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TESI DI LAUREA

Transperineal Ultrasound-MRI Fusion-Guided Biopsy for the Detection of Prostate Cancer: A Comparison of Cognitive and Software-Assisted Techniques

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ABSTRACT

Background: Prostate cancer (PCa) is one of the most prevalent malignancies in men worldwide. Its diagnosis primarily relies on prostate biopsy, which includes systematic biopsies and targeted biopsies directed at suspicious lesions detected by MRI. The introduction of targeted prostate biopsies improved diagnostic accuracy, but the relative efficacy of cognitive versus software-assisted techniques remains debated.

Purpose: This study aimed to compare the diagnostic performance of cognitive and software-assisted targeted biopsies in detecting PCa and clinically significant prostate cancer (csPCa) in a cohort of patients undergoing transperineal prostate biopsy. A secondary aim was to investigate clinical and radiological predictors of PCa and csPCa.

Patients and methods: This retrospective monocentric study included 445 patients who underwent transperineal prostate biopsy at the University Hospital of Padova from January 2023 to June 2024. Among these, 261 underwent cognitive targeted biopsy and 184 underwent software-assisted targeted biopsy. Systematic biopsies were performed alongside targeted biopsies in all patients. Detection rates for PCa and csPCa were compared between the two groups and multivariable logistic regression was used to identify significant predictors of PCa and csPCa.

Results: No statistically significant differences were found between detection rates of cognitive and software-assisted techniques, either when only considering targeted biopsies (csPCa: 27.7% vs 34.1%, p = 0.3) or when combining targeted and systematic biopsies (csPCa: 44.4% vs 38.6%, p = 0.4). However, a slight trend favoring a sotware-assisted technique was observed. Multivariable analysis identified key predictors of csPCa, including age, prostate volume, lesion localisation (anterior vs posterior), PI-RADS score and lesion diameter.

Conclusions: Cognitive and software-assisted targeted biopsies demonstrated similar diagnostic accuracy for PCa and csPCa detection. These findings suggest that, to date, the choice between the two techniques is influenced more by practical considerations, such as operator expertise and resource availability, rather than differences in diagnostic efficacy. Regarding predictors of PCa and csPCa, the identification of robust predictors, particularly PI-RADS score and anterior lesion localisation, highlights their critical role in improving biopsy planning.

RIASSUNTO

Presupposti dello studio: Il carcinoma della prostata (PCa) è uno delle neoplasie maligne più comuni negli uomini. La diagnosi si basa principalmente sulla biopsia prostatica, che comprende biopsie sistematiche e biopsie mirate alle lesioni sospette identificate alla risonanza magnetica (RM). L'introduzione delle biopsie mirate ha migliorato l'accuratezza diagnostica, ma l'efficacia relativa delle tecniche cognitive rispetto a quelle assistite da software è ancora dibattuta.

Scopo dello studio: Lo scopo di questo studio è quello di confrontare la performance diagnostica delle biopsie mirate cognitive e di quelle assistite da software nel rilevare PCa e carcinoma prostatico clinicamente significativo (csPCa) in pazienti sottoposti a biopsia prostatica transperineale. L'obiettivo secondario era investigare i predittori clinici e radiologici di PCa e csPCa.

Pazienti e metodi: Questo studio retrospettivo monocentrico ha incluso 445 pazienti sottoposti a biopsia prostatica transperineale presso l'Azienda Ospedale-Università di Padova tra gennaio 2023 e giugno 2024. Di questi, 261 hanno eseguito una biopsia mirata con tecnica cognitiva e 184 con tecnica assistita da software. In tutti i pazienti sono state effettuate anche biopsie sistematiche. I tassi di rilevamento di PCa e csPCa sono stati confrontati tra i due gruppi e un'analisi di regressione logistica multivariata è stata utilizzata per identificare i predittori significativi di PCa e csPCa.

Risultati: non sono state rilevate differenze statisticamente significative nei tassi di rilevamento di tra le tecniche cognitive e assistite da software, né considerando solo le biopsie mirate (csPCa: 27,7% vs 34,1%, p = 0.3) né considerando la combinazione di biopsie mirate e sistematiche (csPCa: 44.4% vs 38.6%, p = 0.4). Tuttavia, è stata osservata una tendenza verso una maggiore rilevazione da parte delle tecniche assistite da software. L'analisi multivariata ha identificato diversi predittori di csPCa, tra cui età, volume prostatico, localizzazione della lesione (anteriore vs posteriore), punteggio PI-RADS e diametro della lesione.

Conclusioni: Le biopsie mirate e quelle assistite da software hanno dimostrato un'accuratezza diagnostica simile nel rilevare PCa e csPCa. Questi risultati suggeriscono che la scelta tra le due tecniche possa dipendere più da fattori pratici, quali l'esperienza, dell'operatore e le risorse disponibili, piuttosto che differenze nell'efficacia diagnostica. Riguardo i predittori di PCa e csPCa, l'identificazione di forti predittori, in particolare il punteggio PI-RADS e la localizzazione anteriore

della lesione, sottolinea il loro ruolo fondamentale nel migliorare la pianificazione della biopsia.

1. INTRODUCTION: PROSTATE CANCER

1.1. EPIDEMIOLOGY AND RISK FACTORS

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men worldwide, with over 1.467.000 new cases reported in 2022. In both Italy and Europe, it holds the highest incidence among male cancers, accounting for about 47.000 and 380.000 cases respectively in the same year, making it the most common type of cancer both in the European and the Italian male population. (1,2)

The incidence of PCa can vary significantly across different geographic areas: countries located in areas with high or very high human development such as Australia and New Zealand, the United States of America, Western and Northern Europe have a higher incidence rate compared to other areas of the world. (3) These differences can be explained not only by socioeconomic heterogeneity, but also by the different healthcare policies adopted in each country. The main factor that is considered to influence the number of diagnoses is the strategy adopted for early detection of cancer based on the measuring of prostate-specific antigen (PSA). (4) This theory is supported by the fact that incidence trends have been stabilizing or declining over the past five years, in accord with the reduction in PSA testing as a screening method, which has led to fewer diagnosis of indolent cases of PCa. (3)

Despite its high incidence, PCa has a much lower mortality rate compared to most types of cancer. Overall, PCa is the fifth cause of cancer-related death worldwide, with around 397.000 deaths accounted in 2022. (1,2) The variation among mortality rates among different countries is relatively lower compared to incidence rates. However, some differences persist, as PCa still is the leading cause of cancer-related deaths among men in 52 countries. (5) The highest estimated mortality rates recorded in the Caribbean, sub-Saharan Africa, parts of the former Soviet Union, and Asia. (3)

In most Western countries PCa mortality has decreased in the last five years, but the extent of this reduction varies from country to country. This ongoing decline in most high human development countries is likely due to advancement in treatments, such as surgery, hormone therapy and radiation therapy, as well as the improved access of these medical interventions. (3)

PCa risk is influenced by a variety of factors. Some of the most significant non modifiable risk factors, such as family history and ethnic background, suggest the importance of genetic predisposition. Moreover, more than 17% of PCa patients have an underlying germline mutation. (5)

Regarding family history, over 20% of men that are diagnosed with PCa have a first-degree relative who received the same diagnosis, and having an affected family member doubles the risk of PCa. The risk is even higher if said family member is 60 years old or younger. (4)

Differences in incidence and mortality rates have been observed across various racial and ethnic groups, which could also partially explain the epidemiological variation among different countries. (4) In particular, men of African descent in Western countries tend to present with more advanced disease at the time of diagnosis and generally experience worse outcomes. (5)

Another highly relevant factor is age. The risk of PCa is relatively low for men younger than 40 years of age, but it increases significantly after the age of 55. The average age at diagnosis has decreased in the past few years after some changes in the criteria for PSA testing for screening, which is usually avoided in men with a life expectancy shorter than ten years. (6)

Older age, black race, and a family history of PCa are the only well-established risk factors for the disease, but some environmental and clinical history factors are also thought to be associated with a higher risk of developing PCa, such as metabolic syndrome, obesity, diabetes and metformin use, cholesterol and statins use, dietary factors, hormonally active medication (testosterone). On the contrary, other hormonal drugs like 5-alpha-reductase inhibitors (5-ARIs) act as a protective factor and reduce the risk of developing PCa. (5)

1.2. DIAGNOSIS

The definitive diagnosis of PCa relies on prostate biopsy, as histological examination remains the only method to confirm malignancy. However, the decision to perform a biopsy is guided by a combination of clinical findings and additional diagnostic tools.

Elevated levels of prostate-specific antigen (PSA) on laboratory testing and abnormal results on digital rectal examination (DRE) are often the first signs that

raise suspicion of potential PCa. However, these findings alone are insufficient to confirm or exclude the diagnosis and they do not necessarily indicate the immediate need for a prostate biopsy. Additional testing may be performed, including multiparametric magnetic resonance imaging (mpMRI), which plays an increasingly important role not only in detecting suspicious lesions but also in guiding biopsy procedures and risk assessment. Additionally, transrectal ultrasound (TRUS) remains a key technique, commonly employed to guide biopsy needle placement and improve the precision of tissue sampling.

While these tools enhance diagnostic accuracy, individualized patient factors such as genetic predisposition, family history and other risk factors also play a critical role in the diagnostic process, helping to identify patients at higher risk who may benefit from further investigation. At the same time, the decision to proceed with biopsy must account for the patient's biological age, life expectancy (with further investigations often unnecessary if life expectancy is below 10 years), overall health status and comorbidities. These considerations aim to minimize unnecessary procedures while ensuring timely detection of clinically significant cases. Ultimately, this decision must be made collaboratively with the patient, incorporating their values and preferences into the process.(5,7–9)

1.2.1. CLINICAL PRESENTATION

PCa is typically asymptomatic at the time of diagnosis, as it is most often detected at a localised stage. Less frequently, usually following local tumor progression, it can cause symptoms such as lower urinary tract symptoms (LUTS), erectile dysfunction, urinary retention, hematuria, hematospermia or pain. These manifestations, however, are highly nonspecific and may be caused by other prostatic or urinary conditions of benign etiology. In particular, LUTS are more commonly indicative of benign prostate hyperplasia rather than of PCa, considering they both affect the same age group. (5)

Since the skeleton is the most common site of metastasis in PCa, some patients may present bone pain or pathological fractures as initial symptoms. However, it is uncommon nowadays, as only 6% of patients have metastatic cancer at the time of diagnosis. (10)

1.2.2. DIGITAL RECTAL EXAMINATION

Digital rectal examination (DRE) can detect abnormalities in the surface or consistency of the prostate, such as nodules, diffuse induration or asymmetries, and it simultaneously allows an assessment of the gland's volume.
Approximately 18% of PCa cases are detected based solely on a positive DRE finding, regardless of PSA levels. The positive predictive value (PPV) in patients with a suspect DRE and a PSA level ≤ 2 ng/mL ranges from 5 to 30%. (11)

Although digital rectal examination (DRE) is a cost-effective and rapid method for identifying potential tumor masses, it has significant limitations as a diagnostic tool, primarily its high interobserver variability. Moreover, in older men a symmetrically enlarged and firmer prostate is common, particularly in cases of benign prostatic hyperplasia. Therefore, when abnormalities are detected on DRE, the execution of additional diagnostic tests is appropriate in order to determine whether a biopsy should be performed.
At the same time, a normal DRE does not rule out the possibility of PCa. This technique can only detect tumors located in the posterior and lateral portions of the gland, which are the only ones palpable through the rectum. Besides, early stage cancers, even if localised in these regions, may be too small to be identified. (12)

1.2.3. PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen (PSA) is a glycoprotein enzyme secreted by the prostatic epithelium. Serum PSA levels represent one of the most valuable and commonly used tests for the early detection of PCa, as elevated values of PSA correlate with a greater likelihood of the disease. However, while PSA is an organ-specific marker, it is not cancer-specific; several non-malignant conditions can influence its secretion, including benign prostatic hyperplasia, prostatitis or urinary tract infections. Additionally, PSA levels may be increased by other confounding factors such as manipulation of the prostate (e.g. during digital rectal examination), recent ejaculation, cycling or the use of certain medications. (5,10) On the other hand, other elements can influence PSA levels by reducing them, including 5-alpha reductase inhibitors (5-ARIs), obesity, aspirin, thiazide diuretics, statins or herbal supplements. (10) 5-ARIs, such as finasteride and dutasteride, which belong to a

class of medications commonly used for treatment of benign prostatic hyperplasia, can cause a decline in PSA levels by approximately 50%. (13)

PSA level is a continuous variable and, as previously stated, higher levels indicate a greater chance of PCa. Generally, a cut-off of ≤ 4 ng/ml is considered to be normal, given that it has been shown to achieve a sensitivity of 93% and a specificity of 20% for detecting PCa. (14) However, a study conducted on men who had a PSA level of 4.0 ng/ml or lower showed that over 15% of these individuals still had clinically significant PCa. (15) Therefore, a low PSA level does not ensure the absence of the disease and no PSA cut-off can be applied with absolute certainty. In fact, there is currently no universally accepted standard for defining an optimal threshold.

