FINAL YEAR PROJECT

VALIDATION OF THE MRI PROSTATE IMAGING FOR RECURRENCE REPORTING ASSESSMENT SCORE - PI-RR

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ACRONYMS AND ABBREVIATION

PCa: Prostate cancer.

PSA: Prostate-specific antigen.

DRE: Digital rectal examination.

MRI: Magnetic resonance imaging.

BCR: Biochemical recurrence.

T2 w: T2-weighted.

DWI: Diffusion-weighted imaging.

ADC: Apparent-diffusion coefficient.

mpMRI: Multiparametric-magnetic resonance imaging.

T1 w: T1-weighted.

DCE: Dynamic contrast enhanced.

PZ: Peripheral zone.

CZ: Central zone.

TZ: Transition zone.

PIRADS v2.1: Prostate Imaging-Reporting and Data System version 2.1.

EAU: European Association of Urology.

TNM: Primary Tumour, lymph Nodes and Metastases.

CT: Computed tomography scans.

PET-CT: Positron emission tomography/computed tomography scans.

PSMA PET-CT: Prostate-specific membrane antigen positron emission tomography /computed tomography scans.

RP: Radical prostatectomy.

RT: Radiotherapy.

EBRT: External beam radiotherapy.

PI-RR: Prostate Imaging for Recurrence Reporting.

NPV: Negative predictive value.

PPV: Positive predictive value.

IDI: Institut Diagnòstic per Imatge.

SPSS: Statistical Package for the Social Sciences.

CEIC: Comitè d'Ètica i Investigació Clínica.

ABSTRACT

Background: The increase in prostate-specific antigen (PSA) levels among patients who underwent treatment for localized prostate cancer (PCa) varies from 27-53%, with the variability depending on the tumor stage or type of treatment (radical prostatectomy or radiotherapy). The use of multiparametric magnetic resonance imaging (mpMRI) to evaluate patients with biochemical recurrences (BCR) is a disputed topic. In 2021, genitourinary radiology experts established the Prostate Imaging for Recurrence Reporting (PI-RR) System, a clinical practice guideline designed to standardize mpMRI acquisition, interpretation, and reporting for patients. The guideline's primary aim is to improve the assessment of patients with recurrent PCa by enhancing diagnostic performance and personalizing treatment.

Objective: The primary aim of this study is to evaluate the efficacy of the PI-RR scoring system in precisely detecting localized prostate cancer via mpMRI in patients with biochemical recurrence and who have undergone radical prostatectomy or radiotherapy.

Design and Methods: This is a bicentric, retrospective, and descriptive study that aims to collect images of patients with BCR who underwent mpMRI, covering the period from September 12, 2013, to November 14, 2023. The images will be interpreted by four radiologists with varying levels of expertise through the utilization of the PI-RR system. The PI-RR score from the reports will be classified as either positive or negative. A PI-RR score of 3 or higher will be considered positive, while a score less than 3 will be negative. The results will then be compared with standard references to compute sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio.

Keys: prostate cancer, biochemical recurrence, multiparametric magnetic resonance imaging, radical prostatectomy, radiotherapy.

1.-INTRODUCTION

1.1.-OVERVIEW OF PROSTATE CANCER

1.1.1.-EPIDEMIOLOGY AND CLINICAL RELEVANCE

Worldwide, prostate cancer (PCa) is one of the most common cancers in men. It is particularly prevalent in developed countries and is, therefore, one of the major concerns of the population. (1)

The global incidence of PCa is estimated to be around 1.4 million in 2020, making it the second most common cancer after lung cancer. However, the prevalence rate indicates that PCa is the most common cancer of all non-cutaneous cancers, with lung cancer in second place, which may be explained by the difference in mortality rates between lung cancer and PCa.

