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MASTER THESIS

Title: « Micro-ultrasound vs multiparametric MRI guided prostate biopsy in the diagnosis of prostate cancer: a systematic review »

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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Θέμα: «Μικρο-υπέρηχος έναντι πολυπαραμετρικής μαγνητικής τομογραφίας στην καθοδηγούμενη βιοψία προστάτη για τη διάγνωση του καρκίνου του προστάτη: Συστηματική ανασκόπηση»

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Preface

I would like to extend my heartfelt gratitude to my supervisor, Dr. Chrysoula Doxani, whose unwavering guidance and support have been invaluable throughout this journey. I am also deeply thankful to the members of the advisory committee, Professor Ioannis Stefanidis and Mr. Theodoros Mprotsis, for their insightful feedback and encouragement. This work would not have reached its current form without their dedicated assistance.

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Abstract

Background: Accurate diagnosis of prostate cancer (PCa) remains challenging. Traditional ultrasound-guided biopsy has limited sensitivity and a high false-negative rate. Although MRI-guided biopsy improves detection, it is limited by inter-reader variability, steep learning curve, high cost, and may still miss up to 15% of clinically significant cases. Micro-ultrasound (micro-US) is a novel imaging technique offering high-resolution, real-time guidance with diagnostic performance potentially comparable to multiparametric MRI (mpMRI).

Objective: To systematically compare the diagnostic performance of micro-US-guided and mpMRI-targeted prostate biopsies in detecting clinically significant prostate cancer (csPCa).

Methods: In accordance with PRISMA-DTA guidelines, a systematic review was registered in PROSPERO (CRD42024513987). Searches were conducted across PubMed, Scopus, the Cochrane Library, and grey literature sources up to April 30, 2025. Studies involving men who underwent both biopsy methods were included. Data were extracted on detection rates, sensitivity, specificity, and predictive values for csPCa. Methodological quality was assessed using the QUADAS-2 tool.

Results: A total of 4,689 patients were included across sixteen studies. Among 3,707 patients with a positive micro-US (PRIMUS ≥ 3), 1,586 (42.8%) cases of clinically csPCa were detected. In comparison, among 3,813 patients with a positive mpMRI (PIRADS ≥ 3), 1,449 (38%) cases of csPCa were identified. In nine studies, micro-US outperformed mpMRI. The sensitivity of micro-US ranged from 67% to 93.9%, while specificity ranged from 7.1% to 57%.

Conclusions: Micro-US provides diagnostic accuracy comparable to mpMRI, with additional advantages in cost, accessibility, and ease of implementation.

Keywords: prostate cancer, micro-ultrasound, multiparametric MRI, prostate biopsy, clinically significant prostate cancer, diagnostic accuracy, systematic review

Περίληψη

Εισαγωγή: Η διάγνωση του καρκίνου του προστάτη (PCa) παραμένει απαιτητική. Η παραδοσιακή βιοψία έχει χαμηλή ευαισθησία και υψηλό ποσοστό ψευδώς αρνητικών αποτελεσμάτων. Αν και η MRI-καθοδηγούμενη βιοψία είναι πιο ακριβής, παρουσιάζει υψηλότερο κόστος, μεγαλύτερη πολυπλοκότητα και εξαρτάται σε μεγάλο βαθμό από την εμπειρία του εξεταστή. Ο μικρο-υπέρηχος (micro-US) αποτελεί μια νεότερη τεχνική απεικόνισης υψηλής ανάλυσης, με προοπτική να προσφέρει ανάλογη διαγνωστική ακρίβεια με την πολυπαραμετρική MRI (mpMRI).

Στόχος: Η παρούσα μελέτη στοχεύει στη συστηματική σύγκριση της διαγνωστικής ακρίβειας της βιοψίας με micro-US και mpMRI για την ανίχνευση κλινικά σημαντικού καρκίνου του προστάτη (csPCa)

Μέθοδος: Πραγματοποιήθηκε συστηματική ανασκόπηση σύμφωνα με τις οδηγίες PRISMA-DTA και καταχωρήθηκε στη βάση δεδομένων PROSPERO (CRD42024513987). Περιλήφθηκαν μελέτες στις οποίες οι ασθενείς υποβλήθηκαν και στις δύο τεχνικές έως τις 30/04/2025. Αξιολογήθηκαν δείκτες ευαισθησίας, ειδικότητας και ανίχνευσης. Η μεθοδολογική ποιότητα των μελετών εκτιμήθηκε με το εργαλείο QUADAS-2.

Αποτελέσματα: Συνολικά 4.689 ασθενείς συμπεριλήφθηκαν σε δεκαέξι μελέτες. Μεταξύ 3.707 ασθενών που υποβλήθηκαν σε μικρο-υπερηχογράφημα (micro-US) με ταξινόμηση PRIMUS ≥ 3, ανιχνεύθηκαν 1.586 (42,8%) περιπτώσεις csPCa. Αντίστοιχα, μεταξύ 3.813 ασθενών με θετική mpMRI (PIRADS ≥ 3), ανιχνεύθηκαν 1.449 (38%) περιπτώσεις csPCa. Σε εννέα μελέτες, ο micro-US υπερίσχυσε της mpMRI. Η ευαισθησία του micro-US κυμάνθηκε από 67% έως 93,9%, ενώ η ειδικότητα κυμάνθηκε από 7,1% έως 57%.

Συμπεράσματα: Ο micro-US προσφέρει συγκρίσιμη διαγνωστική ακρίβεια με την mpMRI, με πλεονεκτήματα το χαμηλότερο κόστος, την ευκολότερη διαθεσιμότητα και εφαρμογή.

