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Ultrasound and histopathological aspects of prostate cancer

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List of abbreviations

PSA - antigenul specific prostatic

DRE - tușeul rectal

TRUS - ultrasonografie transrectală

HBP - hiperplazia benignă de prostată

RMNmp - Rezonanță Magnetică Multiparametrică

ASAP - proliferare atipică de mici acini (Atypical Small Acinar Proliferation)

HMWK - citocheratine de înaltă greutate moleculară

ISUP - Societatea Internațională de Patologie Urologică

EAU - Asociația Europeană de Urologie

NCI - Institutul Național al Cancerului din Statele Unite

AUA - Asociația Americană de Urologie

NCCN - Rețeaua Națională Comprehensivă pentru Cancer

SUO – Societatea de Urologie Oncologică

LUTS - simptomatologia urinară joasă

PSAD - densitatea PSA

PSAV - viteza PSA

PHI - Indicele de sănătate prostatică

PI-RADS - Prostate Imaging Reporting and Data System

GCO - Observatorul Global al Cancerului

OMS - Organizația Mondială a Sănătății

GUPS - Societatea de Patologie Genitourinară

CAP - Colegiul American al Anatomopatologilor

IDC-P - Carcinom intraductal de prostate

IIEF - indexul internațional al funcției erectile

VAS - scala analogică vizuală

PPNB - Blocarea Nervilor Periprostatici

mpUS-MRI-TRUS - ultrasunete multiparametrice - rezonanță magnetică multiparametrică - ghidaj ecografic transrectal

ADC - coeficientul de difuzie apparent

DCE - contrastul dinamic îmbunătățit

AI Radiomics - Radiomica bazată pe Inteligență Artificială

Introduction

Prostate cancer is a major public health issue worldwide, ranking as the second most common neoplasm diagnosed among men and a leading cause of cancer mortality. The management of this condition has evolved significantly, shifting from late detection in advanced clinical stages to complex screening strategies and early diagnosis.

The diagnostic process for patients suspected of having prostatic neoplasia relies on a classic triad: serum determination of prostate-specific antigen (PSA), digital rectal examination (DRE), and transrectal ultrasound (TRUS). However, definitive confirmation and assessment of tumor aggressiveness depend exclusively on histopathological examination obtained by image-guided biopsy.

Histopathological examination is a crucial component of the diagnostic algorithm. It not only confirms malignancy but also provides essential prognostic parameters that guide therapy: histological type, Gleason score, presence of perineural invasion, and status of resection margins [1].

The vast majority of prostate cancers are classic acinar adenocarcinomas. Histopathological diagnosis on biopsy fragments is based on strict architectural and cytological criteria. Neoplastic glands display abnormal distribution, typically appearing smaller, crowded, and infiltrative among normal benign acini (architectural disturbance). Normal and hyperplastic prostatic acini have a bilayered structure (luminal secretory cells and flattened basal cells). Prostatic carcinoma is characterized by complete loss of the basal cell layer. Tumor cells exhibit enlarged, monomorphic nuclei with prominent nucleoli, single or multiple, visible under low magnification. The cytoplasm may appear amphophilic (lightly basophilic). The presence of tumor cells surrounding or infiltrating perineural spaces in the prostatic stroma is a strong indicator of malignancy and a poor prognostic factor correlated with extraprostatic extension (perineural invasion).

The Gleason system is based solely on the architectural pattern of tumor cell growth (from grade 1, the best differentiated, to grade 5, the least differentiated). In current practice, the Gleason score is obtained by adding the most common architectural pattern (primary component) to the second most common pattern (secondary component) [2].

Prostate ultrasound and histopathology are interdependent components in the management of prostate cancer. Modern ultrasound techniques, including fusion methods, provide a topographic map and guide the biopsy needle to areas of high suspicion, while histopathological analysis ultimately determines the diagnosis. Accurate correlation between the lesion's volume and ultrasound features (such as hypoechogenicity and elastographic rigidity) and the microscopic ISUP/Gleason grading enables proper stratification of the patient's oncological risk, paving the way for personalized therapy, ranging from active surveillance to radical prostatectomy or targeted radiotherapy in aggressive cases [3].

In this doctoral thesis, our initial objective was to centralize published data from the specialized literature regarding both the complications of TRUS-guided prostate biopsies and the procedural difficulties that may occur during this procedure.

We then highlighted the complementary roles of fusion-guided prostate biopsies and systematic randomized biopsies in improving prostate cancer detection rates through a large retrospective study.

We also assessed the incremental diagnostic yield of fusion biopsy for overall prostate cancer detection, based on a single-center paired analysis comparing MRI-ultrasound fusion biopsy with systematic biopsy in the same cohort. We compared clinically significant prostate cancer detection, examined concordance and discordance between biopsy methods, evaluated PI-RADS–stratified detection patterns, and explored biopsy–surgical pathology concordance in the subgroup of patients who underwent radical prostatectomy.

I. GENERAL PART

1. Risk factors and diagnostic markers in prostate cancer: genetic, metabolic, clinical and imaging perspectives

1.1. Risk factors for prostate cancer

The analysis of prostate cancer risk factors enhances understanding of the mechanisms involved in the onset and progression of the disease. Prostate cancer is currently considered the result of a complex interaction among genetic predisposition, biological processes associated with aging, metabolic factors, environmental exposures, and the individual clinical context.

Interpreting risk factors in prostate cancer requires a specific approach, as this disease is characterized by significant biological heterogeneity and major differences between indolent and clinically significant forms. In this context, the concept of "risk" should not refer solely to the

probability of diagnosis, but also to tumor aggressiveness, disease progression, and disease-specific mortality [4].

According to current data from the European Association of Urology (EAU), the United States National Cancer Institute (NCI), the American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN), prostate cancer risk factors can be divided into major non-modifiable factors and modifiable or partially modifiable factors [5].

1.2.Diagnosis of prostate cancer

The diagnosis of prostate cancer has changed significantly in recent decades with the development of biological markers, modern imaging techniques, and targeted biopsy strategies. In the past, diagnosis relied mainly on digital rectal examination and histopathological confirmation from systematic biopsies. Today, evaluating a patient with suspected prostate cancer involves integrating clinical, biological, and imaging data into a complex, individualized algorithm [6].

The goal of modern diagnosis is not simply to identify any prostate cancer, but to distinguish clinically significant tumors from indolent lesions with low biological risk. This approach aims to reduce overdiagnosis and overtreatment, which are major issues associated with screening and the widespread use of prostate-specific antigen (PSA) [7].

Current recommendations from the European Association of Urology (EAU), the American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN) advise that diagnostic evaluation be tailored to the individual risk profile and include PSA analysis, clinical examination, multiparametric magnetic resonance imaging, and histopathological confirmation by biopsy.

In this context, the introduction of multiparametric prostate magnetic resonance imaging and the development of targeted biopsies have profoundly changed the traditional diagnostic algorithm and improved the ability to identify clinically significant prostate cancer.

2. Epidemiology and histopathology of prostate cancer: from historical evolution to modern classification and the role of immunohistochemistry

2.1. The epidemiological importance of prostate cancer

Prostate cancer is one of the most important male oncological problems worldwide, both due to its high frequency and biological and epidemiological heterogeneity. This pathology is characterized by a significant variability in evolution, from indolent forms with slow progression to aggressive forms associated with increased mortality. According to the GLOBOCAN 2022

estimates of the International Agency for Research on Cancer (IARC), prostate cancer generated 1,467,854 new cases and 397,430 deaths worldwide in 2022. At the same time, the 5-year prevalence was estimated at 5,033,178 cases, representing one of the highest prevalences among solid male cancers. In the global male population, this neoplasm ranks second in frequency after lung cancer, and in the ranking of all cancers, in both sexes, it ranks fourth in terms of incidence [8].

