspicious for cancer. Then the patient was placed into the imaging bore of the open intraoperative magnet in the lithotomy position under general anesthesia. Intraoperatively, new MRI images were obtained and according to the correlation of both MRI examinations and using appropriate software, a stereotactic transperineal approach to the lesion was achieved. The histopathologic evaluation revealed a Gleason 6 prostate adenocarcinoma, while no complications were reported [45].

The second case report involves a patient with PSA level of 8.84 ng/ml who underwent total colectomy due to ulcerative colitis. The biopsy locations were pre-planned based on a pre-biopsy CT. Intraoperatively, the patient under intravenous (IV) sedation was placed in dorsal lithotomy position, then saline with dilute contrast were administered into the bladder and into the catheter bulb, while a brachytherapy template was used for needle placement. The needle position was confirmed via antero-posterior and lateral fluoroscopy. At biopsy 32 cores were obtained and established the diagnosis of a Gleason 9 prostatic adenocarcinoma [46].

## DISCUSSION

To our knowledge this is the first systematic review and meta-analysis evaluating prostate biopsy techniques in patients without rectal access. Based on the current data available the majority of the procedures were described in diminutive patient numbers, while only the transperineal approach under US guidance and the transgluteal approach under CT guidance were reported in an adequate number of studies with bearable heterogeneity making it feasible to perform a pooled proportional meta-analysis. The studies' risk of bias was assessed using the NIH quality assessment tool and the ROBINS-E tool for case series and single arm retrospective studies, respectively.

The non-consecutive nature of the cases, the lack of baseline characteristics presentation and the concealment of the follow-up period were features that in some cases undermined the quality of the case series studies (Table 2). Regarding the single arm retrospective studies, during the planning stage of ROBINS-E assessment, age, PSA level, prior unsuccessful biopsies, Gleason score, prostate size, comorbidities, inflammation or prostatic intraepithelial neoplasia and radiation dose were noted as

potential confounding factors. After diligent examination of the available single arm retrospective studies it was concluded that there was sufficient potential for confounding that an unadjusted result was not reliable. Thus, these studies were considered of very high risk of bias [33, 37–39, 41].

Prostate cancer and rectosigmoid cancer hold 2 positions among the most frequent diagnosed cancers in men [47]. In fact, it has been observed that these 2 types of cancer tend to co-occur within the same patient in a rate that ranges from 1.9% to 5.0% [48, 49]. In most of the cases the cancers do not occur simultaneously, but they follow a subsequent path, with the rectosigmoid cancer being the first one detected in 41.0% of the cases [50].

Given abdominoperineal resection is required not only in 40.0% of patients with rectal cancer but also occasionally for the management of inflammatory bowel disease, Fournier gangrene and fecal incontinence not amenable to sphincter sparing surgery the need for a standardized protocol regarding the prostate cancer diagnosis in men without rectal access is of paramount importance [51, 52].

One of the major advantages of the transperineal route to the prostatic capsule is the improved sampling of the far lateral peripheral zone. This is attributed to the relatively parallel course of the needle to the long axis of the prostate at the mid portion and the base allowing to obtain more prostatic tissue from the peripheral zone [53].

According to our analysis, the transperineal approach of the prostate under transperineal ultrasound guidance was associated with a diagnostic yield of 0.74 [0.48; 0.94]. This result complies with the pooled detection rate of a previously published meta-analysis, which evaluated the diagnostic effectiveness of free hand transperineal prostate biopsy with the Precision Point Transperineal Access System in patients with rectal access and achieved a prostate cancer detection rate of 68.0% [54]. The slightly higher detection rate in our analysis might be explained by the fact that patients without rectal access might present with larger and more clinically significant cancers due to delayed diagnosis [55].

To our surprise, the visual registration of prior mpMRI did not seem to affect the diagnostic yield of the technique. This does not accord with preceding studies that had proven the superiority of cognitively combining pre-biopsy magnetic resonance imaging with transrectal ultrasound than ultrasound guidance alone [56].

Moreover, in order for an invasive procedure to become the mainstay in diagnosis of a condition it is essential to be accurate as well as safe for the patient. According to our analysis, the pooled compli-

cation rate estimate of transperineal biopsy under TPUS guidance was calculated to be as low as 1.0%. The most recent systematic review comparing the transperineal with the traditional transrectal route stated that the transperineal approach seems to protect patients from rectal bleeding and fever but significantly increases patient pain [57]. These reports come to an agreement with our included studies where no infectious complications were observed and only one patient felt mild perineal discomfort. One of the major concerns when utilizing the transperineal course to the prostate is the association of the procedure with increased danger for post-biopsy urinary retention. More specifically, in a recent nationwide study where 73,630 patients were included, it was indicated that the patients who underwent a transperineal prostate biopsy were of higher risk for urinary retention and were more likely to have stayed overnight immediately post-operatively [58]. In our analysis, acute urinary retention occurred in 2 patients postoperatively [34].

The higher risk of urinary retention might be related to general anaesthesia use or to the higher number of cores obtained.

Our systematic literature review has proven the feasibility of the transperineal biopsy under local anaesthesia given that local anesthesia was preferred in the majority of the cases [27–30, 33].