Regardless of external factors that can influence their value, PSA serum levels are subjected to biological fluctuations. For this reason, a single elevated reading is not sufficient to indicate the presence of PCa, as it carries a significant risk of the abnormal finding being a false positive. Supporting this, research has shown that nearly half of men who have a single elevated PSA finding return to normal upon the following reading. (16) Consequently, an isolated elevation should be confirmed by a second measurement after a few weeks before proceeding with further testing, including a prostate biopsy. (5,16) This is particularly relevant in men with a moderately elevated PSA (i.e. ≤ 10 ng/ml), where a repeat test has been demonstrated to reduce the indication for biopsy in over 16% of cases. (17)

Among the factors that must be considered when interpreting a PSA test, the patient's age is particularly significant, as it can influence the interpretation of PSA levels and, consequently, the decision to proceed with further evaluation. There is a well-established direct correlation between serum PSA concentration and age, primarily attributed to the influence of prostate volume on PSA production. Prostate volume also physiologically increases with advancing age, often alongside the presence of benign prostatic hyperplasia. Thus, research has suggested it is appropriate to take into account age-specific reference ranges when reading PSA tests. (18,19)

In case of equivocal PSA results, adjunctive laboratory tests can be performed to attempt to better estimate the likelihood of PCa, such as PSA density and free-to-total PSA ratio.

PSA density (PSAD) is calculated by dividing the PSA level by the prostate volume, with higher PSAD values being associated with an increased risk of PCa. However, since PSAD can be elevated in both benign and malignant conditions, it is particularly meaningful parameter in patients with smaller prostate volumes. Nonetheless, PSAD has some limitations, primarily due to the lack of standardisation of prostate volume estimation, which can be measured with imaging techniques (TRUS or MRI) or less precisely during digital rectal examination. (5,20)

Prostate-specific antigen is present in the serum in multiple forms: the majority is bound to protease inhibitors, while a smaller fraction remains unbound, referred to as free PSA. The ratio between these two forms, the free-to-total PSA ratio (f/t PSA ratio), has been shown to help distinguish between malignant and benign prostatic disease. Specifically, men with PCa tend to have a lower percentage of free PSA compared to those with a normal prostate or benign conditions, although the underlying reason for this phenomenon remains unclear. (12,21)

In summary, while PSA serum levels are an important factor in risk assessment, they are not sufficient on their own to justify the execution of a prostate biopsy. Instead, they should be considered alongside other diagnostic tools.

1.2.4. MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) plays a prominent role in multiple aspects of PCa diagnosis and management. It provides accurate visualization of potentially significant PCa, making it a valuable tool for detecting PCa and improving patient selection for biopsy.

Specifically, the advancement of multiparametric magnetic resonance imaging (mpMRI), which integrates a specific combination of imaging sequences, has significantly enhanced the clinical utility of prostate MRI and improved lesion identification and characterization. MpMRI combines three distinct imaging sequences: high-resolution T2-weighted images (T2W), which provides an evaluation of the gland’s anatomy, and two functional techniques, diffusion weighted imaging (DWI) and dynamic contrast enhanced MRI (DCE-MRI), which has a high sensitivity in cancer detection. (22)

PCa lesions typically appear as round, low signal intensity areas on T2W imaging due to increased cell density, high signal intensity on DWI sequences and early enhancement on DCE-MRI, reflecting the presence of abnormal neovascularization. (23,24)

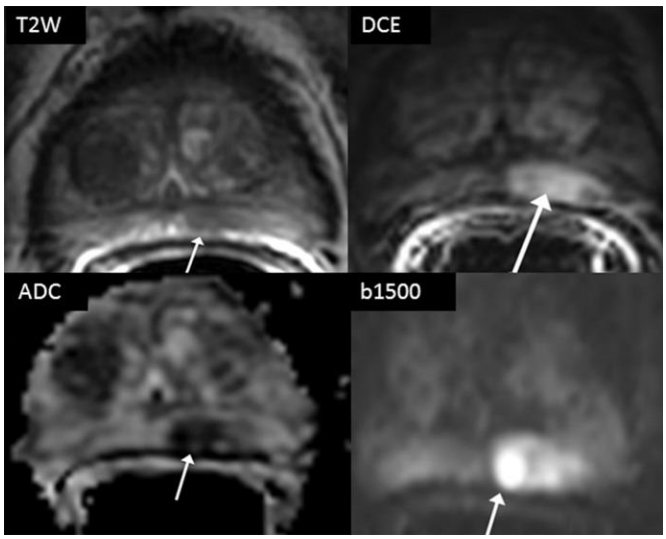

Figure 1 - Multiparametric MRI of the prostate.

The International Prostate MRI Working Group developed the Prostate Imaging-Reporting and Data System (PI-RADS) in order to standardize the image acquisition techniques of prostate MRI, its interpretation and the terminology used in reporting. (23,25)

The PI-RADS assessment assigns each lesion a score on a five-point scale, indicating the likelihood of csPCa. According to the PI-RADS version 2 criteria (25), the categories are defined as follows:

- PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be present)
- PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)
- PI-RADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)
- PI-RADS 4 – High (clinically significant cancer is likely to be present)
- PI-RADS 5 – Very high (clinically significant cancer is highly likely to be present)

Evidence on the performance of MRI conducted in accordance with PI-RADS v2 demonstrates high sensitivity and moderate specificity in the detection of csPCa (i.e. ISUP grade group 2 or higher). A Cochrane meta-analysis, which included 21 studies and over 3.800 patients, compared MRI findings with template biopsy results, reporting an overall pooled sensitivity of 91% (95% CI: 0.83–0.95) and an overall pooled specificity of 73% (95% CI: 0.29–0.46). (26) Furthermore, in a study comparing pre-operative MRI and histopathology results following radical prostatectomy, MRI showed a good sensitivity for detection and localisation of csPCa particularly for lesions with a diameter greater than 10 mm. In fact, detection rates were observed to increase in correlation with tumor volume and Gleason score. (27)

In the diagnostic pathway for PCa, the execution of mpMRI is indicated in naive patients (i.e. with no prior biopsy) when there is a suspicion of significant disease. The decision to perform the exam is based on one or more of the other diagnostic tools, such as elevated PSA levels or abnormalities detected during DRE, in conjunction with additional factors including age, comorbidities, life expectancy, potential therapeutic implications and the patient's preferences. (5,28)

Despite its recognized utility, there is no universal consensus on the role of MRI prior to prostate biopsy. While several international associations, including the European Association of Urology (EAU), the American Urological Association (AUA) and the United Kingdom's National Institute for Health and Care Excellence (NICE), support the use of routine pre-biopsy prostate MRI, not all endorse its role as the sole determinant for deciding whether patients should undergo biopsy. (5,29,30) Specifically, the 2024 guidelines from the EAU endorse the use of prostate MRI as a triage test for biopsy, other guidelines, such as those of the AUA, argue that the available data is insufficient to recommend routine MRI in biopsy-naive men. (5,29) Nonetheless, several studies have demonstrated that mpMRI could play an important role in selecting patients for biopsy, in order to avoid undertaking unnecessary biopsies in patients with no visible lesions at imaging. (31) Due to its high sensitivity, MRI has shown a strong negative predictive value (NPV) for ruling out the presence of csPCa when the result was compared to biopsy outcomes. (32–34) For instance, the PROMIS trial reported that the NPV of mpMRI for detecting clinically significant cancer was higher than that of standard biopsy (89% vs 74%). This study also demonstrated that using MRI as a triage test prior to

the first prostate biopsy, by limiting the procedure to patients with lesions classified as PI-RADS ≥3, could have avoided unnecessary biopsies in 27% of cases. (35) Similarly, the Cochrane review reported that, with a threshold of PI-RADS ≥3, 30% of procedures would have been avoided while 11% of csPCa diagnosis would have been missed, including both biopsy-naive patients and patients with prior negative biopsies. (26)

However, the so-called "MRI pathway", where only patients with suspicious MRI findings undergo biopsy, is not yet part of standard clinical practice due to insufficient supporting evidence. For this reason, men with suspected PCa and no visible lesions on MRI are typically still referred for biopsy.

Beyond its role in the diagnostic phase, prostate MRI is also employed in the evaluation of patients with a confirmed PCa diagnosis in various clinical contexts. It is particularly useful for optimizing tumor localization during staging and risk stratification, as it provides valuable information regarding the presence of extracapsular disease as well as neurovascular bundle or seminal vesicle invasion. Additionally, MRI plays a key role in the management of men enrolled in active surveillance (AS) programs, assisting both in the selection of appropriate candidates and in monitoring throughout the surveillance period. Furthermore, it may be used to detect local recurrence following radiation therapy.
The exam is also valuable in patients with a previous negative biopsy that produced clinically inconclusive results but who present with persistently elevated PSA. (36)

In conclusion, pre-biopsy MRI plays a pivotal role in the diagnostic pathway for PCa, both in biopsy-naive patients and in those with a prior negative biopsy. Its importance lies in its ability to identify suspicious lesions, opening to the possibility of guiding targeted biopsies. This capability marks the transition from standard systematic biopsy to a more precise and individualized diagnostic approach.

1.3. PROSTATE BIOPSY

The diagnosis of PCa is confirmed through a histopathological examination of a prostate biopsy. This remains the only definitive method for confirming or excluding the diagnosis, as serological and imaging standards alone do not provide sufficient diagnostic accuracy.

Over the years, significant advancements have been made in biopsy techniques to enhance diagnostic accuracy. Among these, the use of transrectal ultrasound (TRUS) enabled real-time visualization and a guide for systematic sampling of tissue. More recently, the introduction of pre-biopsy mpMRI opened for the adoption of targeted biopsy strategies, as it provides detailed information on the presence, the localization and the radiological grade of suspicious areas within the prostate gland.
Unlike traditional systematic biopsies, which sample the prostate in a random, sector-based manner, targeted biopsies focus specifically on the PI-RADS lesions from MRI imaging.

This shift has also allowed the development of software capable of fusing MRI and real time ultrasound images, enabling a precise localization and sampling during biopsy.

1.3.1. IMAGING GUIDANCE

Imaging techniques play a crucial role in guiding prostate biopsies. Originally, these procedures relied on manual guidance and blind sampling of palpable abnormalities of the gland. (37) Since then, significant advances have revolutionized this process, with TRUS now considered the standard approach for biopsy guidance. TRUS provides a real time visualisation of the prostate, essential for correctly directing the needle while also allowing an evaluation of the gland's anatomy and volume.

During the procedure, following the administration of local anaesthesia, the TRUS probe is introduced. The prostate is then examined for its anatomical features and its volume is calculated by measuring its three diameters using transverse and sagittal plane images. (38) Subsequently, the gland is evaluated for suspected areas or irregularities. Normally, the prostatic parenchyma has a uniform echotexture, whereas on conventional B-mode TRUS PCa often appears as hypoechoic lesions. In fact, hypoechoic regions and lesions that correlate with abnormal findings on digital rectal examination are more likely to be indicative of PCa. (39)
However, this observation alone is not definitive and cannot reliably distinguish between malignant and benign conditions. Studies have shown that 30-40% of PCas are isoechoic and, when comparing detection rates of PCa from hypoechoic and isoechoic areas, no significant difference was found. (38,40,41) Additionally, TRUS

struggles to adequately visualize lesions located in the anterior and has difficulty differentiating proliferative nodules in the transition zone from malignant lesions. (38)

This lack of reliability in detecting PCa reduces the utility of TRUS in the diagnostic setting and highlights the crucial role of mpMRI, which offers superior accuracy in identifying and characterising suspicious lesions.

To compensate for the limitations of conventional ultrasound, enhanced US techniques are being investigated to improve PCa detection. Emerging sonographic modalities, such as micro-Doppler, sonoelastography, contrast-enhanced ultrasound (CEUS) and especially multiparametric ultrasound (mpUS, a combination of these approaches) are being studied and have shown promise in enhancing diagnostic accuracy. (42,43)

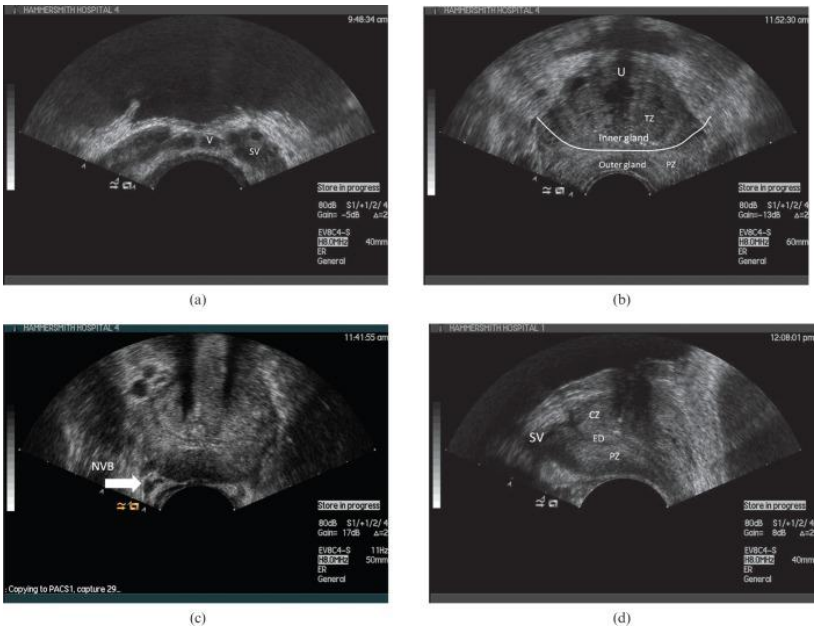

Figure 2 - Axial transrectal ultrasound (a-c) and longitudinal images of the normal prostate (d).