This combination of very high incidence, intermediate mortality and high prevalence reflects the fact that a significant number of tumors are diagnosed at treatable stages or have a relatively slow evolution. At the same time, these data highlight the fact that the burden of the disease on health systems remains considerable [9].

Prostate cancer has a wide geographical distribution, being in more than half of the countries of the world the most common cancer diagnosed in men, and in approximately a quarter of the countries it is the main cause of cancer-related death in men. In Europe, this pathology is the most common cancer in men and the third cause of cancer-related mortality [10].

From an epidemiological perspective, one of the defining characteristics of prostate cancer is the contrast between the highly variable incidence and the relatively less variable mortality. Geographic differences in incidence are significantly influenced by the intensity of PSA testing, access to diagnostic services, population age structure, and reporting practices [11].

2.2. Histopathology of prostate cancer

In continuation of the epidemiological data presented above, the histopathological evaluation of prostate cancer represents a central element in understanding tumor biology, in assessing the aggressiveness of the disease and in establishing the therapeutic conduct. The evolution of knowledge regarding this pathology has been closely linked to the development of microscopy, histological techniques, modern grading systems, immunohistochemistry and, more recently, molecular biology

Currently, the modern histopathological diagnosis of prostate cancer is based on the criteria developed by the World Health Organization (WHO), the International Society of Urological Pathology (ISUP), the Genitourinary Pathology Society (GUPS) and the protocols of the American College of Anatomopathologists (CAP), clinically integrated by the recommendations of the European Association of Urology (EAU). These modern systems allow not only the confirmation

of the diagnosis, but also the prognostic assessment, risk stratification and individualization of therapeutic management.

From the current perspective, prostate cancer histopathology no longer has an exclusively descriptive role, but represents an essential tool in assessing the extent of the disease, in assessing the biological aggressiveness and in guiding modern therapeutic decisions [12].

The Gleason system continues to be the basis for grading prostatic adenocarcinoma and one of the most important prognostic factors used in clinical and pathological practice [99]. This system evaluates the two dominant tumor growth patterns and generates a final score resulting from the sum of the two predominant components. Its importance derives from the close correlation between glandular architecture and biological aggressiveness of the tumor. Over time, the Gleason system has undergone multiple updates through the international ISUP consensuses of 2005, 2014 and 2019, with the introduction of the modern Histological Grade Groups (Grade Groups) 1–5 system, with the aim of simplifying clinical interpretation and improving prognostic correlation.

The current classification includes:

- Grade Group 1 = Gleason 3+3=6
- Grade Group 2 = Gleason 3+4=7
- Grade Group 3 = Gleason 4+3=7
- Grade Group 4 = Gleason 8
- Grade Group 5 = Gleason 9–10

This classification is considered more clinically intuitive and has a better correlation with oncological prognosis, risk of biochemical recurrence, and disease-specific survival [13].

II. OWN CONTRIBUTIONS

3. Working hypothesis, research directions and study objectives

3.1.Working hypothesis

For the early detection of small-volume prostate cancer, most countries use a combination of PSA screening, digital rectal examination, and systematic transrectal ultrasound-guided prostate biopsy [14]. Long-term studies have shown that PSA-based screening reduces the risk of mortality from prostate cancer, but there is still debate about this issue due to the considerable overdiagnosis that may occur [15,16].

Prostate biopsy is the basic investigative tool for establishing a definitive diagnosis, and with the recent diagnostic revolution and technological advances, the accuracy of this biopsy has increased even more. In recent years, 12-probe transrectal ultrasound-guided prostate biopsy (TRUS) has been considered the gold standard procedure for detecting prostate cancer [17]. The actual ability of transrectal ultrasound to detect prostate cancer itself is limited, with a sensitivity of approximately 73.6% and a specificity of 61.3%. Thus, the diagnostic accuracy of prostate biopsies varies depending on the imaging techniques used [18]. However, TRUS prostate biopsy has been shown to have a high specificity of 96%, but a sensitivity of only 48% [19,20].

In Romania, cancer mortality trends have been described as an important public health concern, supporting the need for locally generated diagnostic and outcome data [21]. Modern diagnostic pathways increasingly aim not only to identify prostate cancer, but also to preferentially detect clinically significant disease, while reducing overdiagnosis of indolent tumors [22].

The fusion of real-time TRUS-guided biopsy and mpMRI has enabled targeting of high-risk areas, thereby reducing the number of punctures [23]. There are numerous studies demonstrating that fusion biopsy increases the chance of detecting prostate cancer [24,25]. One of the most valuable tools provided by mpMRI is the Prostate Imaging Data and Reporting System (PI-RADS). PI-RADS divides the prostate into multiple regions, typically between 16 and 27, and assigns a score to individual lesions based on their likelihood of being clinically significant prostate cancer. This standardized approach improves the consistency of lesion characterization, helping to stratify risk and guide biopsy decisions [26]. As of September 2019, version 2.1 of PI-RADS is available.

Key updates to this revised version include the reclassification of certain imaging features. In particular, round, encapsulated nodules are now classified as PI-RADS 1, reflecting their benign appearance.

In addition, transition zone lesions with a T2-weighted (T2W) score of 2 remain PI-RADS 2 if the DCE/Apparent Diffusion Coefficient (ADC) score is equal to or less than 3, but are upgraded to PI-RADS 3 if the DCE/ADC score is equal to or greater than 4 [27].

False-negative results with guided biopsy are not uncommon, raising concerns about missed diagnoses, particularly when multiparametric MRI (MPMRI) identifies a potential lesion.

Conversely, MPMRI can also produce false-positive results, detecting lesions that mimic prostate cancer (prostate cancer mimics), which can lead to unnecessary biopsies [28].

Serum PSA measurement is one of the most important biomarkers in the detection of prostate cancer; however, its widespread use has also led to an increase in the diagnosis of clinically insignificant tumors worldwide [29,30].

3.2.Research directions and study objectives

The common general objective of the studies conducted in this doctoral thesis focuses on optimizing the peri-procedural management of transrectal prostate biopsy, by balancing diagnostic yield (cancer detection efficiency) with clinical patient safety (minimization and management of complications), based on clinical evidence from both the literature and our own studies.

To achieve this general goal, we aimed to achieve several specific objectives:

1. The first specific objective was to centralize data from the literature regarding both the complications of TRUS-guided prostate biopsies and the procedural difficulties that may arise during this procedure, focusing on identifying and overcoming anatomical or technical difficulties during the actual ultrasound-guided procedure [20].
2. The second specific objective was to compare randomized prostate biopsy with fusion-guided biopsy in patients with low PSA values, both being performed in all patients, thus addressing a key question in the literature: which method is superior? The aim is to overcome this problem by demonstrating that the answer lies in combining both methods. This retrospective study evaluated and compared the diagnostic performance of multiparametric MRI-guided fusion biopsy and randomized systematic biopsy for the detection of prostate cancer in 138 patients with PSA levels below 25 ng/ml. By incorporating clinical risk factors—including PSA, prostate volume, PI-RADS score, and age—into a multivariate logistic regression model, this study provides a robust assessment of their individual and combined predictive values. The structured methodology and comprehensive reporting align with current research standards, ensuring suitability for inclusion in future systematic reviews and meta-analyses on biopsy accuracy and prostate cancer diagnostic strategies [30].

3. The third specific objective was to evaluate the incremental diagnostic yield of fusion biopsy for the overall detection of prostate cancer. This objective was achieved by developing a study designed as a single-center paired-data analysis that compared MRI-ultrasound fusion biopsy with systematic biopsy in the same cohort. Secondary objectives were to compare clinically significant prostate cancer detection, examine concordance and discordance between biopsy methods, evaluate PI-RADS stratified detection patterns, and explore biopsy-surgical pathology concordance in the subgroup of patients who underwent radical prostatectomy [31].