The highest age-standardized incidence rates are found in northern and western Europe, the Caribbean, Australia/New Zealand, north and south America and southern Africa. The lowest incidence is in Asia. The global variation in incidence may be due to differences in screening, imaging, access to care and health care infrastructure. (2,3)

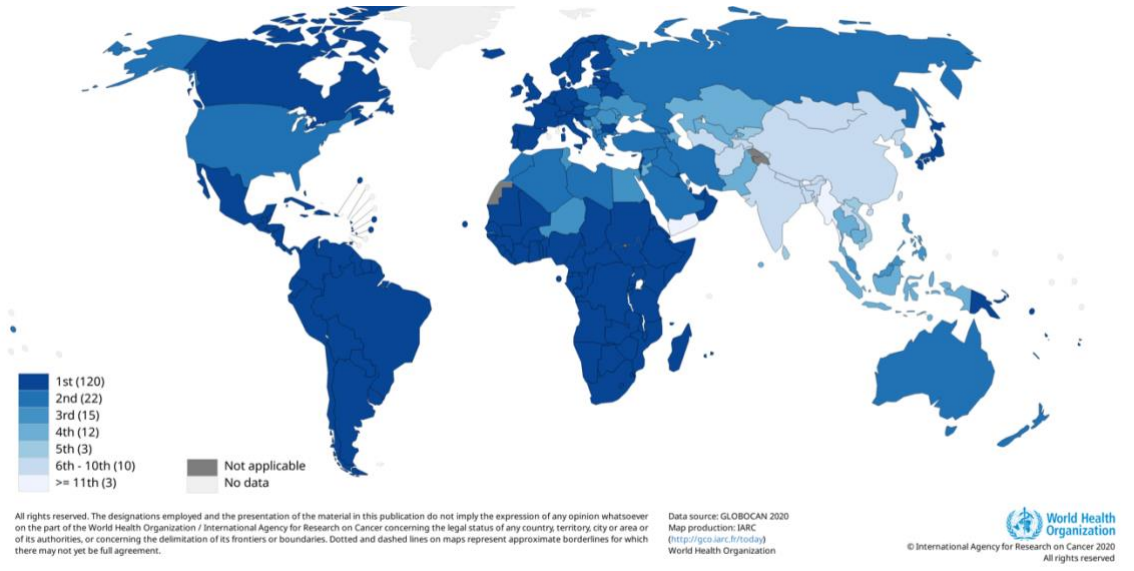

Figure 1.1 *Ranking (Prostate), estimated age-standardized incidence rates (World) in 2020, males, all ages. Obtained from (3).*

In addition, germline genetic factors, life expectancy and lifestyle factors in the population also contribute to geographic differences. Men living in regions with a short life expectancy are more likely to develop and die from competing causes than from PCa,

due to its median age of diagnosis and relatively long natural history. Furthermore, the epidemiological contrast of PCa in northern and southern Europe, which have similar life expectancies, may be influenced by environmental risk factors. The relative importance of these determinants compared to genetic factors is still unknown. (4)

1.1.2.-DIAGNOSTIC MANAGEMENT

1.1.2.1.-CLINICAL MANIFESTATIONS AND PSA SCREENING PROGRAMME

Age is the main risk factor for PCa, the older the age, the higher the risk. The average age at diagnosis is 72 years old. African-Americans are at higher risk for the disease, as well as higher rates of advanced cancer, usually diagnosed at younger ages. (5)

PCa is usually diagnosed in the early stages incidentally or through screening, as patients are usually asymptomatic. As tumours begin to grow, they can cause urinary symptoms like those of benign prostatic hyperplasia. These symptoms include difficulty urinating, straining to start, frequency of urination and nycturia. In advanced stages of the disease, symptoms may include bone pain and pathological fractures, as the axial skeleton is the usual site of metastasis. Patients may also experience fatigue and weight loss, oedema or swelling of the legs, as venous and lymphatic return may be impeded by enlarged lymph nodes, or severe complications such as loss of leg strength due to spinal cord compression in cases where the spinal column is affected. (5,6)

As mentioned above, PCa is now being diagnosed in patients who had no clinical involvement, thanks to prostate specific antigen (PSA) screening programs. PSA is a glycoprotein produced by either benign or malignant cells of the prostate gland, produced specifically by prostate epithelium and periurethral gland. It is important to understand that PSA is an organ-specific protein and not a prostate cancer-specific protein. Therefore, it may be increased in different pathologies or situations that are not necessarily cancer, such as prostatitis and benign pathologies. (5,7)

The fact that PSA has become the most widely used screening test has impacted the incidence and distribution of PCa. In countries where PSA was used as a screening test, there was a significant increase in incidence. Concerns have been raised about the possibility of duration bias arising from early detection of cancer in its asymptomatic

stage, which may result in an apparent increase in survival after treatment. Another screening bias is the detection of slow-growing tumours that may have little to no clinical significance. Therefore, questions remain about the efficiency and effectiveness of PSA screening. (8)