The most commonly utilized prostate biopsy technique in patients without rectal access was the transgluteal approach under CT guidance. One of the most important features of this technique is the clear depiction of the pelvis anatomy and the higher quality of the prostate visualization when compared with the ultrasound. These 2 characteristics not only diminish the likelihood of bowel, bladder and surrounding vasculature injury but also help overcome the intrinsic complexity of prostate sampling in patients that had undergone anorectal resection [22].

According to our analysis, the transgluteal approach of the prostate under CT guidance was associated with a pooled diagnostic yield of 0.70 [0.49; 0.89].

**Table 2.** Case series quality evaluation using the NIH quality assessment tool

	Twidwell et al. [27]	Filderman et al. [28]	Seaman et al. [43]	Papanicolaou et al. [36]	Shinohara et al. [31]	Hansen et al. [34]	Kailavasan et al. [32]
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	No	NR	NR	Yes	Yes	Yes	Yes
4. Were the subjects comparable?	NR	No	Yes	Yes	No	Yes	Yes
5. Was the intervention clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the length of follow-up adequate?	NA	NA	NA	NA	NR	NA	NA
8. Were the statistical methods well described?	No	No	No	No	No	No	No
9. Were the results well described?	No	Yes	No	No	Yes	Yes	Yes
Quality rating (good, fair, poor)	Poor (non-consecutive nature of cases, no baseline characteristics available, no statistical methods description and no risk classification)	Poor (great differences in baseline PSA and age, the statistical methods and follow-up duration were not reported)	Fair (a description of the statistical methods used and a more adequate interpretation of the results would be desired)	Fair (a description of the statistical methods used and a more adequate interpretation of the results would be desired)	Fair (there were great differences in baseline PSA)	Good	Good

NA – not applicable; NR – not reported

This might be explained by the fact that in most cases biopsies were performed according to a quadrant approach, while an extended peripheral zone biopsy scheme where 12 cores are acquired may increase cancer detection rates with this technique [59].

There are no prior data in respect of the efficacy of CT as a needle guide during prostate biopsy. This might be related to the superiority of other techniques and especially MRI in prostate visualization, which can also improve the initial detection of prostate cancer [60]. In fact our moderator analysis regarding the pooled diagnostic yield of CT-guided transgluteal prostate biopsy demonstrated that prior mpMRI prostate visualization significantly affected the result ( $p = 0.0002$ ). Moreover, it has been described that CT can also be combined with prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and achieve a prostate cancer detection rate of 96.0% [61].

Concerning its safety profile, CT-guided transgluteal biopsy in patients without rectal access has a pooled complication rate estimate of 0% [0%; 1.0%]. In the included studies only 4 minor complication events were recorded, including 1 event of gross spontaneously resolving hematuria and 3 periprostatic hematomas, while no major complications were observed. At this point it is important to underline that in contrast with the conventional transrectal US-guided prostate biopsy where post-biopsy infection is an issue of great concern, when following the transgluteal approach to the prostate as the rectum is not transgressed the risk of infectious complications is diminished [62]. Thus, no antibiotic prophylaxis was routinely administered in virtually all the studies utilizing the transgluteal approach, minimizing the potential burden of antibiotic-resistant bacteria development [63].

Towards the direction of vanishing infectious complications from prostate biopsy favors the transperineal approach as well, which seems to lower the incidence of post-biopsy sepsis in comparison with the traditional transrectal approach (0.1% vs 0.8%, respectively) [64]. Both the transperineal and the transgluteal approach could be considered as alternative choices in patients receiving immunosuppression or transplant recipients who have usually been exposed in extended hospitalizations or complex antibiotic regimens and their colon is colonized by multi-resistant bacteria [65, 66].

This systematic review and proportional meta-analysis has several limitations. First of all, both the lack of head-to-head comparisons between the techniques and the studies' design, that were almost exclusively in case series or single arm

retrospective studies format, made pooled proportional meta-analysis the sole feasible choice and inserted great risk of bias in the resulting evidence, respectively. Also, the limited number of patients included in the analysis undermined the certainty of evidence emerging from the analysis. Last but not least, most of the techniques were described once or twice in case reports and as a result a statistical analysis of their results would not be reliable and thus a narrative presentation was preferred in order to achieve historical thoroughness on the subject.

Given that transperineal prostate fusion biopsy constitutes a safe and reliable prostate biopsy technique for selected patients with rectal access, it could be considered the standard of care as well for patients without a rectum [67]. However, this novel approach is not available in all clinical settings due to both limited equipment and technical knowledge.

## CONCLUSIONS

Taking into account that prostate cancer and rectosigmoid cancer are 2 malignancies with prevailing occurrence in men aged over 50 and that ano-rectal resection is indicated in a significant proportion of men with rectosigmoid cancer and men suffering from other conditions, such as inflammatory bowel disease (IBD) or Fournier gangrene, a thorough evaluation of the available prostate biopsy techniques that omit the traditional transrectal route was necessary. Several procedures have been reported in the current literature including with the most commonly utilized techniques being the transperineal approach under concurrent TPUS and the transgluteal approach guided by CT which were associated with 0.74 [0.48; 0.94] and 0.70 [0.49; 0.89] pooled diagnostic yield estimates as well as 0.01 [0.00; 0.01] and 0 [0.00; 0.01] pooled complication rate estimates. However, the level of evidence is still suboptimal due to the small retrospective, case series and case report format of the included studies. Thus, well designed multi-institutional prospective studies are required to elucidate the diagnostic efficacy of each different technique in this unique population.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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## ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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