Λέξεις-κλειδιά: καρκίνος προστάτη, micro U/S, πολυπαραμετρική μαγνητική τομογραφία, βιοψία προστάτη, κλινικά σημαντικός καρκίνος προστάτη, διαγνωστική ακρίβεια, συστηματική ανασκόπηση

1. Background

1.1. Prostate cancer incidence and screening methods

Prostate cancer (PCa) is the most frequently diagnosed malignancy among men in Europe and represents the third leading cause of cancer-related mortality. In 2020 alone, approximately 1.4 million new cases were diagnosed worldwide, with over 375,000 related deaths, underscoring its significant global burden. These figures placed it as the fifth most common cause of cancer-related mortality in men (1). Geographical differences in prostate cancer incidence are strongly associated with the degree of PSA screening uptake, with countries such as those in North America and Western Europe showing higher detection rates due to widespread testing(2), compared to regions with limited screening uptake, including South-Central Asia and parts of Eastern Europe (3,4). Statistically, about 12.9% of men are expected to be diagnosed with the disease during their lifetime, and nearly 2.3% will eventually die from it. Most diagnoses occur at around the age of 67, and nearly 60% affect men aged 65 or older. Conversely, the disease is rare in those under the age of 40. In the United States alone, projections for 2025 indicate that 313,780 new cases will be reported, with 35,770 deaths anticipated (5).

Prostate cancer incidence shows considerable variation by race, with men of African descent experiencing notably higher rates (6). Despite significant reductions in mortality—over 50%—since the adoption of prostate-specific antigen (PSA) testing, racial disparities remain. Research has found that Black men are up to three times more likely than white men to die from prostate cancer, and among younger individuals, this gap can widen to more than four times. These disparities persist across different communities, even within the same state in the U.S. (7,8).

Since PSA testing was introduced in clinical practice in 1987, the number of prostate cancer diagnoses has risen significantly (9). PSA is produced by the epithelial cells of the prostate and the main purpose of this kallikrein protein is to liquify semen and a small proportion is leaked into the circulation and gets detectable. While PSA is specific to the prostate, it is not exclusive to malignancy—elevated levels can be found in non-cancerous conditions such as benign prostatic hyperplasia (BPH), prostatitis, after ejaculation, or following urological procedures. Early implementation of PSA screening led to overdiagnosis and overtreatment, due in part to inconsistent screening practices and variable treatment decisions based on disease stage (10). Despite these shortcomings, PCa mortality rates were reduced by more than 50%, albeit at the cost of excessive avoidable treatment and its associated side effects. To improve diagnostic precision, PSA derivatives such as PSA density (PSAD) and PSA velocity (PSAV) have been introduced. PSA velocity, refers to the rate of change in PSA levels over time. A rapid increase in PSA (e.g., >0.75 ng/mL/year) has been correlated with aggressive disease, although its utility remains limited by biological variability and measurement inconsistency(11).

PSA density, on the other hand, is calculated by dividing the PSA level by the prostate volume, typically measured via transrectal ultrasound or MRI. A higher PSAD—particularly above the commonly cited threshold of 0.15 ng/mL/cm³—is associated with an increased probability of harboring csPCa. However, PSAD does not significantly improve the predictive accuracy of PSA alone, as ultrasound-based volume measurements can be imprecise, and the proportion of PSA-producing glandular tissue to non-producing stromal tissue varies between patients(12–15). Rather than serving as a primary diagnostic marker, PSAD is more useful for risk stratification in patients with confirmed PCa who are candidates for active surveillance (16).

Prostate cancer screening remains a subject of ongoing debate due to the balance between early detection of aggressive disease and the potential harms of overdiagnosis. Traditional population-wide screening using total PSA thresholds (commonly >4.0 ng/mL) has demonstrated limited specificity and led to substantial detection of indolent tumors. Consequently, recent guidelines emphasize a more nuanced, risk-adapted approach that incorporates age, family history, ethnicity, PSA kinetics, and imaging findings (17). The impact of PSA screening on prostate cancer mortality has been primarily evaluated through two large-scale studies: the PLCO trial and the ERSPC trial. The PLCO trial, involving 76,693 men aged 55–74, compared annual screening to usual care but was criticized because over 90% of the control group had at least one PSA test, making it a comparison of routine vs. opportunistic screening (18,19).

In contrast, the ERSPC and Göteborg studies (20,21) showed a significant reduction in prostate cancer deaths with PSA screening. The ERSPC trial reported a 21% reduction in disease-specific mortality, preventing one death per 781 men screened or per 27 cancers detected. After 20 years, this improved to one death prevented per 101 men screened or per 13 cancers detected (22). Recent analyses suggest that, accounting for study differences, the PLCO results may align with the ERSPC findings, supporting the benefit of PSA screening in reducing prostate cancer mortality (23).

According to the EAU guidelines (17), PSA screening should be carefully considered, balancing the benefits of early cancer detection with the risk of overdiagnosis and overtreatment. PSA testing should only be performed after men have been informed about its possible advantages and drawbacks. An individualized, risk-adapted strategy is recommended for well-informed men with a life expectancy of at least 15 years. Early PSA testing is advised for men aged 50 or older, those aged 45 with a family history of prostate cancer or African descent, and men with BRCA2 mutations starting at age 40. For low-risk individuals (PSA < 1 ng/mL at age 40 or < 2 ng/mL at age 60), follow-ups can be extended up to 8 years, while higher-risk individuals may require more frequent monitoring every 2 years.