In Catalunya, PSA is no longer used for population screening. However, it can be used in specific cases, for example in patients at higher risk, such as those with a family history. PSA determination is used for diagnosis in case of suggestive symptoms, suspicious examination and in the follow-up of PCa. (9)

1.1.2.2.-DIGITAL RECTAL EXAMINATION

The systematic examination of prostate pathology encompasses digital rectal examination (DRE). Although limited in its effectiveness for detecting early-stage cancer, DRE has the advantage of detecting non-PSA-secreting cancers. Therefore, if a DRE appears suspicious, a biopsy should always be considered regardless of PSA levels. (7,8)

1.1.2.3.-DIAGNOSIS: PROSTATE-SPECIFIC ANTIGEN

Elevated PSA levels are linked to a heightened risk of PCa. Typically, men without PCa portray PSA levels below 4 ng/mL. In case PCa occurs, the PSA level generally exceeds this threshold. However, a PSA level below 4 does not ensure the absence of cancer. Biopsy results indicate that about 15% of patients with a PSA value below 4 have been diagnosed with prostate cancer. Therefore, there is no cut-off point for PSA below which there is no risk of PCa being found on biopsy.

Although there is no universal agreement, it is still advisable to carry out a biopsy if the PSA level exceeds 4 ng/mL, although nowadays the new clinical guidelines recommend performing a magnetic resonance imaging (MRI) before the biopsy. The range between 4 and 10 ng/mL is considered the "diagnostic grey area". In such instances, PSA density, PSA velocity, and the proportion of free PSA can aid in the diagnosis.

As PSA production increases with age, age-adjusted PSA has been developed to improve the specificity of the test. (7,8,10)

1.1.2.4.-TRANSRECTAL ULTRASONOGRAPHY AND BIOPSIES

A prostate biopsy is conducted when prostate cancer is suspected, which currently happens whenever a positive MRI image shows the existence of a concerning lesion during image examination.

Previously, a blind prostate biopsy without prior imaging was performed at risk of sampling error. This can lead to underdiagnosis of aggressive lesions and overdiagnosis of indolent lesions. Therefore, prior imaging with MRI is recommended to guide targeted biopsy in the case of suspicious lesions on imaging.

There are two approaches to prostate biopsy: the transperineal approach and the transrectal approach. Both approaches can be used, although there is evidence that the infection rate is lower with transperineal prostate biopsies, and they are more commonly used in special situations such as rectal thrust. Ultrasound should always be used to guide sampling. Additionally in-bore MRI biopsy can be performed with accurate results to diagnosis prostate cancer. (7,11–13)

There are two types of baseline biopsy: systematic biopsy and/or targeted biopsy. In cases where the MRI scan shows no lesions, a systematic biopsy will be performed whenever there is high risk for prostate cancer. This involves taking samples bilaterally from the apex to the base of the prostate and should be as lateral as possible to give a better representation of the peripheral zone. A maximum of 12 samples is recommended as there is no evidence that more samples increase the detection rate. If lesions are seen on MRI, targeted biopsies may be added. Sampling of the transition zone in basal biopsies should only be done if suspicious lesions are seen in this zone on MRI imaging or in the event of a repeat biopsy.

Once samples have been taken, they should be sent to anatomical pathology for microscopic examination. They should be correctly labelled to indicate the samples taken from the right and left sides of the prostate. (12)

In the histopathological study, in addition to determining the presence of atypical cellularity, the characteristics of the cell, the histological patterns it presents, among others, one of the elements to be determined corresponds to the Gleason scale. The

determination of this scale is important because it is one of the elements used to assess the patient's treatment and risk of biochemical recurrence (BCR) after treatment (both prostatectomy and radiotherapy).