As previously discussed, the role of pre-biopsy MRI has become essential, not only for diagnosing PCa but also for guiding prostate biopsy, as it enables the visualization of target lesions by the urologist before the procedure. These targeted techniques include MRI-US fusion biopsy, which combines the high-resolution images of mpMRI with the real-time guidance of TRUS. In addition, methods

utilizing MRI in real time for biopsy guidance, such as in-bore prostate biopsy, have recently emerged. This technique facilitates precise needle placement within the target lesion and provides accurate documentation of the biopsy site. (12,38)

1.3.2. ANATOMIC APPROACHES

The two primary approaches that can be used when performing prostate biopsy are the transrectal and the transperineal techniques. The choice between the two varies significantly across countries, as there is inconsistency in guideline recommendations.

In the transrectal approach the needle is inserted through the rectal mucosa into the prostate. Systematic transrectal biopsies, commonly performed in an office setting, have been the standard for decades worldwide. (38)
However, transrectal biopsy is associated with a false negative rate of up to 50%, largely due to difficulty accessing regions like the apex, which is one of the most common localizations of PCa. (44) Moreover, this approach carries a higher risk of complications compared to the transperineal one, including rectal bleeding, fever, haematuria, acute urinary retention, local infections and notably urosepsis. (45–47) The infectious risk, that stems from the transrectal route's exposure to rectal flora, is particularly concerning and has led to routine administration of prophylactic antibiotics. (38)

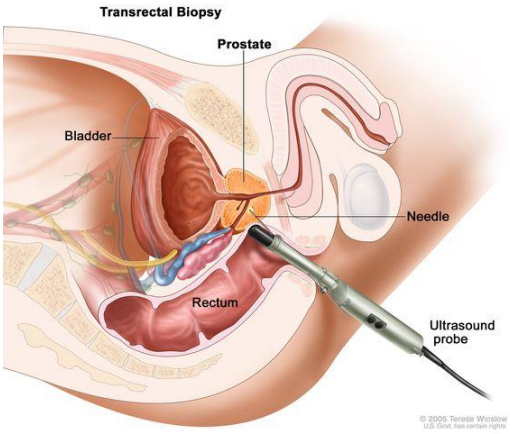

Figure 3 - Transrectal prostate biopsy.

Due to these limitations, the transperineal approach was introduced in order to improve cancer detection and safety of prostate biopsy. In this method, the biopsy needle passes through the perineal skin into the prostate. Since the perineum is more sensitive to pain than the rectal mucosa, the procedure is generally performed under general or spinal anaesthesia, although recently approaches using only local anaesthesia have become increasingly common. Despite this, patients tend to report greater pain and discomfort following transperineal biopsies. (38)

This method offers better sampling coverage of the prostate, particularly of apical and anterior tumors, which are challenging to access via the transrectal route. (38) Furthermore, the perineal route, being clean-contaminated, has a lower incidence of infections. Eight different randomized trials compared complications of the two approaches and found a significantly higher rate of infectious complications with transrectal biopsy, while sepsis rates have been reported to be near zero. (5,47,48)

However, transperineal biopsy has some limitations, including being more time consuming, requiring a longer learning curve and being associated with higher rates of urinary retention. (49,50)

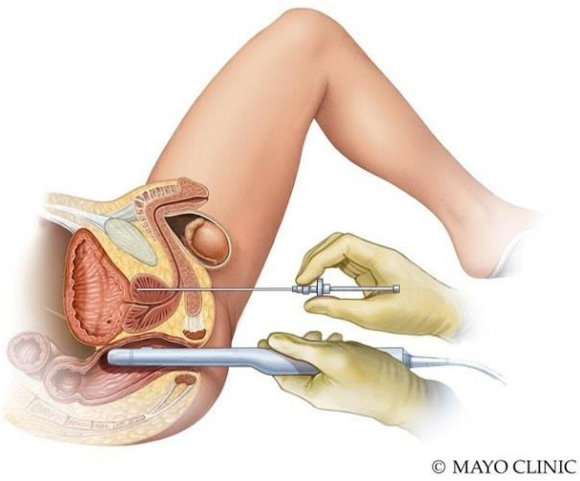

Figure 4 - Transperineal prostate biopsy.

While both approaches are considered valid, they present differences when it comes to accessibility, diagnostic efficacy, safety profiles and procedural practicality. These distinctions are summarised in the following table.

Characteristic	Transrectal	Transperineal
Accessibility	Limited access to anterior zones	Better access to anterior and apical areas
Infection risk	Higher (contamined)	Lower (clean-contamined)
Patient comfort	Quick, less invasive	Requires anesthesia, more resources

Table I – Differences between transrectal and transperineal approaches.

The debate over the preferred approach, however, remains unsolved, leading to varying recommendations from international associations. For instance, the EAU guidelines strongly recommend performing prostate biopsy using the transperineal approach, whenever feasible, due to its lower rates of infection and sepsis-related readmissions. (5,51) On the other hand, the AUA guidelines endorse either approach, arguing that no prospective randomized trials compare the infection risks of the two approaches. (29,51)
Additionally, the current evidence on cancer detection rates for transrectal and transperineal prostate biopsies remains inconsistent, complicating efforts to draw definitive conclusions on the superiority of either approach.

Some studies suggest a higher detection rate for csPCa with the transperineal approach, while others report comparable detection rates or non-statistically significant differences. (52) For instance, a meta-analysis found a cancer detection rate of 36.8% for transperineal biopsies compared to 30% for transrectal biopsies, though this difference was not statistically significant. (53) Another meta-analysis noted similar diagnostic accuracy between the two approaches, with the primary advantage of the transperineal biopsy being a significantly lower risk of fever and rectal bleeding. (45)

These discrepancies often stem from heterogeneity in patients populations, technique used (e.g. systematic vs MRI-fusion) and the experience of the medical teams. Moreover, variations in study design, such as sample sizes, retrospective versus prospective approaches and inclusion criteria, contribute to these inconsistencies. (52) However, one meta-analysis specifically comparing MRI-targeted biopsies performed with the transrectal and transperineal approaches reported a higher sensitivity for detecting csPCa with the transperineal route (86%

vs. 73%), particularly for anterior tumors. (54) This analysis stands out as it minimizes confounding factors by focusing exclusively on the access route.

Nonetheless, further, large-scale prospective studies are still needed to establish a clearer consensus.

1.3.3. BIOPSY STRATEGIES

Systematic ultrasound guided prostate biopsy involves systematic sampling of the prostate, supplemented by additional sampling of suspicious areas, such as a hypoechoic lesion detected on ultrasound or irregularities found during digital rectal examination. (55)

Various sampling schemes have been proposed to improve diagnostic accuracy. The first sector-based scheme to be introduced was the sextant biopsy technique, which is performed by obtaining 6 cores, one sample each from the apex, the base and the mid-prostate on both sides. (39) Over time, extended-core biopsies, which collect 10-14 tissue samples with a more extensive lateral coverage, have demonstrated significantly higher detection rates compared to the original sextant approach. (7,56–58)

A systematic review revealed that 12-core sampling detects 31% more cancers (95% CI:25-37) than the 6-core method. When comparing complications of the two techniques, the same study found that extended-core techniques are not associated with a higher risk of infection, abdominal or rectal pain or voiding difficulties, though bleeding and hematospermia may be more frequent. (59,60)

Schemes involving a higher number of samples, such as 18-core biopsies, have shown cancer detection rates similar to the 12-core biopsy but are associated with an increased incidence of adverse events. (61) Therefore, 12-core biopsies seem to have the optimal balance between detection efficacy and risk of complications. (59) Reflecting this evidence, the EAU guidelines suggest obtaining a minimum of 12 cores. (5)

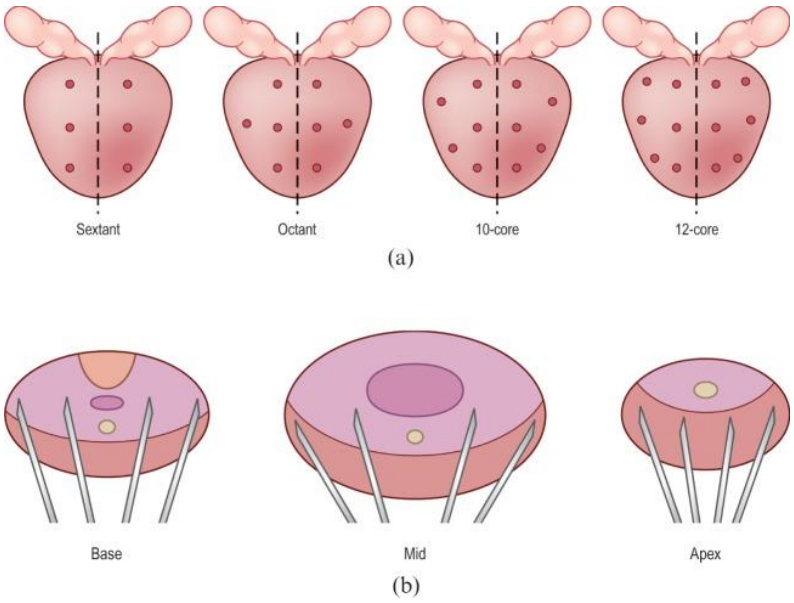

Figure 5 - Schemes for systematic sampling of the prostate.

While extended-core and 12-core biopsies are effective for initial sampling, certain situations, such as repeat biopsies after a prior negative result or active surveillance require more comprehensive techniques. In these cases, saturation biopsy, which involves taking over 20 core samples, is often employed to provide a more thorough evaluation of the prostate, particularly when MRI-targeted biopsy is not feasible. (62)

While systematic biopsy remains the standard diagnostic method, the emergence of pre-biopsy mpMRI for the identification of suspicious lesions has revolutionised diagnostic approaches. This has led to the introduction of targeted biopsy methods, which focus sampling directly on MRI-identified areas of concern. By integrating MRI data with real time ultrasound guidance, targeted biopsy aims to enhance the precision and diagnostic accuracy of PCa detection, minimise unnecessary sampling and reduce the risk of missing clinically significant cancers. The technique is also referred to as “fusion biopsy”, reflecting the merging of MRI and US imaging.
Typically, 3 to 5 cores are taken from each PIRADS lesion to ensure adequate sampling. (63,64)

Two prospective randomized trials, PRECISION and PRECISE, found MRI-targeted biopsy to be either superior or non-inferior, respectively, to systematic biopsy for the detection of csPCa in biopsy-naive men. The PRECISION trial also

noted a reduced diagnosis rate of clinically insignificant cancers with targeted biopsies compared to systematic ones (9% vs 22%). (31,65) Similarly, a large meta-analysis demonstrated that, although the overall tumor detection rates were not significantly different, MRI-guided biopsy identified significantly more ISUP grade group ≥ 2 cancers, with a sensitivity of 91% and an increased the percentage of positive cores. (66) The same results have been corroborated by multiple other studies and systematic reviews. (67–73) Additionally, the FUTURE trial, which included a subgroup analysis of men undergoing both targeted and systematic sampling in a repeat biopsy setting, reported that MRI-guided biopsies detected significantly more clinically significant cancers than systematic biopsies (34% vs. 16%; $p < 0.001$, detection ratio of 2.1). (74) Therefore, this evidence supports the superiority of MRI-targeted biopsy in both biopsy-naive and repeat settings.

Targeted biopsy can be performed using three primary approaches: cognitive fusion, software-assisted fusion and in-bore MRI-guided methods.