1.2. Prostate biopsy in the diagnosis of PCa

1.2.1. TRUS-Guided Biopsy in Prostate Cancer Diagnosis

Until recent years, prostate cancer stood out as the only solid organ malignancy routinely diagnosed without the aid of targeted imaging, relying instead on non-directed tissue sampling in the hope of detecting malignancy by chance (17). Systematic transrectal ultrasound (TRUS)-guided prostate biopsy has long served as the standard diagnostic procedure for histological confirmation of prostate cancer (PCa). It is typically performed with 10 to 12 cores sampled in a non-targeted manner, based on sextant or extended mapping schemes. However, its diagnostic performance is increasingly scrutinized, particularly for its inability to consistently identify clinically significant prostate cancer (csPCa).Despite widespread use, it is estimated that TRUS-guided biopsies are performed more than two million times annually across Europe and the United States (24–26).

A major limitation of TRUS biopsy is its restricted sampling range thereby leading to high false-negative rates, estimated between 25% and 45% (27)**.** In men with PSA levels between 4 and 10 ng/mL, the detection rate for prostate cancer using TRUS biopsy is approximately 40–45%. Moreover, up to 25% of prostate cancers are diagnosed following an initially negative biopsy, illustrating the method's suboptimal sensitivity. The false-negative rate is particularly concerning, ranging from 25% to as high as 45% in some studies. These diagnostic shortcomings are exacerbated in patients with larger prostate volumes, where lesions located in the anterior or apical regions are often inaccessible to conventional TRUS techniques (28).

Technical constraints contribute significantly to missed diagnoses, with evidence indicates that conventional TRUS biopsy may miss many small-volume lesions, limiting its effectiveness in early cancer detection. In response, extended biopsy protocols incorporating additional cores from the lateral peripheral and transition zones have been introduced to enhance cancer detection. However, despite these enhancements, detection rates have not improved substantially, and false-negative results still range between 16% and 41% (28,29).

Data from the PLCO (Prostate, Lung, Colorectal, and Ovarian) cancer screening trial underscore the limitations of this technique, with 43% of patients undergoing a repeat biopsy within three years due to persistently elevated PSA levels (30). Nonetheless, the long-term clinical consequences of missed cancers may be limited; after 13 years of follow-up, only 1.1% of men with an initially negative biopsy had died from prostate cancer, suggesting that many of the missed cases were likely indolent or low-risk (31).

TRUS-guided biopsy is also associated with a notable complication profile. Patients may experience hematuria (22%), rectal bleeding (36%), and prolonged hematospermia (over 50%). The risk of urinary tract infections ranges from 0.5% to 6%, with sepsis occurring in 1–2% of cases (26,32,33)**.** One

large-scale analysis involving over 10,000 biopsy procedures reported febrile urinary infections in 4.2% of patients, with hospitalization required in 0.8% of cases. Prostate volume greater than 40 mL and comorbid diabetes mellitus were identified as risk factors for post-procedural infection (34).

Another key limitation of TRUS is its inability to reliably differentiate clinically significant prostate cancer (csPCa) from benign prostatic hyperplasia or other non-malignant conditions. The echogenic profile of prostate cancer can vary widely, with tumors appearing hyperechoic, isoechoic, or indistinguishable from surrounding benign tissue. At PSA levels below 10 ng/mL, only 30% of prostate cancers are detectable using TRUS imaging alone (35).

A potential solution to the limitations of TRUS lies in the transperineal template mapping biopsy (TPMB) technique. This method involves systematic sampling of the entire prostate at 5 mm intervals through the perineum, offering nearly complete glandular coverage. TPMB has demonstrated high sensitivity (95%) and a similarly high negative predictive value, making it a valuable reference standard for prostate cancer detection. In addition, the transperineal approach minimizes infection risk by avoiding the rectal route, where a meta-analysis reported a 0.9% sepsis rate with TRUS biopsy versus 0.1% with transperineal biopsy, and provides superior access to anterior and apical regions often missed by TRUS (26,36,37).

Nevertheless, TPMB is associated with its own drawbacks. The procedure is resource-intensive, typically requiring general anesthesia due to the large number of cores extracted. It also carries an increased risk of urinary retention (5–10% in large prostates) and may lead to overdiagnosis of clinically insignificant cancers. For these reasons, TPMB is generally reserved for cases with persistently elevated PSA and prior negative biopsies, or when lesions are located in anterior regions of the prostate, which are less accessible with TRUS (38).

1.2.2. mpMRI-Guided Prostate Biopsy

In recent years, multiparametric magnetic resonance imaging (mpMRI) has revolutionized prostate cancer (PCa) diagnostics, introducing a more targeted and individualized approach to biopsy. Current guidelines now recommend the combination of mpMRI with systematic biopsy, particularly in biopsy-naïve men undergoing evaluation for localized PCa (17,39–41).

mpMRI integrates both anatomical and functional imaging sequences—specifically, T2-weighted imaging (T2W), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences. Interpretation of mpMRI is standardized using the Prostate Imaging-Reporting and Data System (PI-RADS), currently in version 2.1 (42). PI-RADS assigns lesions a score from 1 (very low likelihood of clinically significant cancer) to 5 (very high likelihood). A PI-RADS score above 3 is generally considered an indication for biopsy in patients with elevated prostate-specific antigen (PSA) levels or abnormal digital rectal examination (DRE).