4. General research methodology

4.1. Narrative analysis of specialized literature

The study was conducted during 2023 and was created using PubMed articles, with the main search keywords “TRUS” and “prostate biopsy”. Some references were obtained using words from the subfields of TRUS-guided prostate biopsy and comparisons were made with other biopsy techniques. Other references were obtained by cross-referencing key articles. Of the 1628 results returned by the PubMed platform, 79 articles were selected, which met the following criteria: they must contain reliable information (complete articles, with realistic information and achievable results); they must have access to the article; and they must include information related to TRUS-guided prostate biopsies. Articles with confusing titles and keywords were eliminated. With a few exceptions, the proposed references used in this article were published after 2013 (Figure 4.1.) [20].

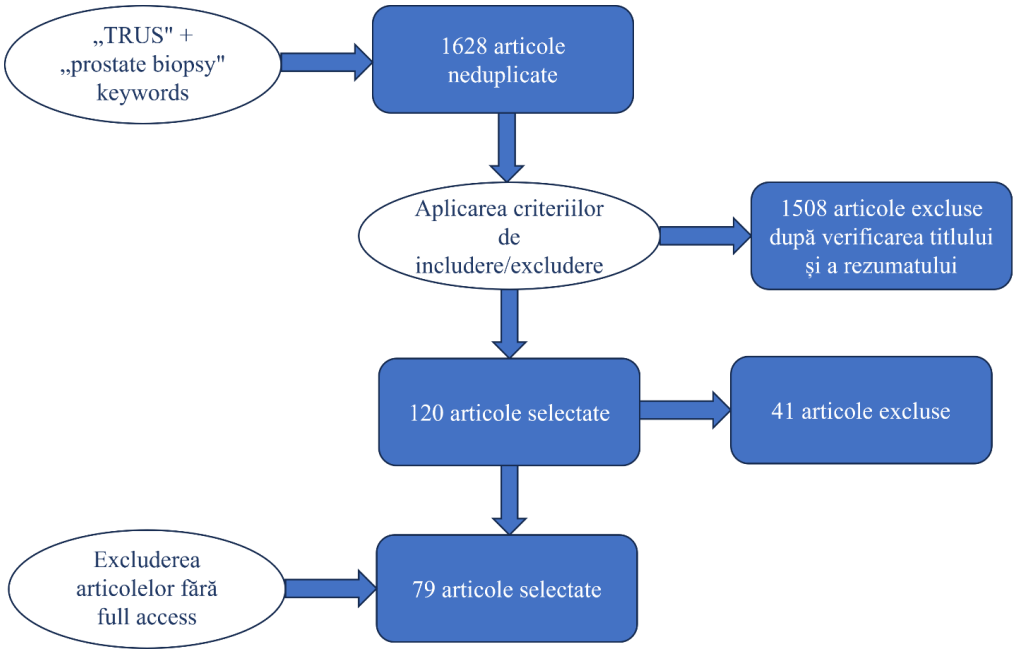

Figure 4.1. Article selection methodology

4.2. Retrospective study on the diagnostic yield of fusion-guided and randomized biopsies in prostate cancer

The retrospective analysis was performed on a database of 891 patients managed in a single medical facility between June 2022 and December 2024. This study was conducted in a private tertiary care facility and was approved by the ethics committee (nr. 17/2024). Data were collected between December 2024 and February 2025.

A total of 891 male patients who underwent prostate evaluation were initially evaluated.

The inclusion criteria were as follows: availability of pre-biopsy prostate-specific antigen (PSA) levels; completion of multiparametric magnetic resonance imaging (MPM-MRI); availability of pathology results; informed consent to receive the institutional prostate biopsy protocol (described in subsequent sections); and performance of both fusion-guided random and systematic biopsies on the same day in a single procedure.

Exclusion criteria included refusal to undergo the procedure, contraindications to anesthesia, a PI-RADS score < 3, PSA levels > 25 ng/ml, and previously localized lesions. After applying these criteria, 138 patients were eligible for the final analysis (Figure 4.2.).

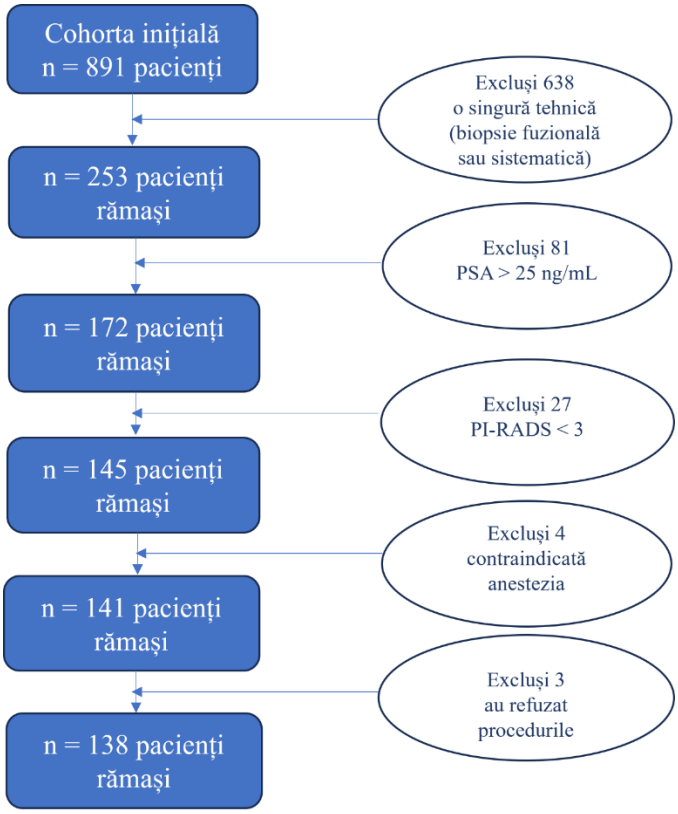

Figure 4.2. Patient selection

All patients received fluoroquinolone antibiotics before biopsy to exclude inflammatory causes of PSA elevation (all included patients had PSA < 25 ng/ml). PSA levels were reassessed after completion of antibiotic treatment, and post-treatment values were recorded for analysis.

All patients were informed of the benefits and risks of the procedure and signed an informed consent form.

Before the procedure, each patient underwent a pre-anesthetic consultation to assess eligibility for intravenous sedation. On the day of biopsy, patients received a microenema and a prophylactic dose of antibiotics.

The mpMRI was performed using a 3 Tesla Siemens Magnetom Skyra system (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). The imaging protocol included triplane T2W imaging, DWI, and dynamic contrast-enhanced pelvic sequences (DCE), as well as post-contrast abdominopelvic imaging.

All scans were interpreted by two experienced radiologists, and lesions were assessed according to PI-RADS version 2.1 criteria. Radiologists were given access to the results of the corresponding blood tests for diagnostic correlation.

Biopsies were obtained by transrectal approach under local anesthesia and supplemented with intravenous sedation. Fusion-guided biopsy was performed using a BK 5000 ultrasound system (Mileparken 34, 2730 Herlev, Denmark) equipped with a 7 MHz endorectal transducer (Mileparken 34, Herlev, Denmark).

Tissue samples were collected using a Bard Magnum gun (Bard, Franklin Lakes, NJ, USA) (250 mm, 18G needle). For the fusion-guided component, two to six tissue samples were obtained from each identified lesion, depending on the lesion volume. The protocol required at least two tissue samples from smaller lesions, obtained from different regions, and up to six tissue samples for lesions larger than 125 cc.