Cognitive targeting involves the urologist identifying suspicious lesions on MRI scans prior to the biopsy. During the procedure, the clinician uses real-time TRUS guidance and their mental correlation of MRI findings with the TRUS images to guide the needle to the target area. This method is the simplest, quickest and cost-effective of the three as it does not require additional equipment if not MRI and TRUS. (12,38,75) However, extrapolating MRI findings onto real time TRUS images demands advanced operator expertise in MRI interpretation, TRUS operation and a detailed understanding of the prostate's zonal anatomy to ensure accurate sampling. Consequently, the accuracy of this method is highly operator-dependent and necessitates longer training compared to other techniques. (76,77) Furthermore, errors may arise from incorrect assessment of the lesion site, especially when clinicians rely solely on MRI reports rather than direct image review. Another limitation is the inability to record the exact biopsy site, which prevents confirmation that the targeted area was sampled and complicates follow-up evaluations in the event of negative results (78)

In order to provide a more standardized and precise integration of mpMRI with real time TRUS imaging, software-assisted fusion techniques have been developed. By automating the process of image alignment and target localization, these methods aim to enhance accuracy and reproducibility. (79)

In this technique, once the MRI scans are acquired, they are transferred onto a specialized software, where the radiologist contours both the prostate and the suspicious lesions. The software then creates a three-dimensional model of the prostate and the lesion. Before the biopsy, the TRUS system, connected to the biopsy device, acquires a two-dimensional image of the prostate, which is as well reconstructed into a three-dimensional volume. The operator manually outlines the prostate on the ultrasound image and the system uses this input to semi-automatically generate the three-dimensional ultrasound volume for more precise alignment with the MRI data. However, the superimposed MRI and TRUS images can differ in geometry and orientation due to variations in patient positioning during acquisition and deformations caused by the rectal probe and the different distention of the bladder. (80) Depending on the correction method employed, software systems are categorized as either rigid or non-rigid (elastic). Rigid systems align images without accounting for deformation, while non-rigid systems compensate for variations like tissue deformation. Despite these differences, studies have found no significant difference between rigid and elastic systems in detecting csPCa. (81) During the procedure, the software guides the needle's movement to guarantee an accurate sampling of the targeted lesion and corrects possible errors resulting from patient movement. After sampling, biopsy tracks can be digitally recorded, offering valuable information for future reference. This feature is particularly useful in scenarios such as planning focal therapy, where precise localization of previously targeted areas is critical for treatment efficacy. (38,82) There are several systems currently available on the market, all of which appear to offer comparable accuracy in detecting PCa. (83)

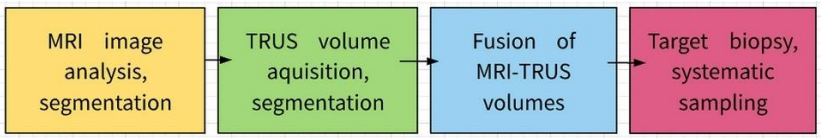

Figure 6 - Steps in software MRI-fusion biopsy.

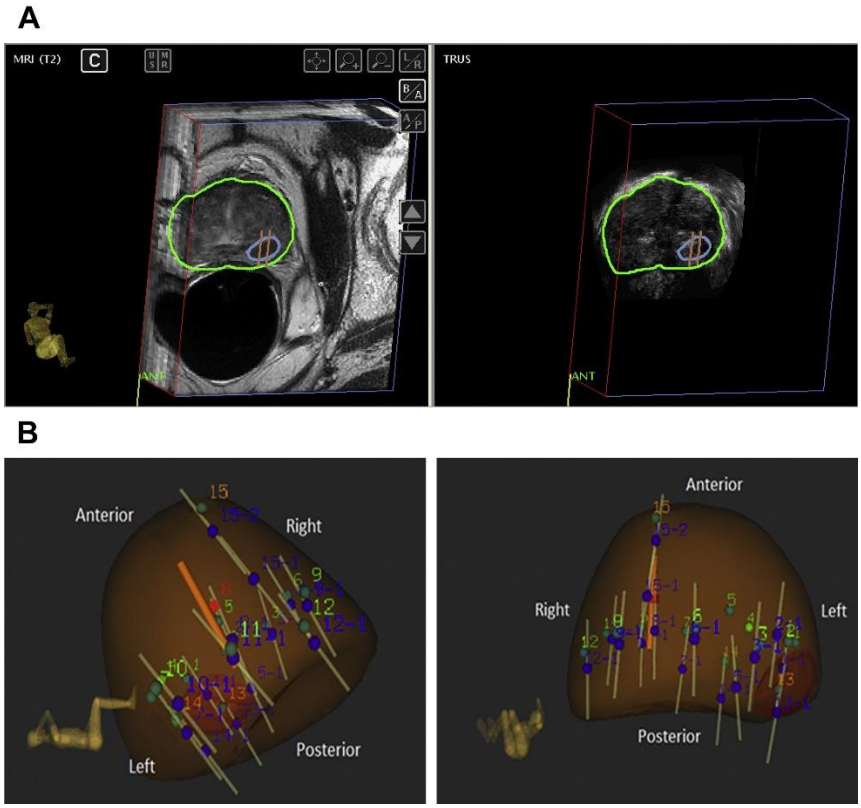

Figure 7 - Software fusion of TRUS and mpMRI images with outlined lesion (A). Three-dimensional model of the prostate showing the location of all biopsy cores (B).

One of the primary benefits of this technique is the standardization of the biopsy process. By relying on software for the fusion of mpMRI and US images, this method reduces the potential for human error and inter-operator variability, which can be present in cognitive fusion. As a result, operator experience becomes less of a limiting factor. (84) Although operator experience can influence diagnostic accuracy, studies have shown that an increase in the experience of the operator improved the PCa detection rate. (85–88)

However, despite these advantages, software-assisted targeted biopsy is not without its drawbacks. Although this technique is simpler than cognitive fusion biopsies and has a lower learning curve, it requires a higher expense for the institution performing the procedure. Given the cost of these technologies and their limited availability, software-assisted targeted biopsy is not yet widely adopted across all urology departments. (84,89) Additionally, a limitation of this approach is that the same software applied across different populations and individuals may struggle to find a common model for the prostate. (84)

A third method, developed to fully take advantage of MRI's superior image resolution, is in-bore biopsy. This technique is performed entirely within the MRI gantry, using real-time MRI guidance to visualize and target suspicious lesions at the same time and directly verify needle placement within them. (12,38) Studies report high detection rates for csPCa (81-93%) with this method, often with fewer cores needed than systematic biopsies. (90) However, this approach is highly demanding in terms of labour, time (requiring up to 2-3 hours of scanning) and financial resources, beside the fact that it reduces scanner availability for routine diagnostics. Consequently, its use is limited to a small number of specialized centers. (38,91)

Each targeted method has unique procedural advantages and limitations. Cognitive fusion is simpler to perform and more cost-effective, requiring only basic imaging tools and the expertise of the operator. On the other hand, software-assisted fusion standardizes the fusion process by automating the alignment of mpMRI and ultrasound images, reducing operator dependency but at the cost of higher expenses and more complex logistics. The in-bore technique, while offering unparalleled precision by performing the biopsy entirely within the MRI scanner, is time-consuming, costly, and limited to highly specialized centers.

When it comes to diagnostic efficacy, however, current evidence has yet to demonstrate clear superiority of one method over the others. Given that cognitive and software-assisted fusion techniques are the most commonly employed than in-bore biopsy, most studies focus on comparing these two approaches.

The only three randomized controlled trials comparing these three techniques found no statistically significant differences in cancer detection rates. The largest, the FUTURE trial, compared all three methods and reported overall PCa detection rates of 44% for cognitive fusion, 49% for software-assisted fusion, and 55% for in-bore biopsy ($p = 0.4$). The rates for csPCa were similarly comparable, at 33%, 34%, and 33%, respectively ($p > 0.9$). (74,92,93)

These findings align with all meta-analyses reviewed, which consistently indicate no significant difference in detection rates between cognitive and software-assisted techniques. (76,89,94,95) For instance, a 2023 meta-analysis by Pirola et al., which analysed eight studies comparing the detection rates of clinically significant and insignificant PCa between software-assisted and cognitive techniques, confirmed

no significant difference (OR 1.01; 95% CI:0.74–1.37; p = 0.95). However, one study included in the analysis showed a statistically significant advantage of the software-assisted method, though this particular study utilized a robot-assisted technique for software-assisted fusion biopsy. (96)

Nonetheless, some other studies reported a trend toward improved rates of csPCa with software-based biopsy compared to cognitive, although not with statistical significance. (67,97)

An even larger and more recent meta-analysis (Falagario et al., 2024) compared cognitive, software-assisted and in-bore biopsy, including twenty studies that directly compared at least two of these techniques to minimize inclusion bias. The study reaffirmed the absence of significant differences in diagnostic accuracy among the methods. (94) Falagario et al. also evaluated complications rates to determine if they might influence the choice of one technique over the others. With the exception of the FUTURE trial, which found a lower complication rate for in-bore biopsies, no significant differences were found overall.

However, limitations exist in these meta-analyses, largely due to the heterogeneity across studies, reflecting the lack of strict guidelines for performing targeted prostate biopsy in patients with MRI lesions. Differences include the definition of csPCa, indications for biopsy (naive, repeat or SA), biopsy approach (Pirola et al. focused on transperineal biopsy, while Falagario included both transrectal and transperineal) and the specific software platforms used. (94)

Therefore, to date, the choice between software-assisted and cognitive fusion techniques is primarily influenced by practical considerations such as resource availability, operator expertise and institutional preferences, rather than by variations in diagnostic performance. (98) Despite software-assisted methods often being marketed as superior, the available data does not allow to draw definitive conclusions and only shows a slight advantage over cognitive fusion. Further research is still needed to reach a consensus on the optimal approach.

1.4. PATHOLOGY

Each core obtained during biopsy sampling is carefully labelled, with details including the number of cores, their length and the specific site from which they

were taken. Subsequently, the samples are processed and analysed by a pathologist, who will assess if cancer is present.

When the term PCa is used without specification, it typically refers to the common or acinar variant of prostatic adenocarcinoma, which is by far the most common type of malignant tumor affecting the prostate. Histologically, the majority of adenocarcinomas are composed of glands arranged in well-defined and easily identifiable patterns, which serve as the basis for tumor grading. (99) Grade is one of the main prognostic factors in PCa and is the most used system worldwide to assess it is the Gleason system. This score stratifies PCa into five grades based on glandular growth patterns, ranging from Grade 1 (well-differentiated glands) to Grade 5 (tumors with no gland formation). The two most prevalent patterns are identified and their grades are summed to calculate the final Gleason Score (GS), which spans from a minimum of 2 to a maximum of 10. (100) The Gleason Score on biopsy material has shown a strong correlation with histological grading from subsequent radical prostatectomy specimens, confirming his critical role as a prognostic factor. (101)

However, the system has shown some limitations as a risk stratification tool, as its 25 possible scores were often grouped based on the assumption of similar prognostic outcomes, with inconsistent criteria across studies. (101,102) For example, Gleason scores 6 and 7 were frequently combined in literature, despite evidence of significant prognostic differences, not only between these two scores but also within Grade 7, where 3+4 is associated with better outcomes than 4+3. (103,104) Similarly, scores 8 to 10 were grouped together, despite scores 9 and 10 indicating markedly poorer prognosis. (105) Moreover, Gleason scores 2 to 4 are rarely encountered in practice, further limiting the system's utility.

Therefore, in 2014, the Gleason system was reorganised by the International Society of Urological Pathology (ISUP) into five Grade Groups, which combine Gleason scores to provide a better correlation with prognosis. (101,102,106) The groups are formed as follows:

ISUP Grade Group	Gleason Score	Gleason pattern
1	≤ 6	≤ 3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9-10	4+5, 5+4, 5+5

Table II – ISUP Grade Group system and Gleason score corresponding values.

This Grade Group system has been widely adopted in clinical practice as it recalibrates the grading scale and matches more precisely PCa behaviour. By offering a standardized risk stratification, it aids clinicians in tailoring treatment strategies and discussing prognosis with patients.

2. AIM OF THE THESIS

The present study aims to compare detection rates for PCa and csPCa of cognitive and software-assisted techniques for US-MRI fusion prostate biopsy. By analysing data collected from patients undergoing transperineal target prostate biopsy at the Urological Unit of the University Hospital of Padova, this thesis seeks to determine which approach offers superior diagnostic accuracy.

The secondary aim is to examine the clinical and radiological predictors of PCa and csPCa in these patients for targeted biopsy, systematic biopsy, and their combination.

3. MATHERIALS AND METHODS

3.1. STUDY DESIGN

This monocentric, retrospective cohort study compared diagnostic outcomes between cognitive and software assisted US-MRI fusion-guided biopsy techniques. The research was conducted at the Urological Unit of the University Hospital of Padova, involving patients who underwent prostate biopsies between January 2023 and June 2024.

3.2. STUDY POPULATION

Eligible participants were selected according to the following inclusion criteria:

- Male patients aged over 18 years referred to prostate biopsy at the Urological Clinic;
- Presence of MRI lesions with a PI-RADS score ≥ 3;
- Biopsy performed using the US-MRI fusion technique.

Patients who underwent only systematic biopsy were excluded.

A total of over 600 patients were reviewed. Approximately 200 were excluded for undergoing only systematic biopsy, while in 20 cases, insufficient data or ambiguity about the biopsy technique led to their exclusion. Ultimately, 445 patients were included in the study.

3.3. TECHNIQUES AND PROCEDURES

All patients underwent multiparametric prostate MRI prior to the biopsy, either at our institution or another center.