The diagnostic superiority of mpMRI has been substantiated by major trials. The PROMIS trial (Prostate MR Imaging Study) provided pivotal evidence

supporting mpMRI as a triage test before biopsy. Involving 740 men with elevated PSA, positive family history, or abnormal DRE, the trial demonstrated that approximately 25% of patients could avoid biopsy based on negative mpMRI findings (PI-RADS <3). mpMRI exhibited a negative predictive value (NPV) of 82% for any prostate cancer and 98% for csPCa, outperforming the 74% NPV associated with TRUS-guided biopsy (43).

Beyond its diagnostic role, mpMRI also offers valuable information for local staging, such as lesion size, capsular involvement, and assessment of regional lymph nodes. Biopsies guided by mpMRI can be performed via three main approaches:

1. In-bore MRI-guided biopsy, where the biopsy is conducted inside the MRI scanner using a rectal probe.
2. MRI/ultrasound (US) fusion biopsy, which overlays mpMRI images onto real-time transrectal ultrasound images using dedicated software, offering greater precision and reduced operator dependency—though at higher cost.
3. Cognitive fusion biopsy, a technique relying on the operator's mental registration of MRI findings onto real-time ultrasound, which is cost-effective but highly dependent on the clinician's experience.

However, a meta-analysis found no significant difference in csPCa detection between the three mpMRI-guided biopsy techniques (44).

MRI/US fusion-guided biopsies have shown improved diagnostic performance compared to traditional TRUS-guided biopsies, with approximately 30% higher detection rates for csPCa and 17% fewer diagnoses of clinically insignificant cancers (45). These results are reinforced by the VISION meta-analysis, which pooled individual patient data from the PRECISION and PRECISE randomized trials. Involving 953 biopsy-naïve men, the study showed that mpMRI-targeted biopsy significantly increased csPCa detection (36.3% vs. 27.6%, $p = 0.004$) while reducing overdiagnosis of clinically insignificant cancer (9.6% vs. 21.9%, $p < 0.001$). Notably, 32.2% of men with negative MRI findings avoided biopsy altogether, underscoring the efficiency and patient-centered value of the mpMRI-based diagnostic pathway (46).

Despite its transformative role in prostate cancer diagnostics, mpMRI presents several limitations. Its sensitivity, while generally high, varies widely (58–96%), and up to 16% of clinically significant prostate cancers (csPCa) may still be missed (47,48). Particularly challenging are cribriform Gleason 4 tumors, which often appear inconspicuous on MRI despite their aggressive behavior (49,50). The interpretation of PI-RADS 3 lesions remains ambiguous, requiring adjunctive tools such as PSA density for risk stratification, with evidence suggesting that biopsy may be avoided when PI-RADS 3 lesions coincide with a PSAD <0.15 ng/mL/cm^3, although this requires careful clinical judgment (51,52). Moreover, although PI-RADS v2.1 upgrading rules have improved detection in transition zone (TZ) lesions, they may also increase false positives,

highlighting the need for individualized decision-making. According to a recent meta-analysis, lesions reclassified as PI-RADS “3+1” due to marked restricted diffusion demonstrate clinically significant prostate cancer (csPCa) detection rates as high as 37%, closely approximating the risk associated with PI-RADS 4 lesions. Similarly, lesions upgraded to “2+1” exhibit a 13% csPCa detection rate, more than double that of unmodified PI-RADS 2 lesions. While this approach improves sensitivity, it may also increase false-positive rates, underscoring the need for tailored biopsy strategies when interpreting TZ findings (53). Operator dependency is another critical factor; diagnostic accuracy is significantly influenced by radiologist experience, with substantial interobserver variability (54,55). From a practical standpoint, mpMRI requires high-cost equipment, specialized training, and infrastructure that may not be widely available. Even when optimally applied, mpMRI-guided biopsy may underestimate tumor burden or fail to detect extracapsular extension, limiting its value in local staging(56).

In summary, mpMRI represents a significant advancement in the diagnostic pathway for prostate cancer. When combined with biopsy, it improves detection of clinically meaningful disease while limiting unnecessary procedures. Nevertheless, its performance is dependent on reader expertise, technical quality, and lesion characteristics—factors that must be accounted for when integrating mpMRI into clinical decision-making.

1.3. High-Resolution Micro-Ultrasound (micro-US): A Novel Imaging Modality in Prostate Cancer Diagnosis

High-resolution micro-ultrasound (micro-US) is an emerging imaging technology developed by Exact Imaging (Toronto, Canada) designed to enhance prostate cancer (PCa) visualization and enable real-time targeted biopsy. Compared to conventional transrectal ultrasound (TRUS), micro-US offers markedly improved image resolution, potentially enabling the detection of subtle architectural changes in prostate tissue associated with malignancy.
Operating at a frequency of 29 MHz—substantially higher than the 8–12 MHz range used in traditional ultrasound systems—micro-US achieves a significantly enhanced axial resolution of less than 70 µm, compared to approximately 200 µm with standard ultrasound. These improvements facilitate the identification of microanatomical alterations linked to high-grade tumors (57).
Interpretation of micro-US findings is guided by the structured PRI-MUS score system, which categorizes lesion risk similarly to PI-RADS in multiparametric MRI (mpMRI). PRI-MUS assigns a score from 1 to 5, reflecting the probability that a given lesion represents clinically significant cancer (58).
One of the key advantages of micro-US is the integration of imaging and biopsy into a single procedure, performed entirely by the urologist. This streamlined workflow reduces reliance on cross-specialty coordination and allows for immediate targeting of suspicious lesions. From a practical standpoint, micro-

US systems share a similar physical footprint and cost profile with conventional ultrasound devices, making them more accessible than MRI-based modalities. Due to its integration ease and accessibility, micro-US presents a viable option for broader clinical deployment.