The fusion-guided biopsy was immediately followed by a randomized systematic biopsy, in which 12 samples were collected according to the standard sextant protocol. Biopsies were performed under local anesthesia combined with intravenous sedation, administered following a preanesthetic consultation.

Each procedure was performed by a team consisting of a urologist, an anesthesiologist, and a surgical nurse.

Two experienced pathologists reviewed all biopsy specimens according to standardized laboratory protocols, with access to blood test results and PI-RADS scores. Diagnoses included Gleason scores between 6 and 9, as well as benign prostatic hyperplasia (BPH), high-grade prostatic intraepithelial neoplasia (HGPIN), atypical glands suspicious for malignancy (ATYP), and a rare case of amyloidosis. A biopsy was classified as positive if at least one biopsy fragment obtained from either method contained malignant cells.

We extracted the following data from each patient's chart: age, most recent pre-biopsy PSA level, prostate volume, PI-RADS score, and biopsy results from both fusion-guided and systematic approaches.

To illustrate the heterogeneity of the data set, all selected patients were male, aged 50–82 years, with an interquartile range indicating a diverse age distribution. PSA levels were below 25 ng/ml, and all patients had PI-RADS scores ≥ 3, with the majority classified as PI-RADS 4 or 5. None of the patients had a history of prostate biopsy.

Prostate volume showed a wide variability, ranging from 25 to 214 cc (Figure 4.4.). For improved interpretation, patients were classified according to key clinical risk factors. PSA levels were grouped into three categories: low (<6 ng/ml), intermediate (6–11 ng/ml), and high (>11 ng/ml).

Prostate volume was stratified into 25 cc intervals to capture granular variation within the cohort. PI-RADS scores were dichotomized into PI-RADS 3 (equivocal) and PI-RADS 4–5 (probably or very likely to represent clinically significant cancer).

Age was categorized into four groups (45–55, 56–65, 66–75, and ≥76 years), consistent with the distribution of the study population. These variables were incorporated into a multivariate logistic regression model to assess their combined predictive value for clinically significant prostate cancer.

The single-center design and selective inclusion criteria—restricting participants to those with PI-RADS scores ≥3 and no history of biopsy—may introduce selection bias and limit external validity.

These factors should be considered when interpreting the generalizability of the results to larger, more heterogeneous populations [30].

4.3. Single-center analysis of complications of transrectal prostate biopsy

This investigation was conducted as a retrospective, single-center, paired-end, diagnostic yield study. The paired-end design was chosen because each included patient underwent both a MRI-ultrasound fusion-guided biopsy and a systematic biopsy, allowing for a within-patient comparison of the two techniques.

The study period extended from 2023 to 2025. The study was conducted in accordance with the Declaration of Helsinki. Given the retrospective design, the requirement for informed consent was waived per institutional policy.

The primary analysis was based on biopsy histopathology, which was available for all included patients. Surgical pathology was not used as a universal reference standard, as it was only available for patients who underwent radical prostatectomy. Therefore, analyses involving surgical pathology were considered exploratory rather than confirmatory.

The final cohort comprised 138 adult men investigated for suspected prostate cancer. Inclusion criteria were pre-biopsy mpMRI, performance of both MRI-ultrasound fusion biopsy and systematic biopsy during the same diagnostic investigation, and availability of analyzable histopathology results for both biopsy components.

Patients with incomplete essential biopsy histopathology, duplicate records, or findings that could not be classified as cancer versus non-cancer were excluded from the analyzable cohort.

The database included demographic, clinical, imaging, biopsy-related, complication-related, and surgical pathology variables. These included age, total PSA, prostate volume, PSA density, PI-RADS category, digital rectal examination findings where available, fusion biopsy histology, systematic biopsy histology, severity of complications, and postoperative pathology variables in surgical patients. PSA density was calculated by dividing total PSA by prostate volume and was expressed in ng/mL/cm³.

All patients underwent pre-biopsy multiparametric MRI according to the institutional prostate MRI protocol using a 3-T scanner. Visible MRI lesions were classified according to PI-RADS version 2.1 and used to guide fusion-targeted sampling [27]. PI-RADS information was available for 135 of the 138 patients included in the analysis. MRI examinations were interpreted by radiologists experienced in prostate imaging.

All patients underwent combined fusion-targeted MRI-ultrasound biopsy and systematic biopsy during the same diagnostic episode. Biopsies were performed transrectally, according to institutional practice.

In the source database, the untargeted component was recorded as “random biopsy”; in the paper, the term “systematic biopsy” is used because the samples were obtained according to a template-based, untargeted sampling strategy.

Fusion biopsy was defined as targeted sampling of suspicious MRI lesions after alignment of the MRI target with real-time ultrasound guidance. Systematic biopsy was defined as untargeted sampling of the prostate under ultrasound guidance [22,32].

Patient-level procedural details, including the exact number of targeted and systematic samples, order of sampling, anesthesia, and antibiotic prophylaxis, were not consistently recorded in the retrospective database.

Biopsy histopathology was evaluated separately for fusion and systematic samples. Adenocarcinoma was classified as cancer. Benign tissue, benign prostatic hyperplasia,

inflammation, HGPIN, and atypia/ASAP-like findings were not considered cancer in the primary dichotomized analysis, although they were descriptively retained in the source dataset. Clinically significant prostate cancer was defined a priori as Gleason score ≥3+4, corresponding to ISUP Grade Group ≥2 [33].

A dedicated surgical pathology status variable was introduced to distinguish between patients with pathology available for radical prostatectomy, patients without biopsy-detected cancer for whom surgical pathology was not applicable, and patients with biopsy-detected cancer for whom surgical pathology was not available in the database.

This distinction was considered methodologically important because the absence of surgical pathology does not imply the absence of disease. Rather, it reflects either the absence of an indication for radical prostatectomy or the lack of a postoperative specimen available in the study database [31].

5. Current approach to complications and difficulties during transrectal ultrasonography-guided prostate biopsies

The advantages of transrectal biopsy are largely related to its cost-effectiveness (in terms of time invested, consumables used, and wide availability) [34]. One of the main disadvantages is the high false-negative rate, which can occur due to operator experience and lack of constant eye contact, leading to uneven distribution of biopsy cores [35]. With experience and practice, this limitation decreases.

A simulator study proposed a real-time 3D simulator to train and train young urologists to maintain the correct position of the probe during lateral prostate biopsy. The results showed that the technique can be learned by participants (the program detected improvements in the urologists compared to the standard deviation), suggesting that this could also reduce the number of false-negative results of prostate biopsies [36]. The second disadvantage concerns the need for antibiotic prophylaxis and the risk of infection and sepsis. The colon is rich in microbiota and perforation of the colon wall can introduce bacteria into the prostate [37]. As described earlier, rates of infectious complications vary.

One study compared several articles and found infection rates ranging from 1-17.5% [38]. Due to recent bacterial resistance to fluoroquinolones, more serious complications of infection requiring hospitalization have occurred [39]. A recent study compared the efficacy of ciprofloxacin

versus ciprofloxacin in combination with fosfomycin in cases of urosepsis following TRUS-guided prostate biopsy. The study concluded that combined prophylaxis of ciprofloxacin with fosfomycin significantly reduced urosepsis rates [41].

Another important aspect of TRUS-guided biopsy is the social impact of the procedure. The role of prostate biopsy has changed from pure cancer detection to general patient management [41]. Pain, potential complications, and outcome certainly have an impact on patients undergoing this procedure. The most frequently encountered psychological symptoms in studies are anxiety and depression [42].

mpUS-MRI-TRUS (multiparametric ultrasound - multiparametric magnetic resonance - transrectal ultrasound-guided) fusion biopsy is receiving increasing attention due to the valuable information it provides about prostate cancer foci. Combining mpUS with mpMRI-TRUS fusion can overcome the clinical detection limits of each imaging modality by superimposing the images in real time [43].