Biopsies were performed by different operators working at our Urological Unit using a transperineal approach with either a 12-core or 14-core technique. All cases involved both systematic and targeted biopsies, which were classified as cognitive or software-assisted MRI-guided biopsies. For the software-based biopsies, the Canon Aplio A ultrasound system was used for image fusion.

The histological analysis of biopsy samples was conducted by the pathologists of the Anatomical Pathology Unit at the University Hospital of Padova, with results expressed using the International Society of Urological Pathology (ISUP) Grade Group classification.

3.4. DATA COLLECTION

Data were retrospectively collected from medical reports and managed using the REDCap software platform. The following data were gathered and analysed:

- Patient characteristics: demographic and anthropometric data;
- Clinical context: whether the patient was biopsy-naive, had prior negative biopsy or was in an Active Surveillance program;
- Medical history: family history, pharmacological treatments (e.g., 5-ARIs)
- Laboratory data: initial PSA, f/t PSA ratio;
- Rectal findings: abnormal findings detected during rectal examination and their site;
- Radiological data: prostate volume, number of lesions, PI-RADS scores, size and localization;
- Biopsy information: biopsy type (cognitive or software-assisted), number of cores, patient pain during the procedure, post-biopsy complications;
- Histological outcomes: results from systematic and targeted biopsies.

3.5. OUTCOME DEFINITION

The outcomes selected to evaluate the diagnostic performance of cognitive and software-assisted targeted biopsy were the presence of PCa and csPCa. PCa was defined as the presence of any tumoral tissue classified within an ISUP Grade Group, while csPCa was specifically defined as cancer with an ISUP Grade Group ≥ 2 (Gleason score ≥ 7). Therefore, clinically insignificant prostate cancer (ciPCa) was defined as cancer with an ISUP Grade Group = 1 (Gleason score ≤ 6).

The detection rates of PCa, csPCa, and ciPCa were defined as the proportion of biopsy results meeting each respective definition relative to the total number of patients who underwent targeted biopsy.

3.6. STATISTICAL ANALYSIS

A descriptive analysis was performed to characterise the studied population. Categorical variables were described with percentage (%), while continuous variables have been expressed as median and interquartile range (IQR). Student's t-test was used to compare continuous variables, while the χ^2 test was used for categorical variables.

Two different logistic regression models were developed, one with the presence of PCa as an outcome, the other with the presence of csPCa as an outcome. Both models were applied to the following scenarios: targeted biopsies, systematic biopsies and a combination of targeted and systematic biopsies.

Statistical analyses were conducted using IBM SPSS version 29. A p-value < 0.05 was considered statistically significant.

3.7. ETHICAL CONSIDERATIONS

The study design has been approved by the Ethics Committee of the University Hospital of Padova 59337/AO/24. Due to the retrospective nature of the study, obtaining informed consent from participants was not required.

4. RESULTS

4.1. POPULATION CHARACTERISTICS

A total of 445 men were included in the analysis during the study, with 261 (58.6%) undergoing cognitive targeted biopsy and 184 (41.3%) software-assisted biopsy.

Clinical and demographic characteristics of the study population and of the two groups are shown in Table IIIII. The median age of the overall population was 68 years (IQR 62-73). The two groups were comparable in terms of age (69 vs 68 years; p = 0.7), PSA (5.6 vs 6.3 ng/ml; p = 0.2), prostatic volume (50 vs 49 ml; p = 0.3), PSA density (0.11 vs 0.14 ng/ml/cc^3; p = 0.3) and clinical stage (6.9% vs 6%; p = 0.7), with no statistically significant differences observed in any of these parameters.
In both groups, most patients were naive to prostate biopsy (~70-74%) and about a third of them had a positive rectal examination.

Regarding MRI lesions, the distribution of PI-RADS score was similar between the two cohorts (p = 0.2), with the majority of lesions classified as PI-RADS 4 (~50-58%). There was no significant difference in the number of lesions (p = 0.4) between the cognitive and software groups, with most men in both cohorts presenting only one lesion (~75-81%). Similarly, no differences were observed in lesion dimensions (p = 0.2) or in lesion position (anterior vs posterior, apex vs intermediate vs base, anterior vs peripheral vs transition; p = 0.4-0.5); the majority of lesions were located in the posterior peripheral zone both in the cognitive and the software group.

When it comes to the bioptic procedure, there was a statistically significant difference in the median number of systematic biopsies in the two groups ($p < 0.01$), with the software group having a slightly higher number of cores sampled. There was a significant difference in the number of targeted cores (p = 0.04), although the median number of cores is the same (3). There was no difference, however, in the total number of samples (systematic + target) between the two groups (p = 0.07).

	Whole cohort (n=445)	**Cognitive** (n=261)	**Software** (n=184)	**p**
Age	68 (62-73)	69(63-74)	68 (62-73)	0.7
Indication				
Biopsy naive	322 (72.4)	194 (74.3)	128 (69.6)	
Patients on AS	56 (12.6)	30 (11.4)	26 (14.1)	0.6
Previous Negative biopsy	65 (14.6)	37 (14.2)	28 (15.2)	
Therapy with 5-ARIs	25 (5.6)	12 (4.6)	13 (7.1)	0.3
PSA at initial biopsy (ng/ml)	5.92 (4.4-8.8)	5.6 (4.3-8)	6.3 (4.4-9.5)	0.2
Prostate volume (cc)	50 (38-70)	50 (39-72)	49 (38-66.5)	0.3
PSAD (ng/ml/cc^3)	0.11	0.11 (0.07-16)	0.14 (0.08-0.2)	0.3
Positive rectal examination	147 (33.1)	88 (33.6)	59 (32)	0.7
Clinical stage ≥ T3 at mpMRI	29 (6.5)	18 (6.9)	11 (6)	0.7
Maximum diameter of the lesion (mm)	10 (7-14)	10 (7.5-14)	10 (7-13.5)	0.8
PI-RADS score index lesion				
3	113 (25.4)	58 (22.2)	55 (29.9)	0.2
4	245 (55.1)	152 (58.2)	93 (50.5)	
5	87 (19.6)	51 (19.5)	36 (19.6)	
Number of lesions				
1 lesion	345 (77.5)	196 (75.1)	149 (81)	0.5
2 lesions	86 (19.3)	55 (21.1)	31 (16.8)	
≥ 3 lesions	14 (3.1)	10 (3.8)	4 (2.2)	
MRI index lesion Position:				
Apex	141 (31.7)	88 (33.7)	53 (28.8)	0.4
Intermediate	201 (45.2)	117 (44.8)	84 (45.7)	
Base	78 (17.5)	50 (19.2)	28 (15.2)	
MRI index lesion Position:				
Anterior Zone	146 (32.8)	84 (32.2)	62 (33.7)	0.5
Posterior Zone	299 (67.2)	177 (67.8)	122 (66.3)	
MRI index lesion Position:				
Anterior	158 (35.5)	87 (33.3)	71 (38.6)	0.5
Peripheral	264 (59.3)	160 (61.3)	104 (56.5)	
Transition	23 (5.2)	14 (5.4)	9 (4.9)	

Number of systematic cores	14 (14-14)	14 (12-14)	14 (14-14)	<0.01
Median number of targets cores	3 (3-3)	3 (3-3)	3 (3-3)	0.04
Number of systematic + target cores	17 (17-17)	17 (16-17)	17 (17-20)	0.07

Table III – Patients characteristics for the entire cohort and separately for the cognitive and software groups. Categorical variables are expressed as absolute numbers (%), while continuous variables are presented as medians (IQR).

4.2. BIOPSY RESULTS

Overall, 40.4% of systematic biopsies (n = 180) did not detect cancer, while 22.7% (n = 101) identified clinically insignificant PCa and 36.9% (n = 164) detected csPCa (Table IV).

This distribution was comparable between the two groups (p = 0.2). However, although the difference was not statistically significant, the csPCa detection rate was higher in the software group (39.7% vs 31.6%).

Regarding targeted biopsies, 49.4% (n = 162) were negative, 18.7% (n = 83) detected clinically insignificant PCa and 31.9% (n = 142) detected csPCa. The proportion of negative cores was higher in the cognitive group (53.2% vs 47.3%), although the difference was not statistically significant (p = 0.3). The detection rates for ciPCa were nearly identical in the two groups (18.7% for cognitive vs 18.6% for software). Similarly to systematic biopsies, the csPCa cancer detection rate is higher in the software group (34.1% vs 27.7%), though this difference was not statistically significant.

The combination of the two techniques detected csPCa in 38.6% of cases in the software group and in 44.4% in the cognitive group, without significant differences between the two (p = 0.4).

Results were not always concordant between systematic and targeted biopsies. In 5.6% of patients from the total cohort, targeted cores were negative while the systematic cores were positive for csPCa. This scenario was slightly more frequent in the cognitive group (7.7% vs 4.5%), although the difference was not statistically significant (p = 0.2).

Conversely, the opposite scenario, where targeted biopsies were positive for csPCa while systematic ones were negative, was observed in a smaller proportion of cases (1.6% of the total cohort), with similarly low percentages in both groups (2.6% for cognitive vs 1.0% for software).

A similar trend was observed for PCa, with the first scenario being more frequent than the second.

	Whole cohort	**Cognitive**	**Software**	**p**
Systematic and perilesional				
Negative	180 (40.4)	70 (45.2)	110 (37.9)	0.2
ciPCa	101 (22.7)	36 (23.2)	65 (22.4)	
csPCa	164 (36.9)	49 (31.6)	115 (39.7)	
Target				
Negative	220 (49.4)	83 (53.2)	137 (47.2)	0.3
ciPCa	83 (18.7)	29 (18.7)	54 (18.6)	
csPCa	142 (31.9)	43 (27.7)	99 (34.1)	
Target and Systematic				
Negative	162 (36.4)	90 (34.5)	72 (39.1)	0.4
ciPCa	96 (21.6)	55 (21.1)	41 (22.3)	
csPCa	187 (42)	116 (44.4)	71 (38.6)	
Tbx negative - Systematic csPca	25 (5.6)	12 (7.7)	13 (4.5)	0.2
Tbx csPca – Negative Systematic	7 (1.6)	4 (2.6)	3 (1.0)	0.2
Tbx negative - Systematic Pca	64 (14.1)	23 (14.8)	41 (14.1)	0.8
Tbx Pca - Negative Systematic	16 (3.6)	9 (5.8)	7 (2.4)	0.07

Table IV – Biopsy results of systematic and targeted (TBx) cores.

4.3. PREDICTORS OF PCa AND csPCa

The multivariable analysis identified several predictors of PCa and csPCa in both targeted and systematic biopsies.

For csPCa in targeted biopsies, the statistically significant predictors included age (OR 1.06, p = .001), PSA (OR 1.11, p < .001), prostate volume (OR 1.11, p < .001), anterior vs posterior localisation (OR 10.51, p = .006), PI-RADS score (5 vs 3: OR 12.80, p < .001) and maximum diameter of the lesion (OR 1.09, p = .008).

An OR of 1.69 furtherly indicates no statistically significant difference in csPCa detection between cognitive and software-assisted techniques in MRI-guided prostate biopsy (95% CI: 0.93-3.06, p = .084). However, a trend towards better csPCa detection with the software-assisted technique was observed.

Similar results were found for PCa in targeted biopsies. Additionally, biopsy-naive patients had a significantly lower likelihood of PCa detection (OR 0.46, p = .005).

MULTIVARIABLE	**OR**	**95% CI**	**p**
Software-based biopsy vs Cognitive biopsy	1.48	0.89 – 2.47	.131
Age	1.07	1.04 – 1.11	< .001
PSA	1.05	1.00 – 1.11	.055
Prostate volume	0.98	0.97 – 0.99	< .001
Anterior vs Posterior	8.29	2.29 – 30.10	.001
Peripheral vs Transition-Anterior	0.27	0.09 – 0.84	.023
Positive rectal examination	1.50	0.89 – 2.54	.128
PI-RADS			< .001
3 vs 4	2.15	1.22 – 3.79	.008
3 vs 5	9.88	3.58 – 27.28	< .001
Maximum diameter of the lesion	1.05	0.99 – 1.11	.131
Biopsy naive	0.46	0.27 – 0.79	.005
n of target cores	1.11	0.96 – 1.29	.154

Table V - Multivariable analysis assessing PCa for target lesions.

MULTIVARIABLE	**OR**	**95% CI**	**p**
Software-based biopsy vs Cognitive biopsy	1.69	0.93 – 3.06	.084
Age	1.06	1.02 – 1.10	.001
PSA	1.11	1.05 – 1.17	< .001
Prostate volume	0.97	0.96 – 0.99	< .001
Anterior vs Posterior	10.51	1.95 – 56.63	.006
Peripheral vs Transition-Anterior	0.27	0.06 – 1.25	.093
Positive rectal examination	1.34	0.76 – 2.36	.317
PI-RADS			< .001
3 vs 4	4.93	2.12 – 11.46	< .001
3 vs 5	12.80	4.39 – 37.36	< .001

Maximum diameter of the lesion	1.09	1.02 – 1.17	.008
Number of target cores	1.17	0.99 – 1.38	.059

Table VI – Multivariable analysis assessing csPCa for target lesions.