Preliminary evidence supports the clinical utility of micro-US in prostate cancer diagnostics. Studies indicate that micro-US-guided prostate biopsy demonstrates higher sensitivity for detecting clinically significant prostate cancer (csPCa) than standard TRUS-guided biopsy (59). Emerging data suggest that micro-ultrasound may offer comparable csPCa detection rates to those achieved with mpMRI-guided biopsies (58)**.** In a recent study by Lokeshwar et al., which compared four biopsy strategies—TRUS-only, MRI-TRUS fusion, microUS-only, and MRI-microUS fusion—in patients undergoing radical prostatectomy, the lowest Gleason upgrading rates were observed with MRI-based techniques (13–15%), while TRUS and microUS alone showed higher rates (28–40%). Notably, combining microUS with MRI achieved performance similar to MRI-TRUS fusion, suggesting that microUS may enhance diagnostic concordance when used in fusion protocols (60) .Given its potential to combine the high-resolution imaging benefits of mpMRI with the convenience and immediacy of ultrasound, micro-US represents a promising diagnostic tool in the evaluation of suspected prostate cancer. In this context, the present systematic review and meta-analysis was conducted to evaluate the diagnostic accuracy of micro-US-guided prostate biopsy compared to mpMRI-targeted biopsy in detecting clinically significant prostate cancer.

2. Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this systematic review(61,62). The study's aims and methods were registered in a protocol on PROSPERO (ID: CRD42024513987).

2.1. Search strategy

A comprehensive systematic search was conducted across three major databases—PubMed, the Cochrane Library, and Scopus—from inception to April 30, 2025. The aim was to identify studies that directly compared the detection rates (DR) of high-resolution micro-ultrasound (micro-US)-guided and multiparametric MRI (mpMRI)-targeted prostate biopsy (PB) in the diagnosis of prostate cancer (PCa). To supplement the database search, additional grey literature sources were reviewed, including conference abstracts from leading urology journals and relevant trial information available on websites such as exactimaging.com. Reference lists of all included articles and related reviews were also manually screened to ensure completeness. All search activities were conducted by the author (KE).

The PubMed search syntax was as follows: *(((((prostat*) OR (prostatic neoplasms[MeSH Terms])) OR (prostatic disease[MeSH Terms])) AND ((biops*)*

OR (biopsy[MeSH Terms])))) AND ((((((mpMRI) OR (multiparametric MRI)) OR (mp Magnetic Resonance Imaging)) OR (multiparametric magnetic resonance imaging)) OR (pMRI)) OR (multiparametric mri))) AND (((((((micro ultrasound) OR (micro US)) OR (mUS)) OR (29Mhz)) OR (29 Mhz)) OR (EXACTVU)) OR (high resolution)) OR (high resolution TRUS))
Equivalent adaptations of this query were used for the Cochrane Library and Scopus databases.

2.2. Inclusion and exclusion criteria

We included diagnostic accuracy studies—either prospective or retrospective—in which all enrolled participants underwent both high-resolution micro-ultrasound (micro-US) and multiparametric MRI (mpMRI)-targeted prostate biopsies performed sequentially. Studies were excluded if they were single-arm, case reports, or focused exclusively on patients under active surveillance following a previous prostate cancer diagnosis. When multiple publications were identified with potentially overlapping cohorts, only the most recent or the most comprehensive full-text version was retained for analysis.

2.3. Data Extraction and Quality Assessment

All identified records were independently screened for eligibility by the author (KE). Data extraction was performed using a standardized Microsoft Excel spreadsheet designed in advance. For each eligible study, we recorded key information including study design, participant demographics, intervention details, and prostate cancer detection of each modality. In our analysis, micro-ultrasound (micro-US)-guided prostate biopsy (PB) was considered the index test, while mpMRI-targeted PB functioned as the reference test.

To assess the methodological rigor and risk of bias in the included studies, we used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (63).

3. Results

3.1. Study Selection

The initial database search yielded a total of 187 records, including 102 from PubMed, 56 from Scopus, and 29 from the Cochrane Library. An additional 5 records were identified through grey literature sources and targeted searches (e.g., Exact Imaging website). After removal of 62 duplicates, 125 unique records underwent title and abstract screening. Of these, 100 were excluded for not meeting the eligibility criteria, leaving 25 full-text articles assessed for eligibility. Eleven articles were subsequently excluded due to background

design (n=7), non-English full text (n=2), and non-comparative study design (n=2). Ultimately, 14 studies were included through database search and 2 additional studies via grey literature, resulting in a total of **16 studies** included in the systematic review. The PRISMA flow diagram detailing the selection process is presented in **Figure 1**