Malignant lesions of the prostate can be very heterogeneous, so the Gleason score is determined by selecting two predominant patterns and assigning a score. The two scores are then added together to give the final Gleason score. For prostate samples with a single predominant pattern, two different malignant areas are examined and the sum of the two gives the final Gleason score. The histological patterns are scored from 1 to 5 according to the malignancy they represent. The Gleason scale is therefore obtained by summing the two scores, which range from 2 to 10. (8,12)

Risk Group	Grade Group	Gleason Score
Low/Very low	*Grade Group 1*	*Gleason Score ≤ 6*
Intermediate (favorable/unfavorable)	*Grade Group 2*	*Gleason Score 7 (3+4)*
	Grade Group 3	*Gleason Score 7 (4+3)*
High/Very high	*Grade Group 4*	*Gleason Score 8*
	Grade Group 5	*Gleason score 9-10*

Table 1.1 *Gleason Scale and International Society of Urology Grade Group System. Obtained from (14)*

1.1.2.5.-CLINICAL USE OF PROSTATIC MRI

1.1.2.5.1.-INTERPRETATION OF PROSTATE mpMRI: RELEVANT ANATOMY AND SEQUENCES

Magnetic resonance imaging (MRI) has been utilized to assess prostate cancer and surrounding structures. Initially, a T2-weighted (T2w) sequence, diffusion-weighted imaging (DWI) sequence, and apparent diffusion coefficient (ADC) map derived from DWI were applied to conduct the morphological analysis of locoregional PCa. This combination of sequences is referred to as biparametric prostate MRI. Today, advanced technologies have led to the development of multiparametric MRI (mpMRI). This combines not only T2w and DWI/ADC sequences, but also T1-weighted (T1w) and dynamic contrast-enhanced (DCE) MRI. (15,16) With all these sequences, the prostate can be assessed not only morphologically, but also functionally. Therefore, mpMRI is used for screening, diagnosis, staging, treatment, and follow-up.

Understanding and interpreting mpMRI sequences is of great importance. Therefore, knowledge of the mpMRI anatomy of the prostate and adjacent organs is essential for accurate interpretation.

The prostate can be divided into the base, which is located at the neck of the bladder, and the apex, which is in the urogenital diaphragm. There are different zones of the prostate: the peripheral zone (PZ), the central zone (CZ) and the transition zone (TZ). The PZ is the largest volume of the prostate and is located behind the base of the prostate and includes the entire apex of the gland. The CZ is conical and lies between the peripheral and transition zones, where the ejaculatory ducts meet. The TZ corresponds to the area of the gland in contact with the urethra. Lastly, the fibromuscular stroma can be seen on mpMRI in the most anteromedial part of the prostate. The majority of PCa (approximately 70%) occurs in the PZ, while 25% occur in the TZ. Only 1% of PCa develops in the CZ. (16–18)

Other relevant extra glandular structures include the bladder, pubic bone, urethral membrane, periprostatic fat and venous complex. In addition, the seminal vesicles, and the vas deferens. (19)

MRI images of prostate in different plans can be found in Annex A.1.

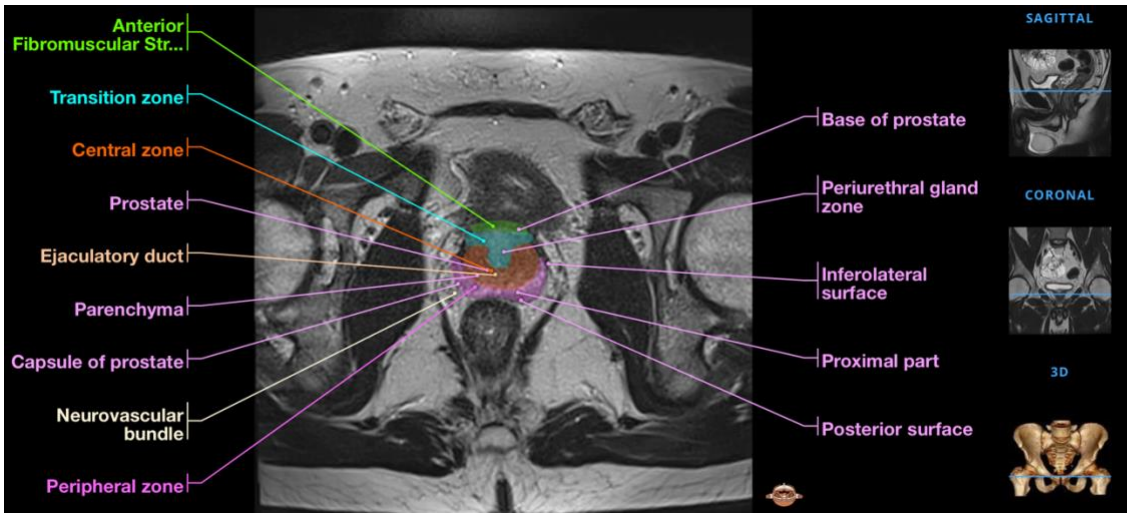

Figure 1.2 *Axial T2-weighted magnetic resonance imaging (MRI) depicts a typical male pelvis at the prostate level. The image shows the prostate's zonal anatomy, which consists of central, peripheral, and transition zones, alongside the fibromuscular stroma. Obtained from (20)*