In systematic and perilesional biopsies, the software-assisted technique demonstrated a statistically significant higher detection rate for both PCa (OR 1.87, p = .020) and csPCa (OR 1.91, p = .025).

Significant predictors for both PCa and csPCa included age, prostate volume, maximum lesion diameter and lesion localisations, not only anterior vs posterior but also peripheral vs transition-anterior. PI-RADS score was a significant predictor for csPCa only (3 vs 4: OR 2.75, p = .004; 3 vs 5: OR 4.62, p = .002).

MULTIVARIABLE	**OR**	**95% CI**	**p**
Software-based biopsy vs Cognitive biopsy	1.87	1.11 – 3.16	.020
Age	1.14	1.09 – 1.18	< .001
PSA	1.03	0.97 – 1.08	.337
Prostate volume	0.97	0.96 – 0.98	< .001
Anterior vs Posterior	7.27	2.03 – 25.98	.002
Peripheral vs Transition-Anterior	0.26	0.09 – 0.79	.017
Positive rectal examination	1.80	1.04 – 3.10	.035
PI-RADS			.178
3 vs 4	1.58	0.89 – 2.80	.115
3 vs 5	2.20	0.83 – 5.82	.112
Maximum diameter of the lesion	1.08	1.01 – 1.15	.021
Biopsy naive	0.59	0.34 – 1.03	.065
Number of systematic cores	1.07	0.94 – 1.22	.282

Table VII - Multivariable analysis assessing PCa for systematic and perilesional biopsies.

MULTIVARIABLE	**OR**	**95% CI**	**p**
Software-based biopsy vs Cognitive biopsy	1.91	1.09 – 3.37	.025
Age	1.09	1.05 – 1.13	< .001
PSA	1.07	1.02 – 1.13	.008

Prostate volume	0.97	0.96 – 0.98	< .001
Anterior vs Posterior	11.46	2.48 – 53.06	.002
Peripheral vs Transition-Anterior	0.25	0.06 – 0.99	.048
Positive rectal examination	1.62	0.95 – 2.75	.074
PI-RADS			.003
3 vs 4	2.75	1.38 – 5.49	.004
3 vs 5	4.62	1.78 – 12.03	.002
Maximum diameter of the lesion	1.08	1.02 – 1.15	.011
Biopsy naive	0.32	0.17 – 0.60	< .001
Number of systematic cores	1.14	0.98 – 1.32	.095

Table VIII - Multivariable analysis assessing csPCa for systematic and perilesional biopsies.

In the multivariable analysis of the combination of systematic and targeted biopsies, the software-based technique showed a tendency toward superior detection for both PCa (OR 1.59, p = .091) and csPCa (OR 1.51, p = .151), although neither result reached statistical significance.

Significant cancer predictors included age, prostate volume, lesion localisation, PI-RADS score and the lesion size, all of which were statistically significant for both PCa and csPCa.

MULTIVARIABLE	**OR**	**95% CI**	**p**
Software-based biopsy vs Cognitive biopsy	1.59	0.93 – 2.74	.091
Age	1.14	1.09 – 1.18	< .001
PSA	1.05	1.00 – 1.11	.064
Prostate volume	0.97	0.96 – 0.98	< .001
Anterior vs Posterior	8.84	2.42 – 32.36	< .001
Peripheral vs Transition-Anterior	0.22	0.07 – 0.67	.008
Positive rectal examination	1.72	0.97 – 3.05	.064
PI-RADS			.008
3 vs 4	1.89	1.07 – 3.35	.029
3 vs 5	5.35	1.72 – 16.63	.004
Maximum diameter of the lesion	1.07	1.00 – 1.15	.043

Biopsy naive	0.65	0.37 – 1.16	.145
Total number of cores	1.05	0.95 – 1.15	.369

Table IX - Multivariable analysis assessing PCa for combination of systematic and perilesional plus targeted biopsies.

MULTIVARIABLE	**OR**	**95% CI**	**p**
Software-based biopsy vs Cognitive biopsy	1.51	0.86 – 2.66	.151
Age	1.11	1.07 – 1.15	< .001
PSA	1.09	1.04 – 1.15	< .001
Prostate volume	0.97	0.96 – 0.98	< .001
Anterior vs Posterior	15.94	3.41 – 74.51	< .001
Peripheral vs Transition-Anterior	0.19	0.05 – 0.77	.020
Positive rectal examination	1.56	0.89 – 2.71	.118
PI-RADS			< .001
3 vs 4	3.32	1.69 – 6.54	< .001
3 vs 5	8.56	3.09 – 23.69	< .001
Maximum diameter of the lesion	1.07	1.00 – 1.14	.037
Biopsy naive	0.21	0.11 – 0.40	< .001
Total number of cores	1.14	1.03 – 1.28	.016

Table X - Multivariable analysis assessing csPCa for combination of systematic and perilesional plus targeted biopsies.

In conclusion, while the software-based technique showed a trend toward a higher detection rate of PCa and csPCa, this difference was statistically significant for systematic biopsies. Among cancer predictors, some demonstrated stronger associations than others. For instance, anterior localisation consistently correlated with a significantly increased likelihood of detecting both PCa and csPCa in all analyses. Similarly, PI-RADS score emerged as a robust predictor in nearly every multivariable model.

5. DISCUSSION

This study demonstrated comparable detection rates for PCa and csPCa between cognitive and software-assisted fusion techniques. However, trends favoring the software-based approach were observed in some analyses. Additionally, several factors were identified as significant predictors with varying strength of PCa and csPCa.

5.1. PCa AND csPCa DETECTION RATE

Although not statistically significant, the software-assisted approach demonstrated higher detection rates in csPCa in both systematic (31.6% vs 39.7%, p = 0.2) and target biopsies (27.7% vs 34.1%, p = 0.3). These findings align with existing literature, where various studies and systematic reviews either report no significant differences in detection rates between targeted biopsy techniques or suggest a trend favoring a greater accuracy of software fusion over cognitive approaches. (76,95,97)

While both of the most recent meta-analyses (Pirola et al. and Falagario et al.) reported no statistically significant differences, Pirola et al. focused exclusively on transperineal biopsies, mirroring the methodology used in this study. (89,94) This specific focus avoids the variability introduced by transrectal biopsies, which were included in Falagario's broader analysis. This alignment strengthens the comparability of the results found in the present study with those of Pirola, further reinforcing the absence of significant differences between the two techniques in the context of transperineal biopsies.

Although consistent with previous studies, the lack of significant differences between the cognitive and software-assisted techniques could be influenced by several factors. Operator experience is one such factor frequently highlighted in the literature. (77,89) In this study both biopsy methods were performed by operators of varying expertise, from more seasoned clinicians to residents in training. Software platforms may reduce inter-operator variability due to their less steep learning curve, potentially impacting the cognitive group more significantly, where clinician skill is critical for both biopsy execution and MRI interpretation. Future

studies stratifying outcomes by operator experience would provide valuable insight on this topic.

Moreover, the fact that MRI was performed in different centers without a standardisation of protocols, may have introduced inconsistencies in imaging interpretation and classification of PI-RADS lesions, potentially affecting the study's outcomes.

The consistency of this study's findings with previous studies suggests that both cognitive and software-assisted techniques can be effectively utilized in clinical practice. Given the lack of significant differences between the two, both approaches may be considered reliable options for MRI-targeted prostate biopsies.

However, the slight trend favoring software-assisted methods suggests that, where available, these technologies may help standardize procedures, particularly in settings where operator variability may affect outcomes.

Furthermore, the multivariable analysis revealed a statistically significant advantage for software-assisted techniques when considering systematic cores alone. This finding may indicate that the use of a software platform could enhance not only lesion targeting, but also the systematic sampling of the prostate. One possible explanation is that the systematic biopsies performed in these patients included cores sampled from areas adjacent to MRI-visible lesions. These perilesional regions are particularly likely to yield positive results due to the tendency of MRI to underestimate tumor volume. (107) Although perilesional sampling enhances detection rates by focusing on areas at high risk for csPCa, its application is not standardised, therefore different centres may incorporate perilesional sampling into systematic biopsy protocols in various way. (108,109) This variability highlights the need for further research to establish clear guidelines and evaluate the true impact of perilesional sampling on biopsy outcomes.

Rather than focusing solely on identifying superiority between the two techniques, future efforts could also prioritize understanding the contexts in which each method may be more appropriate. Factors such as operator experience, resource availability, and patient-specific characteristics might play a decisive role in determining the optimal approach for different clinical scenarios.

Another key finding of this study is the importance of performing systematic biopsies alongside targeted ones, even when suspicious lesions are identified on MRI. The combination of systematic and targeted biopsies detected a higher rate of

csPCa compared to either approach alone (systematic + target: 42%, systematic: 36.9%, target: 31.9%).

This indicates that a targeted-only approach would have missed 5.6% of csPCa diagnoses. The trend was observed consistently across both cognitive and software-assisted techniques, although the missed diagnosis rate was higher for cognitive biopsy (7.7% vs. 4.5%, p = 0.2).

These findings contribute to the ongoing debate about whether targeted biopsy alone is sufficient for detecting csPCa when suspicious lesions are present on MRI. (110,111) While some studies suggest that fusion biopsy alone is non-inferior to combining it with systematic biopsy (112), others have reported that targeted samples alone miss up to 10% of csPCa detected on systematic biopsy. (113) This discrepancy is attributed to discordance in tumor locations, as systematic and targeted biopsies often sample different areas of the prostate. (114)

The discussion also raises concerns about the potential overdiagnosis and overtreatment of clinically insignificant PCa, which could expose patients to unnecessary interventions without improving outcomes. According to the present's study data, while the combined approach detected a slightly higher rate of ciPCa compared to targeted biopsy alone (21.6% vs. 18.7%), it did not surpass systematic biopsy alone (22.7%).

Nonetheless, when focusing on csPCa, the combination of systematic and targeted biopsies demonstrated superior detection rates compared to either approach alone, underscoring the complementary nature of these methods. Therefore, currently, the available evidence does not sufficiently support the safety of using targeted biopsy techniques alone, leading guidelines to recommend the execution of both systematic and targeted biopsies.

5.2. PREDICTORS OF PCa AND csPCa

In this study, a multivariable analysis was performed to identify predictors of PCa and csPCa in different biopsy contexts. Several robust predictors of csPCa were identified across different biopsy techniques, including anterior localisation, PI-RADS score, age, prostate volume, and lesion diameter.

For instance, anterior localisation consistently emerged as a strong predictor of both PCa and csPCa in all analyses, as it was significantly associated with an increased likelihood of detecting both types of cancer. This finding aligns with the clinical observation that anterior lesions, which account for approximately 21% of all PCa, are often under-sampled in standard biopsy techniques. This is due to the difficulty of TRUS imaging in visualizing this part of the prostate, highlighting the importance of targeted strategies in these cases. (115)
Moreover, the use of a transperineal approach in this study may have offered an advantage, as transrectal approaches are often limited in reaching the most anterior part of the gland. (86)

Similar, though weaker, results were observed for the transition-anterior zone. In fact, the transitional zone is particularly prone to being missed in systematic biopsy as well, further supporting the need for targeted biopsy strategies in these areas. (115)

PI-RADS scores of 4 or 5 were also strongly correlated with csPCa especially when considering targeted biopsy alone or combined with the systematic one. The strong predictive value of PI-RADS in detecting for both PCa and csPCa detection reinforces the critical role of mpMRI in guiding targeted biopsies and underlines the importance of targeted biopsy itself. These findings emphasize the need for personalized approaches that consider both lesion localisation and imaging characteristics. While the predictive value of PI-RADS has been extensively studied in the context of targeted biopsies, further exploration of other potential predictive factors could help refine risk stratification models and optimize biopsy planning strategies. (5,29)

Other factors, such as biopsy indication, emerged as weaker cancer predictors. The reduced likelihood of PCa detection in biopsy-naive patients highlights the need for accurate patient stratification based on clinical and imaging characteristics. For these patients, combining parameters such as PSA levels, age and PI-RADS score from MRI can help guide the decision on whether a targeted biopsy is necessary. A careful risk assessment is especially important in biopsy-naive men in order to avoid overdiagnosis and overtreatment of low-risk PCas, as unnecessary biopsies could lead to the detection of indolent tumors that would not have impacted the patient’s health.

5.3. STUDY LIMITATIONS

The lack of statistically significant differences between techniques may reflect some limitations in the study design, such as the sample size and the retrospective, monocentric nature of the study. Furthermore, although there were no specific criteria for patient allocation to cognitive or software-assisted biopsy, the absence of randomization in the assignment to groups may have introduced an unknown bias. Larger, prospective, randomized studies are needed to clarify the observed trends and validate these findings in broader patient populations.

Additionally, the heterogeneity in biopsy practices across different centers (e.g. transrectal vs transperineal approaches, varying software platforms) limits the generalizability of our results to other settings.