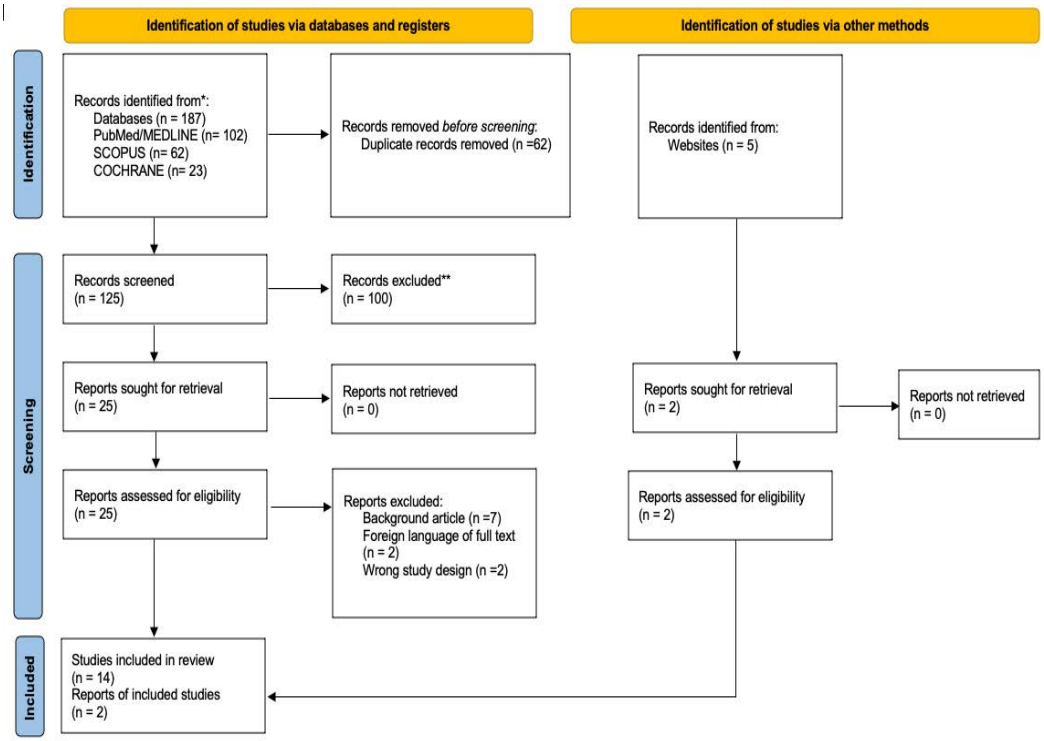

Figure 1 PRISMA flow diagram

3.2. Study Characteristics

The 16 included studies were published between 2020 and 2025 and collectively enrolled 4,689 patients undergoing prostate biopsy. Thirteen studies were prospective in design, while three were retrospective. Most studies were conducted in North America and Europe and included either biopsy-naïve men or those with prior negative biopsy but ongoing clinical suspicion for prostate cancer (PCa).

Across the included studies, the median participant age ranged from 61 to 70 years, PSA levels varied between 5.39 and 8.6 ng/mL, and prostate volume ranged from 38 to 61.3 mL (**Table 1**). All studies performed a paired design, comparing micro-ultrasound (micro-US)-guided biopsy using the 29 MHz ExactVu™ platform and PRI-MUS scoring system with multiparametric MRI (mpMRI)-targeted biopsy using PI-RADS v2 or v2.1, via cognitive or software fusion guidance.

Study ID	Year	Country	Design	Biopsy Setting	Sample Size	Age	PSA (Median/IQR or Mean ± SD)	Prostate Volume
Rodríguez Socarrás et al (64)	2020	Spain	Prospective	Mixed	194	62 (58 – 68)	6.5 (4.7 - 9.2)	58.1 (36.6 - 81.5)
Abouassaly et al (65)	2020	USA	Prospective	Mixed	19	66 (59.5–68.5)	5.39 (4.13-8.74)	38 (24–50)
Klotz et al (58)	2021	Multi-national	Prospective	Mixed	1040	67 (61–72)	7.0 (5.1–10.0)	38 (28–53)
Wiemer et al (66)	2021	Germany	Prospective	Mixed	159	70 (64–74)	7.59 (5.78–1.5)	53 (35.5–76.5)
Ghai et al (67)	2022	Canada	Prospective	Naïve	94	61 (57–68)	6.4 (5.1– 8.4)	48.5 (34.5–63.1)
Hofbauer et al (68)	2022	Germany / Austria	Prospective	Mixed	203	66 (59–70)	6.5 (4.8– 9.3)	48 (37–63)
Dias et al (69)	2023	France / Portugal / Italy	Retrospective	Naïve	139	69 (64–73)	7.5 (5.5– 10.9)	47 (33–65)
García Rojo et al (70)	2024	Spain	Prospective	Naïve	80	69.1 ± 9.02	7.66 ± 6.29	61.34 ± 31.7
Beatrici et al (71)	2024	Italy	Retrospective	Prior negative biopsy	304	66 (61–71)	8.6 (5.8 – 11.5)	52.6
Dagnino et al (72)	2024	Italy	Retrospective	Mixed	178	66 (61–71)	7 (5–9)	49 (35–64)
Avolio et al (73)	2025	Italy	Prospective	Mixed	1423	65(59−71)	7 (5−9)	50(36−67)
Pickersgill et al (74)	2025	USA	Prospective	Mixed	161	65.6 ± 1.5	7.6 ± 0.6	N/A
Maffei et al (75)	2020	Italy	Prospective	Naïve	504	64.8(SD7.7)	7.0 (5.0-9.5)	50 (IQR 36-79)
Lopez et al (76)	2019	France	Prospective	Naïve	51	N/A	N/A	N/A
Perez et al (77)	2019	France	Prospective	Naïve	55	N/A	8.5	N/A
Scuderi et al (78)	2022	Italy	Prospective	Naïve	85	N/A	N/A	N/A

Table 1 Study Characteristics

3.3.Clinically Significant Prostate Cancer Detection

Clinically significant prostate cancer (csPCa), generally defined as ISUP Grade Group ≥2 (Gleason score ≥3+4), was the primary outcome in all included studies. Among the total 4,689 patients, csPCa was detected in 1,866 cases (39.8%).