Several software packages are available that perform fusion in real time, although in some centers the images are mentally superimposed by the biopsy operator [44]. This fusion procedure can detect prostate cancer at higher rates than standard ultrasound biopsy, and it also easily identifies index lesions with extraprostatic extension [45]. mpMRI in the presence of lesions before biopsy has a sensitivity of 93% but a specificity of only 41% for detecting cancerous lesions.

Compared to TRUS-guided biopsy with low sensitivity (48%) and high specificity (96%), mpUS-MRI-TRUS fusion biopsy should cover both sensitivity and specificity [19].

In the future, artificial intelligence assistance could be the key to increase the diagnostic accuracy even for TRUS, which is considered a low-performance modality [46].

In the last decade, a large number of articles have been published on the importance of PSMA PET-CT both in the primary diagnosis of prostate cancer and in recurrences that may occur. Currently, PSMA PET/CT has a greater importance in recurrences where the diagnosis is already known, due to the consistent number of pathologies that can express PSMA receptors. Despite the high cost of this diagnostic method, close collaboration between urologists and nuclear medicine physicians is necessary, and the various influencing factors should be studied in detail to achieve the best results [47].

Strengths of the study include the analysis of both technical difficulties and post-procedural complications in the same article, while also providing information on how to overcome these events.

Due to limitations, the study is not a meta-analysis, so the selection criteria were not very strict. Due to limited access, some interesting and relevant articles had to be eliminated, although they probably would not have changed the conclusions of this paper. Finding articles on technical difficulties during TRUS-guided prostate biopsy proved to be a difficult task, as direct keywords did not return adequate results.

Transurethral ultrasound-guided prostate biopsy remains a robust, cost-effective, and safe procedure for diagnosing prostate cancer. Complications are usually self-limited and do not require additional medical care. Difficulties arising from the procedure can be safely overcome if no other alternatives are available. Open communication with patients improves both pre- and post-procedure compliance [20].

6. Diagnostic benefits of combined use of fusion-targeted and randomized biopsy

The results of the biopsies are summarized in Table VI.1. and Figure 6.1. Histopathological analysis performed following fusion-guided biopsies revealed the following diagnoses: 44 patients with Gleason score 6 (3+3), 34 patients with Gleason 7 (3+4), 10 patients with Gleason 7 (4+3), 5 patients with Gleason 8 (4+4), 13 patients with atypical glands suspicious for malignancy (ATYP), 6 patients with high-grade prostatic intraepithelial neoplasia (HGPIN) and 26 cases of benign prostatic hyperplasia (BPH).

Table VI.1. Number of positive and negative patients at prostate biopsy puncture, depending on technique

Technique	***Positive patients***
Fusion positive	94
Randomization positive	105
Fusion positive, Randomization negative (F+/R-)	16
Fusion negative, Randomization positive (F-/R+)	28
Positive on both ($F+ \cap R+$)	78
Positive on at least one method ($F+ \cup R+$)	122

Negative on both methods (F-/R-)	16
Total number of patients	138

Regarding the randomized systematic biopsy, it identified: 49 patients with Gleason 6 (3+3), 35 patients with Gleason 7 (3+4), 6 patients with Gleason 7 (4+3), 8 patients with Gleason 8 (4+4), one case with Gleason 9 (5+4), 10 patients with ATYP, 20 cases of BPH, 2 cases of HGPIN and a rare case of amyloidosis.

Thus, of the total 138 patients included in the study, 94 had positive results for prostate cancer in the fusion biopsy (F+), and 105 patients were positive in the randomized biopsy (R+). Of these, 16 patients had positive results only in the fusion biopsy (F+R−), and 28 patients were positive only in the randomized biopsy (R+F−). In addition, 16 patients were negative in both types of biopsy.

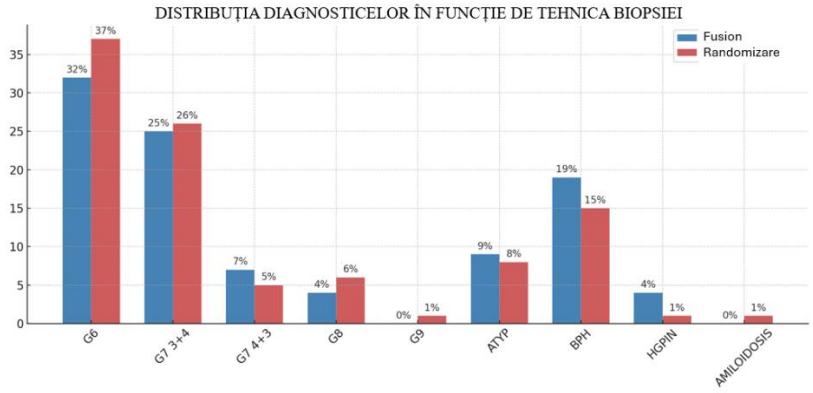

Figure 6.1. Distribution of pathological findings identified by fusion and randomized biopsy, presented as percentages [30]

Within the analyzed cohort, cases were identified in which benign prostatic hyperplasia (BPH) was diagnosed by one method, while the other revealed the presence of clinically significant prostate cancer (Gleason score 6 or 7 [3+4]). This discrepancy potentially reflects intrinsic differences between the two techniques.

Systematic biopsy, by evenly distributing the samples, has the advantage of a wider coverage of the prostate gland, thus increasing the chance of detecting multifocal forms of the disease that may escape targeted imaging.

On the other hand, fusion-guided biopsy benefits from direct visualization of suspicious lesions by mpMRI, allowing targeted sampling from areas with high risk of malignancy. These results

emphasize the complementary nature of the two methods and support their combined use in order to increase diagnostic accuracy.

With aggregated data available, we initially applied the McNemar test to compare the diagnostic value of fusion-guided biopsies with that of randomized biopsies. The test statistic had a value of 2.75, with a significance level (p) of 0.097. Since the p value is > 0.05, the difference between positive cases detected exclusively by fusion biopsy and those identified exclusively by randomized biopsy is not statistically significant. This result suggests that, based on our data, there is no strong evidence to indicate that one of the two techniques, used individually, has a superior detection rate over the other in diagnosing prostate cancer.

In terms of detection rates, fusion biopsy alone identified 68.1% of cases, while randomized biopsy detected 76.1%. However, combining the two methods (fusion positive ∪ randomised positive) resulted in an overall detection rate of 88.4% (122 patients). This represents an absolute gain of 20.3% over fusion biopsy and 12.3% over randomised biopsy.

All discordant cases between the two methods (both fusion-only positive – F+/R− and systematic biopsy-only positive – R+/F−) were confirmed as clinically significant prostate cancers with Gleason scores of 6 or 7 (3+4). This highlights the complementary value of the two approaches in increasing the accuracy of oncological diagnosis.

Prostate volume demonstrated a moderate predictive value (AUC = 0.631), indicating an association with the presence of cancer, but with limited accuracy when used alone. Despite the fact that the PI-RADS score represents a standardized imaging system, it achieved an AUC of 0.619, reflecting modest performance when used in isolation, probably due to interobserver variability or overlapping features between low-risk and significant lesions.

Age had the lowest individual predictive performance (AUC = 0.572), suggesting that although it is an important clinical factor, it does not provide strong discriminatory power independently. These findings highlight the importance of using a multivariate model, in which the combination of multiple clinical and imaging parameters contributes to a more precise and reliable prediction, as evidenced by the overall AUC of the model of 0.751 and the accuracy of 89.6%.