Finally, as previously mentioned, the operators who performed the biopsies had varying levels of experience with the techniques. Moreover, the lack of control over radiologists that reported MRI results may have introduced bias due to inter-operator variability.

6. CONCLUSIONS

This study compared cognitive and software-assisted targeted biopsies for detecting PCa and csPCa. The results showed no significant differences between the two techniques, suggesting similar diagnostic accuracy. However, trends favoring the software-assisted technique highlight the potential for more consistent results, especially in less experienced hands. Where available, the use of software-assisted technique may be advantageous although the current evidence does not justify their adoption in all settings at the expense of higher costs. Future studies should aim to further clarify the specific clinical contexts where software-assisted biopsies can provide the greatest benefit.

The combination of systematic and targeted biopsies demonstrated superior detection rates for csPCa compared to either method alone, emphasizing the importance of using both approaches. While the combination strategy also resulted in a higher detection rate of clinically insignificant PCa, it did not surpass systematic biopsy in this regard.

The analysis of predictive factors revealed that clinical and imaging characteristics, such as anterior localisation and PI-RADS score, were the most consistent and robust predictors of csPCa. These findings emphasize the need for individualized patient stratification based on both clinical and imaging parameters when deciding on the most appropriate biopsy approach, particularly in biopsy-naive patients.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.

2. GLOBOCAN [Internet]. Available from: https://gco.iarc.fr/today/hom

3. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020 Jan;77(1):38–52.

4. Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, Kibel A, et al. Epidemiology and Prevention of Prostate Cancer. Eur Urol Oncol. 2021 Dec;4(6):877–92.

5. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2024 Aug;86(2):148–63.

6. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. Cold Spring Harb Perspect Med. 2018 Dec;8(12):a030361.

7. Ukimura O, Coleman JA, De La Taille A, Emberton M, Epstein JI, Freedland SJ, et al. Contemporary Role of Systematic Prostate Biopsies: Indications, Techniques, and Implications for Patient Care. Eur Urol. 2013 Feb;63(2):214–30.

8. Ficarra V, Bartoletti R, Borghesi M, DE Nunzio C, Falagario UG, Gandaglia G, et al. Prostate cancer diagnostic pathway in men with lower urinary tract symptoms or performing opportunistic screening: The Italian Society of Urology (SIU) position paper. Minerva Urol Nephrol. 2024 Oct;76(5):530–5.

9. Matlaga BR, Eskew LA, McCULLOUGH DL. Prostate Biopsy: Indications and Technique. J Urol. 2003 Jan;169(1):12–9.

10. Daniyal M, Siddiqui ZA, Akram M, Asif HM, Sultana S, Khan A. Epidemiology, Etiology, Diagnosis and Treatment of Prostate Cancer. Asian Pac J Cancer Prev. 2014 Dec 18;15(22):9575–8.

11. Gosselaar C, Kranse R, Roobol MJ, Roemeling S, Schröder FH. The interobserver variability of digital rectal examination in a large randomized trial for the screening of prostate cancer. The Prostate. 2008 Jun 15;68(9):985–93.

12. Whiting D, Bott SR. Current Diagnostics for Prostate Cancer. In: Urology Department, Frimley Park Hospital, Portsmouth Rd, Frimley, Camberley GU16 7UJ, UK, Bott SR, Lim Ng K, editors. Prostate Cancer [Internet]. Exon Publications; 2021 [cited 2024 Nov 5]. p. 43–58. Available from: https://exonpublications.com/index.php/exon/article/view/343

13. Andriole GL, Bostwick D, Brawley OW, Gomella L, Marberger M, Montorsi F, et al. The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: results from the REDUCE study. J Urol. 2011 Jan;185(1):126–31.

14. Merriel SWD, Pocock L, Gilbert E, Creavin S, Walter FM, Spencer A, et al. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. BMC Med. 2022 Feb 7;20(1):54.

15. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004 May 27;350(22):2239–46.

16. Eastham JA, Riedel E, Scardino PT, Shike M, Fleisher M, Schatzkin A, et al. Variation of Serum Prostate-Specific Antigen Levels: An Evaluation of Year-to-Year Fluctuations. JAMA. 2003 May 28;289(20):2695.

17. Nordström T, Adolfsson J, Grönberg H, Eklund M. Repeat Prostate-Specific Antigen Tests Before Prostate Biopsy Decisions. J Natl Cancer Inst. 2016 Dec;108(12):djw165.

18. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA. 1993 Aug 18;270(7):860–4.

19. Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology. 1993 Oct 1;42(4):365–74.

20. Jue JS, Barboza MP, Prakash NS, Venkatramani V, Sinha VR, Pavan N, et al. Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy. Urology. 2017 Jul;105:123–8.

21. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998 May 20;279(19):1542–7.

22. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012 Apr;22(4):746–57.

23. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. PIRADS - Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol. 2019 Sep;76(3):340–51.

24. Horn GL, Hahn PF, Tabatabaei S, Harisinghani M. A practical primer on PI-RADS version 2: a pictorial essay. Abdom Radiol N Y. 2016 May;41(5):899–906.

25. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol. 2016 Jan;69(1):16–40.

26. Drost FJH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019 Apr 25;4(4):CD012663.

27. Bratan F, Niaf E, Melodelima C, Chesnais AL, Souchon R, Mège-Lechevallier F, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol. 2013 Jul 1;23(7):2019–29.

28. Farrell C, Noyes SL, Joslin J, Varma M, Moriarity A, Buchach C, et al. Prostate Multiparametric Magnetic Resonance Imaging Program Implementation and Impact: Initial Clinical Experience in a Community Based Health System. Urol Pract. 2018 May;5(3):165–71.

29. Wei JT, Barocas D, Carlsson S, Coakley F, Eggener S, Etzioni R, et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part II: Considerations for a Prostate Biopsy. J Urol. 2023 Jul;210(1):54–63.

30. NICE Guidance - Prostate cancer: diagnosis and management: © NICE (2019) Prostate cancer: diagnosis and management. BJU Int. 2019 Jul;124(1):9–26.

31. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. PRECISION - MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018 May 10;378(19):1767–77.

32. Moldovan PC, Van den Broeck T, Sylvester R, Marconi L, Bellmunt J, van den Bergh RCN, et al. What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol. 2017 Aug;72(2):250–66.

33. Sathianathen NJ, Omer A, Harriss E, Davies L, Kasivisvanathan V, Punwani S, et al. Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in the Detection of Clinically Significant Prostate Cancer in the Prostate Imaging Reporting and Data System Era: A Systematic Review and Meta-analysis. Eur Urol. 2020 Sep;78(3):402–14.

34. Orecchia L, Nardi A, Fletcher P, Ippoliti S, Grounds J, Dokubo I, et al. Natural History of Patients with Prostate MRI Likert 1-3 and Development of RosCaP: a Multivariate Risk Score for Clinically Significant Cancer. Clin Genitourin Cancer. 2023 Feb;21(1):162–70.

35. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. PROMIS - Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet Lond Engl. 2017 Feb 25;389(10071):815–22.

36. Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol. 2014 Apr;65(4):809–15.

37. Akduman B, Crawford ED. Transrectal ultrasound-guided prostate biopsy: current approach.

38. Das CJ, Razik A, Sharma S, Verma S. Prostate biopsy: when and how to perform. Clin Radiol. 2019 Nov;74(11):853–64.

39. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989 Jul;142(1):71–4; discussion 74-75.

40. Onur R, Littrup PJ, Pontes JE, Bianco FJ. Contemporary impact of transrectal ultrasound lesions for prostate cancer detection. J Urol. 2004 Aug;172(2):512–4.

41. Shinohara K, Wheeler TM, Scardino PT. The appearance of prostate cancer on transrectal ultrasonography: correlation of imaging and pathological examinations. J Urol. 1989 Jul;142(1):76–82.

42. Correas JM, Halpern EJ, Barr RG, Ghai S, Walz J, Bodard S, et al. Advanced ultrasound in the diagnosis of prostate cancer. World J Urol. 2021 Mar;39(3):661–76.

43. Mannaerts CK, Engelbrecht MRW, Postema AW, van Kollenburg RAA, Hoeks CMA, Savci-Heijink CD, et al. Detection of clinically significant prostate cancer in biopsy-naïve men: direct comparison of systematic biopsy, multiparametric MRI- and contrast-ultrasound-dispersion imaging-targeted biopsy. BJU Int. 2020 Oct;126(4):481–93.

44. Sazuka T, Imamoto T, Namekawa T, Utsumi T, Yanagisawa M, Kawamura K, et al. Analysis of preoperative detection for apex prostate cancer by transrectal biopsy. Prostate Cancer. 2013;2013:705865.

45. Xiang J, Yan H, Li J, Wang X, Chen H, Zheng X. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol. 2019 Feb 13;17(1):31.

46. Miller J, Perumalla C, Heap G. Complications of transrectal versus transperineal prostate biopsy. ANZ J Surg. 2005;75(1–2):48–50.

47. Grummet JP, Weerakoon M, Huang S, Lawrentschuk N, Frydenberg M, Moon DA, et al. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? BJU Int. 2014 Sep 1;114(3):384–8.

48. Roberts MJ, Bennett HY, Harris PN, Holmes M, Grummet J, Naber K, et al. Prostate Biopsy-related Infection: A Systematic Review of Risk Factors, Prevention Strategies, and Management Approaches. Urology. 2017 Jun;104:11–21.

49. Chang DTS, Challacombe B, Lawrentschuk N. Transperineal biopsy of the prostate--is this the future? Nat Rev Urol. 2013 Dec;10(12):690–702.

50. Bennett HY, Roberts MJ, Doi SAR, Gardiner RA. The global burden of major infectious complications following prostate biopsy. Epidemiol Infect. 2016;144(8):1784–91.

51. Kaplan-Marans E, Zhang TR, Hu JC. Differing Recommendations on Prostate Biopsy Approach to Minimize Infections: An Examination of the European Association of Urology and American Urological Association Guidelines. Eur Urol. 2023 Nov;84(5):445–6.

52. Oderda M, Diamand R, Abou Zahr R, Anract J, Assenmacher G, Barry Delongchamps N, et al. Transrectal versus transperineal prostate fusion biopsy: a pair-matched analysis to evaluate accuracy and complications. World J Urol. 2024 Sep 25;42(1):535.

53. Nelson AW, Harvey RC, Parker RA, Kastner C, Doble A, Gnanapragasam VJ. Repeat prostate biopsy strategies after initial negative biopsy: meta-regression

comparing cancer detection of transperineal, transrectal saturation and MRI guided biopsy. PloS One. 2013;8(2):e57480.

54. Tu X, Liu Z, Chang T, Qiu S, Xu H, Bao Y, et al. Transperineal Magnetic Resonance Imaging-Targeted Biopsy May Perform Better Than Transrectal Route in the Detection of Clinically Significant Prostate Cancer: Systematic Review and Meta-analysis. Clin Genitourin Cancer. 2019 Oct;17(5):e860–70.

55. Gosselaar C, Roobol MJ, Roemeling S, Wolters T, van Leenders GJLH, Schröder FH. The value of an additional hypoechoic lesion-directed biopsy core for detecting prostate cancer. BJU Int. 2008 Mar;101(6):685–90.

56. Uno H, Nakano M, Ehara H, Deguchi T. Indications for extended 14-core transrectal ultrasound-guided prostate biopsy. Urology. 2008 Jan;71(1):23–7.

57. Eskicorapci SY, Baydar DE, Akbal C, Sofikerim M, Günay M, Ekici S, et al. An extended 10-core transrectal ultrasonography guided prostate biopsy protocol improves the detection of prostate cancer. Eur Urol. 2004 Apr;45(4):444–8; discussion 448-449.

58. Babaian RJ, Toi A, Kamoi K, Troncoso P, Sweet J, Evans R, et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. J Urol. 2000 Jan;163(1):152–7.

59. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol. 2006 May;175(5):1605–12.

60. Ghani KR, Dundas D, Patel U. Bleeding after transrectal ultrasonography-guided prostate biopsy: a study of 7-day morbidity after a six-, eight- and 12-core biopsy protocol. BJU Int. 2004 Nov;94(7):1014–20.

61. Scattoni V, Roscigno M, Raber M, Dehò F, Maga T, Zanoni M, et al. Initial extended transrectal prostate biopsy--are more prostate cancers detected with 18 cores than with 12 cores? J Urol. 2008 Apr;179(4):1327–31; discussion 1331.

62. Scattoni V, Zlotta A, Montironi R, Schulman C, Rigatti P, Montorsi F. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. Eur Urol. 2007 Nov;52(5):1309–22.

63. Deniffel D, Perlis N, Ghai S, Girgis S, Healy GM, Fleshner N, et al. Prostate biopsy in the era of MRI-targeting: towards a judicious use of additional systematic biopsy. Eur Radiol. 2022 Nov;32(11):7544–54.