Micro-US-guided biopsy identified 1,586 csPCa cases, with per-study detection rates ranging from 7% to 42.4%. In comparison, mpMRI-targeted biopsy detected 1,449 csPCa cases across the same cohort, with detection rates ranging from 10% to 43.1%. In 9 out of the 16 studies, micro-US demonstrated

a numerically higher detection rate than mpMRI for csPCa. Summary of the finding are presented in **Table 2**.

Study ID	csPCa (mpMRI)	csPCa (micro-US)	Total csPCa	Detection Rate (%) (mpMRI)	Detection Rate (%) (micro-US)
Rodríguez Socarrás et al (64)	55	47	81	28,4	24,2
Abouassaly et al (65)	3	4	5	15,8	21,1
Klotz et al (58)	371	386	411	35,7	37,1
Wiemer et al (66)	45	59	78	28,3	37,1
Ghai et al (67)	37	33	38	39,4	35,1
Hofbauer et al (68)	60	58	79	29,6	28,6
Dias et al (69)	60	57	62	43,2	41,0
García Rojo et al (70)	17	15	19	21,3	18,8
Beatrici et al (71)	44	52	57	14,5	17,1
Dagnino et al (72)	28	36	51	15,7	20,2
Avolio et al (73)	486	603	691	34,2	42,4
Pickersgill et al (74)	55	58	73	34,2	36,0
Maffei et al (75)	147	137	184	29,2	27,2
Lopez et al (76)	19	21	22	37,3	41,2
Perez et al (77)	13	14	15	23,6	25,5
Scuderi et al (78)	9	6	9	10,6	7,1

Table 2 Clinically Significant Prostate Cancer Detection

3.4. Sensitivity, Specificity, and Predictive Values

The majority of studies provided diagnostic performance metrics. The sensitivity of micro-US for csPCa ranged from 67% to 99.7%, while mpMRI ranged from 54.9% to 100%. Specificity showed more variation: micro-US ranged from 7.1% to 57%, while mpMRI ranged from 2.4% to 58%.

Positive Predictive Value (PPV) was comparable across modalities, generally between 15.8–63%. Negative Predictive Value (NPV) was higher for mpMRI in some studies, but micro-US also demonstrated NPVs above 80% in high-quality prospective studies (**Table 3**).

Study	Sensitivity (%) (mpMRI)	Sensitivity (%) (micro-US)	Specificity (%) (mpMRI)	Specificity (%) (micro-US)	PPV (%) (mpMRI)	PPV (%) (micro-US)	NPV (%) (mpMRI)	NPV (%) (micro-US)
Rodríguez Socarrás et al (64)	84.3	99.7	18.8	23.1	40.7	62.3	64.5	99.2
Abouassaly et al (65)	60	80	**N/A**	**N/A**	15.8	21.1	**N/A**	**N/A**
Klotz et al (58)	90.3	93.9	21.6	21.9	42.9	44	77.3	84.7
Wiemer et al (66)	57.7	75.6	**N/A**	**N/A**	29.6	41.3	**N/A**	**N/A**
Ghai et al (67)	97.4	86.8	55.4	7.1	59.7	38.8	96.9	44.4
Hofbauer et al (68)	75.9	73.4	**N/A**	**N/A**	32.1	31	**N/A**	**N/A**
Dias et al (69)	96.8	91.9	19.5	44.2	49.2	57	88.2	87.2
García Rojo et al (70)	89.5	78.9	**N/A**	**N/A**	21.3	18.8	**N/A**	**N/A**
Beatrici et al (71)	77.2	91.2	36.4	32.0	21.9	23.6	87.4	94.0
Dagnino et al (72)	54.9	70.6	2.4	**N/A**	18.4	20.2	11.5	**N/A**
Avolio et al (73)	91	85	25	53	88	63	21	79
Pickersgill et al (74)	75.3	79.5	58	39.8	59.8	52.3	73.9	70
Maffei et al (75)	97.8	90.2	11.6	26.3	38.9	41.3	90.2	82.4
Lopez et al (76)	86.3	95.4	**N/A**	**N/A**	46.3	48.8	**N/A**	**N/A**
Perez et al (77)	86.7	93.3	40	27.5	35.1	32.6	88.9	91.7
Scuderi et al (78)	100	67	57	57	47	38	100	81

Table 3 Sensitivity, Specificity, and Predictive Values

3.5. Anatomical Considerations and Lesion Localization

Several studies emphasized that micro-US was particularly effective in detecting anterior or apical lesions, regions often missed by mpMRI or traditional TRUS. The improved spatial resolution of micro-US (axial <70 µm) was cited as a major technical advantage, facilitating better lesion delineation in challenging locations.

3.6. Study Quality

A total of 13 studies were assessed for risk of bias and applicability using the QUADAS-2 tool. Most studies demonstrated low applicability concerns across all domains. However, risk of bias varied considerably, especially in patient selection, where 8 of 13 studies were judged at high risk, primarily due to inclusion of only MRI-positive patients or retrospective recruitment.