To support the generalizability and clinical applicability of the study, the cohort was analyzed for heterogeneity, taking into account key demographic and clinical parameters. The study included men with a wide range of ages, varying PSA levels and different prostate volumes, reflecting the diversity encountered in everyday medical practice. This variability is particularly

relevant, as it allows the evaluation of the performance of biopsies and risk prediction models in different risk strata [30].

7. Single-center analysis of complications of transrectal prostate biopsy

PI-RADS information was available for 135 patients. Of these, 24 patients had PI-RADS 3 lesions, 80 had PI-RADS 4 lesions, and 31 had PI-RADS 5 lesions. Therefore, the majority of patients with available PI-RADS information had PI-RADS 4 or 5 lesions.

Table VII.1. Baseline characteristics of the studied cohort

Baseline characteristic	***Value***
Patients, n	138
Age (years) median, range (IQR)	66 (59–71)
PSA (ng/mL) median, range (IQR)	7.46 (5.50–10.00)
Prostate volume (cm^3) median, range (IQR)	54.5 (39.9–76.7)
PSA density ($ng/mL/cm^3$) median, range (IQR)	0.14 (0.085–0.199)
PI-RADS disponibil, n	135 (97.8%)
PI-RADS 3, n (%)	24 (17.4%)
PI-RADS 4, n (%)	80 (58.0%)
PI-RADS 5, n (%)	31 (22.5%)
PI-RADS unavailable, n (%)	3 (2.2%)

Note: Values are presented as median (interquartile range) or n (%). Percentages were calculated using the entire cohort as denominator (n = 138). IQR, interquartile range; PSA, prostate-specific antigen; PI-RADS, Prostate Imaging Data and Reporting System

Fusion biopsy detected prostate cancer in 65 of 138 patients (47.1%), while systematic biopsy detected cancer in 56 patients (40.6%). Combined biopsy detected cancer in 72 patients (52.2%). Therefore, the absolute difference between fusion and systematic biopsy was 6.5 percentage points in favor of fusion biopsy. In the paired analysis, this numerical advantage did not reach statistical significance (McNemar exact $p = 0.093$).

Clinically significant prostate cancer was detected by fusion biopsy in 37 patients (26.8%) and by systematic biopsy in 35 patients (25.4%). Combined biopsy detected clinically significant disease in 45 patients (32.6%). The pairwise difference between the two biopsy components was small and nonsignificant (McNemar exact $p = 0.815$), while the combined biopsy detected more clinically significant cancers than either component alone.

At the patient level, both biopsy techniques were negative in 66 patients (47.8%) and positive in 49 patients (35.5%). Fusion biopsy was positive, while systematic biopsy was negative in 16 patients (11.6%), while systematic biopsy was positive, while fusion biopsy was negative in 7 patients (5.1%).

Therefore, discordant results were observed in 23 patients (16.7%). Fusion-only positive cases were more common than systematic-only positive cases, consistent with an observed greater incremental contribution of MRI-guided sampling to overall cancer detection in this cohort.

The highest detection rates were observed for PI-RADS 5 lesions. In this subgroup, fusion biopsy detected overall prostate cancer in 26 of 31 patients (83.9%) and clinically significant disease in 20 of 31 patients (64.5%), compared with 21 of 31 patients (67.7%) and 17 of 31 patients (54.8%), respectively, for systematic biopsy. The numerical difference between fusion and systematic biopsy was greatest in the PI-RADS 5 subgroup.

Pathological surgery was available in 45 patients who underwent radical prostatectomy. Of the remaining patients, 66 had no cancer on biopsy and were therefore classified as ineligible for surgical pathology, while 27 had cancer detected on biopsy but no surgical pathology available in the database. This latter category included patients with cancer detected on biopsy for whom no radical prostatectomy specimen was available in the study database.

In the operated subgroup, clinically significant prostate cancer was confirmed on surgical pathology in 43 of 45 patients (95.6%). Postoperative grade change from biopsy to postoperative grade occurred in 21 patients (46.7%), while concordance between the highest biopsy grade and final surgical grade was observed in 24 patients (53.3%). Adverse pathological features were identified in 18 patients (40.0%).

The severity of complications was recorded for all patients. No complications were documented in 52 patients (37.7%), mild complications in 49 patients (35.5%), moderate complications in 25 patients (18.1%), and severe complications in 12 patients (8.7%). Because both biopsy components were obtained during the same diagnostic episode, complications were attributed to the biopsy episode as a whole rather than to each of the biopsy components separately.

In office-based transrectal prostate biopsy procedures, careful antibiotic administration appears to be a safe and appropriate approach to preventing and managing complications. Postoperative pathological findings are clinically informative but should remain exploratory because they are limited to the operated subgroup [31].

8. Critical analysis of study limitations and innovative perspectives

8.1. Study limitations

Rigorous evaluation of an invasive diagnostic technique, such as transrectal ultrasound (TRUS)-guided prostate biopsy, requires not only an analysis of the raw clinical data, but also a methodological self-reflection on how the literature was selected, processed and synthesized.

Most studies published in the literature tend to isolate surgical performance parameters from the medium-term safety profile of the patient. Thus, infectious or hemorrhagic complications are most frequently analyzed in extensive epidemiological registries, while anatomical or technical difficulties during ultrasound guidance are relegated to purely technical or experimental surgery sections.

The absence of rigid mathematical constraints specific to meta-analyses allowed greater flexibility in literature sampling. Although this may increase the risk of a degree of heterogeneity, the approach was necessary to ensure a holistic perspective on the subject.

The emphasis was placed on the conceptual depth and clinical relevance of the data analyzed, rather than a purely quantitative standardization, thus providing a contextualized interpretation of the realities of urological practice.

A significant logistical challenge during the documentation phase was represented by the restricted access to the full text of certain indexed publications. For this reason, a number of articles with high informative potential had to be negatively sampled and eliminated from the final bibliography.

Although the exclusion of these resources is a recognized limitation, the conceptual sensitivity analysis suggests that their absence does not exert a confounding influence on the final conclusions of the paper. The fundamental ideas and guidelines identified in the fully analyzed studies show a high degree of convergence with the hard core of the global urological literature, thus validating the scientific stability of the resolution model.

One of the most complex obstacles encountered in the database query phase (PubMed, Embase) was the difficulty of identifying articles dedicated strictly to technical difficulties during TRUS-guided biopsy. Searches based on direct and standardized keywords (such as MeSH terms) initially returned insufficient or highly non-specific results.

The retrospective nature of the research inevitably introduces the risk of systematic selection and information bias. Despite the rigorous application of pre-established inclusion and exclusion criteria, absolute control over past confounding variables is limited.

The lack of prospective randomization may lead to an asymmetric distribution of latent clinical characteristics of the patients, subtly influencing the established correlations.

The conduct of the study in a single medical center represents an important barrier to the generalization of the results (external validity). The cohort reflects a specific demographic profile, a certain clinical addressability and a local urological management protocol. Extrapolation of these data to larger populations, with different ethnic, socio-economic characteristics or access to different levels of healthcare, should be done with caution, as the case-mix may vary significantly.

The efficiency of invasive and non-invasive diagnostic techniques is strongly influenced by the human factor and the technological infrastructure.

The learning curve in performing MRI-ultrasound guided biopsies is long. Subtle differences in the technical skills of the urologists involved may introduce undocumented variability in the accuracy of biopsy sampling.

The resolution of transrectal ultrasound (TRUS) and the accuracy of elastic or rigid fusion software algorithms can differ. These technical variations can alter the visibility of lesions and the accuracy of the biopsy needle, directly influencing the reported diagnostic performance.