64. Barrett T, de Rooij M, Giganti F, Allen C, Barentsz JO, Padhani AR. Quality checkpoints in the MRI-directed prostate cancer diagnostic pathway. Nat Rev Urol. 2023 Jan;20(1):9–22.

65. Klotz L, Chin J, Black PC, Finelli A, Anidjar M, Machado A, et al. Magnetic Resonance Imaging-Targeted Versus Systematic Prostate Biopsies: 2-year Follow-up of a Prospective Randomized Trial (PRECISE). Eur Urol Oncol. 2024 Jun;7(3):456–61.

66. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MGM. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal

ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol. 2015 Sep;68(3):438–50.

67. Kam J, Yuminaga Y, Kim R, Aluwihare K, Macneil F, Ouyang R, et al. Does magnetic resonance imaging–guided biopsy improve prostate cancer detection? A comparison of systematic, cognitive fusion and ultrasound fusion prostate biopsy. Prostate Int. 2018 Sep;6(3):88–93.

68. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. J Urol. 2013 Mar;189(3):860–6.

69. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. Eur Urol. 2019 Apr;75(4):570–8.

70. Goldberg H, Ahmad AE, Chandrasekar T, Klotz L, Emberton M, Haider MA, et al. Comparison of Magnetic Resonance Imaging and Transrectal Ultrasound Informed Prostate Biopsy for Prostate Cancer Diagnosis in Biopsy Naïve Men: A Systematic Review and Meta-Analysis. J Urol. 2020 Jun;203(6):1085–93.

71. Yakar D, Hambrock T, Hoeks C, Barentsz JO, Fütterer JJ. Magnetic resonance-guided biopsy of the prostate: feasibility, technique, and clinical applications. Top Magn Reson Imaging TMRI. 2008 Dec;19(6):291–5.

72. Gayet M, Van Der Aa A, Beerlage HP, Schrier BPh, Mulders PFA, Wijkstra H. The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review. BJU Int. 2016 Mar;117(3):392–400.

73. Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol. 2013 Jan;63(1):125–40.

74. Wegelin O, Exterkate L, van der Leest M, Kummer JA, Vreuls W, de Bruin PC, et al. The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. Eur Urol. 2019 Apr;75(4):582–90.

75. Rebez G, Barbiero M, Simonato FA, Claps F, Siracusano S, Giaimo R, et al. Targeted Prostate Biopsy: How, When, and Why? A Systematic Review. Diagn Basel Switz. 2024 Aug 26;14(17):1864.

76. Wegelin O, van Melick HHE, Hooft L, Bosch JLHR, Reitsma HB, Barentsz JO, et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? Eur Urol. 2017 Apr;71(4):517–31.

77. Stabile A, Dell'Oglio P, Gandaglia G, Fossati N, Brembilla G, Cristel G, et al. Not All Multiparametric Magnetic Resonance Imaging–targeted Biopsies Are

Equal: The Impact of the Type of Approach and Operator Expertise on the Detection of Clinically Significant Prostate Cancer. Eur Urol Oncol. 2018 Jun;1(2):120–8.

78. Puech P, Rouvière O, Renard-Penna R, Villers A, Devos P, Colombel M, et al. Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy--prospective multicenter study. Radiology. 2013 Aug;268(2):461–9.

79. Pinto PA, Chung PH, Rastinehad AR, Baccala AA, Kruecker J, Benjamin CJ, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol. 2011 Oct;186(4):1281–5.

80. Ukimura O, Hirahara N, Fujihara A, Yamada T, Iwata T, Kamoi K, et al. Technique for a hybrid system of real-time transrectal ultrasound with preoperative magnetic resonance imaging in the guidance of targeted prostate biopsy. Int J Urol. 2010 Oct;17(10):890–3.

81. Venderink W, de Rooij M, Sedelaar JPM, Huisman HJ, Fütterer JJ. Elastic Versus Rigid Image Registration in Magnetic Resonance Imaging-transrectal Ultrasound Fusion Prostate Biopsy: A Systematic Review and Meta-analysis. Eur Urol Focus. 2018 Mar;4(2):219–27.

82. Verma S, Bhavsar AS, Donovan J. MR Imaging–Guided Prostate Biopsy Techniques. Magn Reson Imaging Clin N Am. 2014 May;22(2):135–44.

83. Galante Romo MI, Ciappara Paniagua M, Moreno Sierra J. [Fusion biopsy. Analysis of fusion software platforms.]. Arch Esp Urol. 2019 Oct;72(8):794–803.

84. Liang L, Cheng Y, Qi F, Zhang L, Cao D, Cheng G, et al. A Comparative Study of Prostate Cancer Detection Rate Between Transperineal COG-TB and Transperineal FUS-TB in Patients with PSA ≤20 ng/mL. J Endourol. 2020 Oct 1;34(10):1008–14.

85. Bjurlin MA, Rosenkrantz AB, Taneja SS. MRI-fusion biopsy: the contemporary experience. Transl Androl Urol. 2017 Jun;6(3):483–9.

86. Das CJ, Razik A, Sharma S. Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsy of the Prostate-An Update. Semin Roentgenol. 2018 Jul;53(3):219–26.

87. Gaziev G, Wadhwa K, Barrett T, Koo BC, Gallagher FA, Serrao E, et al. Defining the learning curve for multiparametric magnetic resonance imaging (MRI) of the prostate using MRI-transrectal ultrasonography (TRUS) fusion-guided transperineal prostate biopsies as a validation tool. BJU Int. 2016;117(1):80–6.

88. Latchamsetty KC, Borden LS, Porter CR, Lacrampe M, Vaughan M, Lin E, et al. Experience improves staging accuracy of endorectal magnetic resonance imaging in prostate cancer: what is the learning curve? Can J Urol. 2007 Feb;14(1):3429–34.

89. Pirola GM, Castellani D, Orecchia L, Giulioni C, Gubbiotti M, Rubilotta E, et al. Transperineal US-MRI Fusion-Guided Biopsy for the Detection of Clinical Significant Prostate Cancer: A Systematic Review and Meta-Analysis Comparing Cognitive and Software-Assisted Technique. Cancers. 2023 Jun 30;15(13):3443.

90. Overduin CG, Fütterer JJ, Barentsz JO. MRI-Guided Biopsy for Prostate Cancer Detection: A Systematic Review of Current Clinical Results. Curr Urol Rep. 2013 Jun 1;14(3):209–13.

91. Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, Scheenen T, Fütterer J, Bouwense S, et al. Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. Eur Urol. 2012 Jan;61(1):177–84.

92. Arsov C, Rabenalt R, Blondin D, Quentin M, Hiester A, Godehardt E, et al. Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. Eur Urol. 2015 Oct;68(4):713–20.

93. Hamid S, Donaldson IA, Hu Y, Rodell R, Villarini B, Bonmati E, et al. The SmartTarget Biopsy Trial: A Prospective, Within-person Randomised, Blinded Trial Comparing the Accuracy of Visual-registration and Magnetic Resonance Imaging/Ultrasound Image-fusion Targeted Biopsies for Prostate Cancer Risk Stratification. Eur Urol. 2019 May;75(5):733–40.

94. Falagario UG, Pellegrino F, Fanelli A, Guzzi F, Bartoletti R, Cash H, et al. Prostate cancer detection and complications of MRI-targeted prostate biopsy using cognitive registration, software-assisted image fusion or in-bore guidance: a systematic review and meta-analysis of comparative studies. Prostate Cancer Prostatic Dis. 2024 Apr 5;

95. Bass EJ, Pantovic A, Connor MJ, Loeb S, Rastinehad AR, Winkler M, et al. Diagnostic accuracy of magnetic resonance imaging targeted biopsy techniques compared to transrectal ultrasound guided biopsy of the prostate: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2022 Feb;25(2):174–9.

96. Patel MI, Muter S, Vladica P, Gillatt D. Robotic-assisted magnetic resonance imaging ultrasound fusion results in higher significant cancer detection compared to cognitive prostate targeting in biopsy naive men. Transl Androl Urol. 2020 Apr;9(2):601–8.

97. Watts KL, Frechette L, Muller B, Ilinksy D, Kovac E, Sankin A, et al. Systematic review and meta-analysis comparing cognitive vs. image-guided fusion prostate biopsy for the detection of prostate cancer. Urol Oncol. 2020 Sep;38(9):734.e19-734.e25.

98. Verma S, Choyke PL, Eberhardt SC, Oto A, Tempany CM, Turkbey B, et al. The Current State of MR Imaging–targeted Biopsy Techniques for Detection of Prostate Cancer. Radiology. 2017 Oct;285(2):343–56.

99. Kumar V, Abbas AK, Aster JC, Turner JR. Robbins & Cotran Pathologic Basis of Disease Tenth Edition [Internet]. 2021 [cited 2024 Nov 21]. Available from: https://www.mendeley.com/catalogue/30d2a4ef-c846-3ac0-8e84-fe71965cd9a8/

100. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974 Jan;111(1):58–64.

101. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol. 2016 Mar;69(3):428–35.

102. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016 Feb;40(2):244–52.

103. Stark JR, Perner S, Stampfer MJ, Sinnott JA, Finn S, Eisenstein AS, et al. Gleason Score and Lethal Prostate Cancer: Does 3 + 4 = 4 + 3? J Clin Oncol. 2009 Jul 20;27(21):3459–64.

104. Chan TY, Partin AW, Walsh PC, Epstein JI. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology. 2000 Nov;56(5):823–7.

105. Tsao C kai, Gray KP, Nakabayashi M, Evan C, Kantoff PW, Huang J, et al. Patients with Biopsy Gleason 9 and 10 Prostate Cancer Have Significantly Worse Outcomes Compared to Patients with Gleason 8 Disease. J Urol. 2015 Jul;194(1):91–7.

106. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: Data based on the modified Gleason scoring system. BJU Int. 2013;111(5):753–60.

107. Priester A, Natarajan S, Khoshnoodi P, Margolis DJ, Raman SS, Reiter RE, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. J Urol. 2017 Feb;197(2):320–6.

108. Brisbane WG, Priester AM, Ballon J, Kwan L, Delfin MK, Felker ER, et al. Targeted Prostate Biopsy: Umbra, Penumbra, and Value of Perilesional Sampling. Eur Urol. 2022 Sep;82(3):303–10.

109. Rouvière O, van Leenders GJLH, Eberli D, EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel. Systematic Prostate Biopsy Versus Perilesional Sampling: If It Isn't Broke, Why Fix It? Eur Urol. 2024 Oct;86(4):295–6.

110. Connor MJ, Eldred-Evans D, van Son M, Hosking-Jervis F, Bertoncelli Tanaka M, Reddy D, et al. A Multicenter Study of the Clinical Utility of Nontargeted Systematic Transperineal Prostate Biopsies in Patients Undergoing Pre-Biopsy Multiparametric Magnetic Resonance Imaging. J Urol. 2020 Dec;204(6):1195–201.

111. Tschirdewahn S, Wiesenfarth M, Bonekamp D, Püllen L, Reis H, Panic A, et al. Detection of Significant Prostate Cancer Using Target Saturation in Transperineal Magnetic Resonance Imaging/Transrectal Ultrasonography–fusion Biopsy. Eur Urol Focus. 2021 Nov;7(6):1300–7.

112. Porpiglia F, Checcucci E, DE Cillis S, Piramide F, Amparore D, Piana A, et al. A prospective randomized controlled trial comparing target prostate biopsy alone approach vs. target plus standard in naïve patients with positive mpMRI. Minerva Urol Nephrol. 2023 Feb;75(1):31–41.

113. Venderink W, van der Leest M, van Luijtelaar A, van de Ven WJM, Fütterer JJ, Sedelaar JPM, et al. Retrospective comparison of direct in-bore magnetic resonance imaging (MRI)-guided biopsy and fusion-guided biopsy in patients with MRI lesions which are likely or highly likely to be clinically significant prostate cancer. World J Urol. 2017 Dec;35(12):1849–55.

114. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, et al. Comparison of Targeted vs Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. JAMA Surg. 2019 Sep 1;154(9):811–8.

115. Massanova M, Barone B, Caputo VF, Napolitano L, Ponsiglione A, Del Giudice F, et al. The detection rate for prostate cancer in systematic and targeted prostate biopsy in biopsy-naive patients, according to the localization of the lesion at the mpMRI: A single-center retrospective observational study. The Prostate. 2024 Sep;84(13):1234–43.

116. Lockhart K, Martin J, White M, Raman A, Grant A, Chong P. Fusion versus cognitive MRI-guided prostate biopsies in diagnosing clinically significant prostate cancer. J Clin Urol. 2024 Sep;17(5):504–10.

117. Khoo CC, Eldred-Evans D, Peters M, Van Son M, Van Rossum PSN, Connor MJ, et al. A Comparison of Prostate Cancer Detection between Visual Estimation (Cognitive Registration) and Image Fusion (Software Registration) Targeted Transperineal Prostate Biopsy. J Urol. 2021 Apr;205(4):1075–81.

118. Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng FM, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. Eur Urol. 2014 Aug;66(2):343–51.