In the T2w sequence, fluid-containing tissues and structures appear hypertensive. In this sequence is usually not possible to distinguish the CZ from the TZ, so these zones are examined simultaneously. On the other hand, the PZ is easier to distinguish from other zones. It has a signal intensity equal to or greater than the fat or vessels due to the presence of the acinar component and ducts containing fluid. In the T2w sequence, the PZ appears homogeneous. In contrast, the TZ appears heterogeneous due to the presence of hypertensive (glandular) and hypotensive (stromal) zones. Another anatomical landmark to assess is the capsule. The capsule is visualized as a hypotensive line separating the prostate from the fat and periprostatic vessels. Involvement of this area by the cancer can increase staging. This is known as extracapsular extension and its involvement often carries a risk of recurrence. (19)

DWI is diffusion-weighted imaging, which asses the diffusion of water molecules in different tissues. Prostate tissue has a higher diffusion than cancerous tissue because the latter has more compacted cells that impede the passage of water. It is possible to study the diffusion of extracellular fluid, such as blood vessels, as well as intracellular fluid. Different B values are used for this purpose. The B-value corresponds to the degree of the diffusion gradients which can be varied by changing the amplitude of the weighted diffusion gradients. At lower b-values, the movement of water molecules or blood capillaries is enhanced, and at higher b-values, the movement of intracellular fluid is enhanced. Normally, when obtaining DWI sequences, two sequences should be obtained each with a different b-value: b-value 50-1000 s/mm^2.and b-value ≥ 1,400 s/mm^2.

The ADC corresponds to the degree of diffusion of water molecules in the tissue and is calculated from the DWI. This value is automatically calculated by the software, which then produces a parametric map reflecting the degree of diffusion. ADC is expressed in mm^2/s.

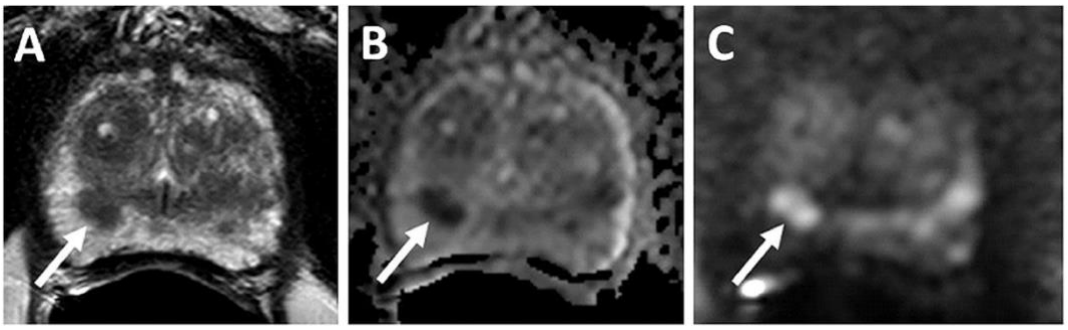

Figure 1.3 *Multiparametric MRI of a 69-year-old man with a PSA of 34.95 ng/mL and the corresponding lesion of the prostate cancer, marked with arrows. (**A**) T2w sequence, (**B**) ADC map, (**C**) B-2000 DWI. Obtained from (21)*

The DCE sequence imaging technique requires the use of contrast, in this case an intravenous bolus of gadolinium. Once injected, serial sequences should be obtained quickly. It is used to assess blood supply, so areas of suspected cancer will show increased enhancement due to angiogenesis. In addition, PCa usually has a larger capillary bed than the rest of the benign prostate parenchyma, so the enhancement of the cancer will appear faster than the rest of the tissue. The use of DCE alone is limited because there are other causes that could have this pattern and therefore give a false positive. (22,23)