An unexpected finding of the studies was the unusually low area under the ROC curve for the PI-RADS v2.1 score, where we recorded a value of AUC = 0.619. This indicator clearly contrasts with the values consistently reported in large multicenter meta-analyses, which place the discriminative accuracy of the method in a much higher range (AUC ≈ 0.86–0.89).

This discrepancy does not indicate a lack of utility of the PI-RADS system per se, but is a direct result of methodological characteristics specific to the studied cohort.

8.2. Innovative perspectives

Conventional medical imaging, including Multiparametric Magnetic Resonance Imaging (mpMRI) interpreted by PI-RADS v2.1 guidelines, is based on qualitative or semi-quantitative assessment of tissue structures. The radiologist analyzes signal changes in T2-weighted (T2W) sequences, apparent diffusion coefficient (ADC) maps, and enhanced dynamic contrast (DCE).

This traditional approach has a fundamental limitation: the human eye is unable to perceive subtle texture variations, complex gray gradients, and spatial heterogeneity distributed at the voxel level.

Artificial Intelligence-based Radiomics (AI Radiomics) redefines the medical image, transforming it from a simple visual support into a mineable digital database composed of a massive number of quantitative biomarkers (high-throughput quantitative features).

This innovative approach starts from the premise that the pathophysiological, genetic and architectural changes of prostate adenocarcinoma are directly reflected in the spatial organization of pixels/voxels in radiological images [48].

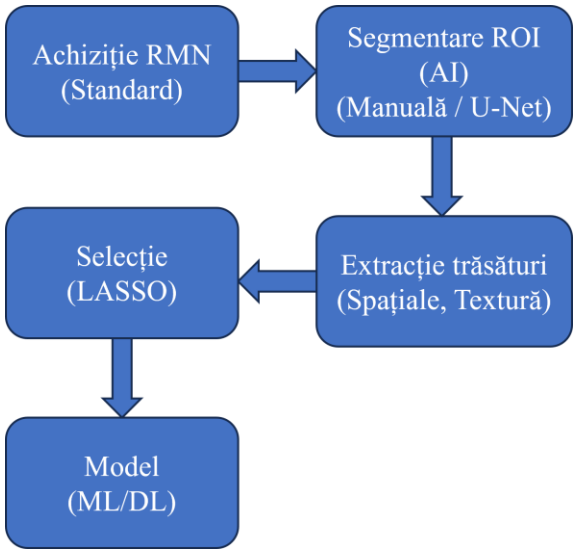

Figure 8.1. Technological flow in AI Radiomics [49]

The implementation of a radiomics algorithm applied to prostate cancer involves following a standardized, rigorously controlled path, divided into four macro-technological stages:

1. Image acquisition and preprocessing: Standardization of acquisition protocols dictates data quality. Preprocessing involves spatial resampling (bringing voxels to isotropic dimensions), signal intensity normalization (to eliminate variations caused by different MRI scanner hardware) and correction of motion artifacts or magnetic field inhomogeneity.

2. Region of interest (ROI) segmentation: Volumetric delineation of the suspicious lesion and the total prostate gland. Segmentation can be manual (performed by the radiologist), semi-automatic or fully automated through deep convolutional neural networks (3D U-Net type).

3. Feature Extraction: Computational algorithms extract thousands of mathematical parameters from the segmented volume, classified according to their architectural complexity.

4. Feature Selection and Predictive Modeling: Dimensionality reduction to avoid overfitting. Algorithms such as LASSO (Least Absolute Shrinkage and Selection Operator) or Random Forest select only the features with the highest discriminatory power, which are then used to train Machine Learning or Deep Learning models [50,51].

The innovative transition brought about by AI Radiomics culminates in the development of radiogenomics. This hybrid discipline seeks mathematical bridges between noninvasively extracted radiomic features and the tumor's gene expression profile (obtained by RNA sequencing or genomic assays such as Decipher or Oncotype DX).

Currently implemented radiogenomic models use deep neural networks to associate specific textural signatures from mpMRI with key genetic mutations implicated in prostate cancer aggressiveness, such as TMPRSS2-ERG gene rearrangements, loss of the tumor suppressor gene PTEN, or TP53 mutations [52].

Early detection of these molecular alterations directly through computational imaging mapping revolutionizes triage strategies, allowing for the most accurate selection of patients eligible for strict active surveillance, eliminating the need for tedious serial re-biopsies.

These advanced technological solutions pave the way for the widespread integration of radiomics programs into hospital PACS systems, transforming AI Radiomics from a research tool into a standardized clinical pillar of precision medicine.

9. Conclusions and personal contributions

9.1. Conclusions

The investigations undertaken in the framework of this doctoral thesis aimed at the current approach to prostate biopsies for cancer detection, analyzing the effectiveness of different types of procedures, but also the management of complications and difficulties encountered during sample collection.

The doctoral thesis is structured in two distinct parts: ***The general part***, which carries out a critical synthesis of data from the specialized literature to anchor the investigated topic in the current scientific context, and ***The own scientific contributions***, which reflect the original contribution by detailing the working methodology, presenting and discussing the results, and stating the final conclusions.

Chapter 1, entitled "Risk factors and diagnostic markers in prostate cancer: genetic, metabolic, clinical, and imaging perspectives", opens the general part of the work by carrying out a rigorous synthesis of the etiopathogenic elements and the tools for early detection of the disease. In this chapter, molecular mechanisms, hereditary susceptibility and the impact of metabolic deregulation on the links of tumor initiation and progression are extensively investigated. At the same time, the section systematizes the classical and emerging biological markers used in modern clinic, critically analyzing the evolution of imaging algorithms in patient stratification.

Chapter 2, entitled "Epidemiology and histopathology of prostate cancer: from historical evolution to modern classification and the role of immunohistochemistry", continues the theoretical foundation of the work by connecting population dynamics with the microscopic reality of the disease. In its first part, the chapter analyzes global and national epidemiological indicators, highlighting the socio-economic impact and incidence trends of prostate adenocarcinoma. Subsequently, the focus shifts to morphological analysis, making an incursion from the first reference histopathological descriptions to current diagnostic criteria. Special attention is paid to the transition to modern architectural classification systems (Gleason score and ISUP Grade Groups) and the practical utility of immunohistochemistry.

The section dedicated to original scientific contributions is developed over five distinct chapters, the sequence of which reflects the pronounced multidisciplinary nature of the experimental investigations undertaken.

Chapter 3 configures the conceptual and strategic pillar of the original contributions section, marking the transition from theoretical references in the literature to the personal application approach. Within this chapter, the working hypothesis is rigorously defined, clarifying the scientific premises and the reasoning from which the experimental design was started. At the same time, the section systematizes the matrix of general and specific objectives, presenting each investigative stage to be completed. Through this logical structuring, the chapter provides an overview of the architecture of the entire study, ensuring the coherence, convergence and traceability of all subsequent experimental determinations.

Chapter 4 is intended to describe the applied methodology, constituting the procedural pillar of the entire experimental section. Within this section, all the working protocols, analytical systems and experimental techniques put into practice for the implementation of the studies are detailed.

The systematic and detailed presentation of the methods used provides the necessary tools for the validation and interpretation of the original results presented in the following chapters.

Chapter 5, entitled "Current approach to complications and difficulties during prostate biopsies guided by transrectal ultrasound", is designed as a review study, carrying out a critical and exhaustive synthesis of the latest clinical data. This section analyzes in depth the working incidents, the problematic anatomical particularities and the spectrum of complications — from hemorrhagic and painful ones, to major infectious risks — associated with the TRUS procedure. By centralizing and evaluating international guidelines and the literature, the chapter provides an updated perspective on peri-procedural prevention and management protocols.