The index test domain showed a mix of low and unclear risk, largely depending on whether the micro-ultrasound operators were blinded to mpMRI findings. Only three studies demonstrated high risk in the reference standard, typically due to lack of a gold-standard such as radical prostatectomy. Flow and timing were generally well managed, although two studies had unclear or high risk due to incomplete follow-up or partial verification. Summary of the findings are presented in **Table 4.**

Study	Patient Selection	Index Test	Reference Standard	Flow & Timing
Abouassaly et al (65)	Low	Unclear	Low	Unclear
Klotz et al (58)	High	High	High	Unclear
Wiemer et al (66)	High	Low	Unclear	Low
Ghai et al (67)	Low	Low	Low	Low
Hofbauer et al (68)	High	Low	Unclear	Low
Dias et al (69)	High	Unclear	Unclear	Low
García Rojo et al (70)	High	Low	Unclear	Low
Beatrici et al (71)	High	Low	Unclear	Low
Dagnino et al (72)	High	Low	Unclear	Low
Avolio et al (73)	Low	Low	Unclear	Low
Pickersgill et al (74)	Low	Low	Unclear	Low
Rodríguez Socarrás et al (64)	Low	Low	Unclear	Low
Scuderi et al (78)	Low	Unclear	Unclear	High

Table 4 Study Quality Assessment (QUADAS-2)

4. Discussion

This systematic review evaluated the current evidence comparing the diagnostic performance of micro-ultrasound (micro-US)-guided prostate biopsy to multiparametric MRI (mpMRI)-guided biopsy for the detection of clinically significant prostate cancer (csPCa). Our findings indicate that micro-US-guided biopsy achieves csPCa detection rates broadly comparable to those

of mpMRI-targeted biopsy, suggesting that micro-US may serve as a promising alternative or adjunct in the diagnostic pathway for prostate cancer.

The introduction of mpMRI has transformed prostate cancer diagnostics by enabling targeted biopsies and improving the detection of clinically significant disease while reducing overdiagnosis of indolent cancers (40,43). However, mpMRI is not without limitations: it is resource-intensive, costly, and subject to significant inter-reader variability and a steep learning curve (47,79). Even with expert interpretation, mpMRI may miss up to 15% of csPCa cases (48) Furthermore, the need for specialized radiological infrastructure and expertise can limit the accessibility and widespread adoption of mpMRI-guided biopsy, particularly in resource-constrained settings.

In contrast, micro-US operates at 29 MHz, achieving sub-70 µm spatial resolution—much finer than conventional transrectal ultrasound (TRUS)—enabling near-histologic visualization of prostatic architecture (57),(59). This technology is designed to address some of the limitations of both traditional TRUS and mpMRI, offering a potentially more accessible and cost-effective solution for targeted prostate biopsy. Several recent studies have reported that micro-US can achieve csPCa detection rates similar to those of mpMRI, with the added benefits of ease of integration into standard urological workflows and reduced procedural complexity (80).

A notable strength of this review is the rigorous and systematic approach to literature identification and selection, ensuring a comprehensive and unbiased synthesis of the available evidence. By focusing on studies that directly compare micro-US and mpMRI-guided biopsy, this review provides clinically relevant insights into the relative diagnostic performance of these modalities.

However, several limitations in the current evidence base must be acknowledged. Firstly, all studies utilized the ExactVu™ system from a single manufacturer (Exact Imaging), introducing potential for publication or sponsorship bias (81,81). Secondly, although most included studies were prospective, many were conducted in expert centers, and 8 of 13 assessed studies were judged at high risk of bias in patient selection. Blinding between modalities was inconsistently reported, and the reference standard varied. Third, heterogeneity in study design, patient selection and operator experience may have influenced the reported diagnostic performance.

Our findings are consistent with recent prospective studies and systematic reviews, which have demonstrated that micro-US-guided biopsy can match the diagnostic accuracy of mpMRI-guided approaches for csPCa (80). Additionally, micro-US may offer a shorter learning curve and greater reproducibility, given its similarity to conventional ultrasound workflows and real-time imaging capabilities. However, the current evidence base remains limited, and direct head-to-head randomized controlled trials are needed to confirm these preliminary observations.

A pivotal advancement in the evaluation of micro-ultrasound is the recent publication of the first randomized controlled trial (RCT) directly comparing micro-US-guided biopsy to mpMRI-targeted biopsy in biopsy-naïve men. In this multicenter noninferiority trial by Kinnaird et al (82), conducted across 20 centers in 8 countries, 802 men were enrolled, of whom 678 underwent biopsy. The primary outcome—detection of Gleason Grade Group ≥2 prostate cancer—was achieved in 47.1% of the microultrasound group and 42.6% of the MRI/conventional US fusion group. The difference of 3.52% (95% CI, −3.95% to 10.92%) confirmed the noninferiority of microultrasound-guided biopsy (noninferiority $P < .001$). Notably, a subgroup combining micro ultrasound with MRI guidance showed similar diagnostic performance (46.9%), without superiority over standalone microultrasound. These results validate microultrasound as a noninferior alternative to MRI-guided biopsy for detecting clinically significant prostate cancer, particularly in biopsy-naïve men. Given its real-time imaging capability, lower cost, and integration into standard urological workflow, microultrasound may serve as a pragmatic first-line option, especially in settings where MRI access is limited or cost-prohibitive.

Future research should focus on more large-scale, multicenter studies that reflect real-world clinical practice, including diverse patient populations and operator experience levels. Cost-effectiveness analyses and health technology assessments will be crucial to inform policy decisions and guideline updates. Additionally, the development and validation of alternative micro-ultrasound systems by other manufacturers would enhance the robustness and generalizability of the evidence.

5. Conclusions

In summary, micro-US-guided prostate biopsy appears to offer diagnostic performance for clinically significant prostate cancer detection comparable to that of mpMRI-guided biopsy, with potential advantages in accessibility, cost, and workflow integration. However, the current evidence is limited by the exclusive use of a single micro-ultrasound system (ExactVu™), highlighting the need for further independent studies and technological innovation. Until such data are available, mpMRI remains the reference standard, but micro-US represents a promising and practical alternative, especially in settings where mpMRI is not feasible or available.

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