Chapter 6, entitled "Diagnostic Benefits of the Combined Use of Fusion-TRUS-Guided Biopsy", is dedicated to the presentation of an original retrospective study, providing solid clinical evidence in support of an optimized diagnostic strategy. In this section, clinicopathological data from a cohort of patients are analyzed and correlated, with the aim of statistically evaluating the synergy between fusion-guided MRI-TRUS biopsy and the systematic, randomized approach. The retrospective study rigorously demonstrates how the association of the two techniques maximizes the detection rate of clinically significant prostate adenocarcinoma and substantially reduces the risk of tumor downgrading, providing clear benchmarks for personalizing and calibrating subsequent therapeutic conduct.

Chapter 7, entitled "Single-center analysis of complications of transrectal prostate biopsy", brings a pragmatic and original contribution to the applied section of the thesis, being configured in the form of a clinical study based on case studies evaluated in a single medical center. This section is dedicated to the systematic monitoring and accurate quantification of the incidence, severity and typology of adverse events secondary to the invasive procedure. Both the immediate manifestations of hemorrhagic and painful nature, as well as the post-procedural infectious risks, are analyzed in detail, evaluated in close correlation with the antibiotic prophylaxis schemes implemented locally. By statistically processing these empirical data, the chapter provides a faithful picture of the clinical reality and identifies the predictive factors for the occurrence of incidents, with the direct aim of optimizing periprocedural safety measures and reducing the morbidity associated with TRUS biopsy.

Chapter 8, entitled "Critical Analysis of Study Limitations and Innovative Perspectives", represents the self-reflection and synthesis section of the state of knowledge of the thesis, with the

role of critically evaluating the methodological vulnerabilities of previous research and proposing state-of-the-art technological solutions.

9.2. Personal contributions

A first direction of the experimental approach consisted in carrying out an exhaustive narrative analysis of the specialized literature. This synthesis study, carried out during 2023, was based on a rigorous selection of scientific articles indexed in the PubMed reference database. The literature documentation and query strategy was guided by the combined use of specific key terms, namely "TRUS" (Transrectal Ultrasound) and "prostate biopsy", thus ensuring a faithful mapping of the current clinical evidence regarding this invasive diagnostic procedure.

This section retrospectively synthesizes the research performance, reviewing the points of resistance of the conceptual design, the assumed methodological vulnerabilities and the conclusions with immediate practical applicability in modern urology.

The strength of the study lies in the ability to synergistically analyze both the technical impediments encountered intraprocedurally and the morbidity represented by post-biopsy complications. Beyond the simple inventory of work incidents, the study has a strong applicational character, offering concrete clinical guidelines and adaptive strategies for overcoming and recovering from these adverse events.

Identifying studies focused strictly on technical difficulties during ecoguidance proved to be a laborious endeavor, due to the lack of direct and standardized descriptors or keywords in the specialized literature.

The second research direction materialized in the form of a rigorous retrospective study, dedicated to the comparative evaluation of the diagnostic yield obtained by the imaging fusion technique (MRI-TRUS) versus the classic, randomized biopsy approach. This applied section analyzes clinical performance indicators in the detection of prostate adenocarcinoma, aiming to provide solid evidence in support of the implementation of an integrated and personalized diagnostic algorithm.

This study highlights the complementary roles of systematic randomized and fusion-guided prostate biopsies in improving prostate cancer detection rates. Although the McNemar test did not demonstrate any statistically significant difference between fusion and randomized biopsy when considered independently, the combined approach significantly outperformed each technique used in isolation, highlighting the added diagnostic value of integrating both strategies. These findings

suggest that the use of a single biopsy method risks underdiagnosis, while a combined approach maximizes the detection of clinically significant cancers.

In addition, multivariate analysis confirmed that clinical parameters such as PSA levels, prostate volume, age, and PI-RADS score each contributed independently to cancer prediction, with PSA demonstrating the greatest individual discriminatory power. The absence of significant multicollinearity among predictors reinforces the robustness and interpretability of the multivariate model.

The third research direction focused on the single-center analysis of complications of transrectal prostate biopsy, being conceived as an observational clinical study addressing a critical dimension of patient safety and quality of medical practice in modern urology. This original clinical study was structured around the systematic monitoring and accurate quantification of the incidence, typology and severity of adverse events associated with the invasive TRUS procedure. By retrospectively evaluating the case history from a single medical center, the investigation analyzed the direct correlations between the occurrence of infectious or hemorrhagic complications and the antibiotic prophylaxis protocols applied locally. The data obtained within this experimental axis provide a faithful image of the clinical reality in routine activity, bringing solid arguments for optimizing peri-procedural preventive algorithms and reducing the morbidity associated with biopsy diagnosis.

The fourth research direction is dedicated, in its first part, to the constraints of applied clinical studies, recognizing the impact of the retrospective design in the occurrence of systematic selection and information errors. Also, the limitations derived from the monocentric character of the case study, which may restrict the external validity of the results, are analyzed, together with the technical variability dependent on the operator and the hardware performance of the transrectal ultrasonography (TRUS) equipment used in tissue sampling.

A major point of interest within the critical analysis is dedicated to investigating the diagnostic performance of the PI-RADS v2.1 score, which in the studied group recorded an unexpectedly low value of the discriminative slope (AUC = 0.619) compared to the large international registries. The paper statistically demonstrates that this discrepancy does not invalidate the PI-RADS system itself, but rather reflects a narrowing effect of the clinical spectrum by excluding cases with extended PSA (>25 ng/mL) and eliminating very low-risk lesions (PI-RADS 1-2). This artificial homogeneity of the cohort, amplified by a probable cognitive bias of

medical anchoring at the time of imaging interpretation and by the absence of integration of hidden confounding factors — such as lifestyle, metabolic comorbidities or history of drug therapies with stromal impact (metformin, statins, aspirin) — fully justifies the need to reconfigure the classic diagnostic algorithm.

In direct response to these human visual and interpretive limitations, the second part of the research direction introduces the innovative perspective of Artificial Intelligence-based radiomics (AI Radiomics), defined as a radical paradigm shift in urology and oncology radiology. This computational discipline translates medical imaging from a purely descriptive, qualitative and implicitly subjective assessment, to a high-resolution quantitative science, capable of transforming pixels and voxels into mineable digital databases (high-throughput quantitative features). Radiomics algorithms completely eliminate interobserver variability by automatically extracting thousands of mathematical parameters from multiparametric MRI sequences, providing an objective tissue mapping, capable of isolating subtle biological changes in the prostatic stroma, completely independent of the clinician's visual experience.

Next, the taxonomy of radiomic descriptors (first-order statistics, second-order textural features extracted from the GLCM matrix or higher-order parameters obtained by Wavelet transforms) is detailed and demonstrates how they decode sub-visual tumor heterogeneity. By analyzing the spatial ordering of gray intensities at the voxel level, AI Radiomics achieves a highly accurate predictive correlation with acinar architectural disorganization described by ISUP Grade Groups and Gleason scores. This ability to capture the fingerprint of cellular chaos directly from standardized imaging sequences validates radiomics as a “non-invasive virtual biopsy” tool, capable of preventing geographic sampling errors or the risk of tumor downgrading inherent to standard transrectal biopsies. Finally, the horizon of future clinical research is opened through the prism of radiogenomics and multimodal predictive models, aligned with current standards of precision medicine. The ability of deep neural networks to associate imaging texture signatures with key oncogenic mutations and molecular rearrangements (such as TMPRSS2-ERG fusion or loss of the tumor suppressor gene PTEN) is analyzed, providing an early biological prognosis without the need for serial re-biopsy of patients. The chapter concludes by drawing a technological roadmap, concluding that the synergistic integration of AI Radiomics with clinical-biological and metabolic data represents the optimal solution for overcoming the limitations of conventional

medicine, reducing overdiagnosis and radically personalizing the management of prostate cancer patients.

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