The T1w sequence allows us to detect the presence of adenopathy, the presence of osseous metastases, identify subsequent haemorrhage biopsy if present and the analysis of the pelvis. The T2w sequence allows us to evaluate the TZ and the DWI sequence the PZ. Therefore, if there is a suspected lesion in the TZ, the Prostate Imaging-Reporting and Data System version2.1 (PIRADS v2.1) categorization depends only on the T2w sequence, independent of any other criteria from other sequences. This is also the case for suspected lesions in the PZ, where the PIRADS score should be determined from the DWI sequence. The DCE sequence is important in the presence of a peripheral lesion with PIRADS 3 obtained from the DWI sequence; in these cases, focal early enhancement changes the score to PIRADS 4. It is also used in the presence of artefacts on the DWI sequence. (24,25)

1.1.2.5.2.-INDICATION FOR MULTIPARAMETRIC PROSTATE MRI

Several studies have shown that the use of mpMRI can reduce the number of unnecessary biopsies and help diagnose clinically insignificant PCa due to its high negative predictive value. mpMRI has a high diagnostic accuracy for PCa. (16) To

maintain its effectiveness, a clinical practice guideline has been developed to ensure its correct use and to avoid variability in the acquisition, interpretation or reporting of mpMRI prostate scans. This guideline is known as Prostate Imaging-Reporting and Data System version2.1 and is the most recent validated publication.

As mentioned above, mpMRI can distinguish between clinically significant and non-significant PCa. According to PIRADSv2.1, clinically significant findings are defined at histology as: "*pathology/histology as Gleason score > 7 (including 3+4 with prominent but not predominant Gleason 4 component), and/or volume > 0.5cc, and/or extra prostatic extension."* (15)

The PIRADSv2.1. categories are shown in the following table.

$\boldsymbol{PIRADS_1}$**:** Very low (clinically significant cancer is highly unlikely to be present).
$\boldsymbol{PIRADS_2}$**:** Low (clinically significant cancer is unlikely to be present).
$\boldsymbol{PIRADS_3}$**:** Intermediate (the presence of clinically significant cancer is equivocal).
$\boldsymbol{PIRADS_4}$**:** High (clinically significant cancer is likely to be present).
$\boldsymbol{PIRADS_5}$**:** Very high (clinically significant cancer is highly likely to be present).

Table 1.2 *PI-RADS™ v2.1 Assessment Categories. Obtained from (15)*

According to the European Association of Urology (EAU) guidelines, the recommendations for the use of mpMRI are as follows:

- In naive patients (no previous biopsy), mpMRI should be performed before biopsy (level of evidence 1a). If the results of PIRADS are ≥3, a targeted and systematic biopsy should be used to obtain samples. If the results of PIRADS are <3, clinical suspicion needs to be assessed. If there is a high risk of PCa, a systematic biopsy should be performed based on the consensus opinion of the experts.
- In patients with a negative previous biopsy and clinical persistence or progression, mpMRI should be performed prior to biopsy. If PIRADS ≥3, a targeted biopsy should be performed (level of evidence 2a). For PIRADS ≤2, systematic biopsy should be performed, based on the consensus opinion of experts. (26)

1.1.2.6.-CLINICAL WORKUP AFTER CONFIRMATION OF DIAGNOSIS ON BIOPSY

One of the factors considered when choosing a treatment is the extent and boundaries of the PCa. Nowadays, a classification based on T (primary tumour), N (lymph nodes) and M (metastases) is used. The T category is based on clinical examination, imaging results, endoscopy, biopsy, and biochemical tests. Category N is based on clinical examination and imaging. Category M is based on clinical examination, imaging, skeletal assessment, and biochemistry. For the complete table of TNM staging for prostate cancer, please refer to Annex A.2.

For localized cancers, stage is the most important prognostic indicator. There are nomograms that can predict T stage, considering information such as clinical status, PSA levels and the Gleason scale, which is a well-validated tool. The role of MRI in localized cancer is not very reliable, as its sensitivity for detecting extra-prostatic extension is very low. Therefore, the EAU does not recommend its use in low-risk patients, although it can be used for treatment planning in selected patients.

The presence of lymph node involvement can predict tumour extension and therefore progression. The risk of lymph node involvement can also be determined using nomograms, although in this case imaging assessment is very important, especially in patients at high risk of metastasis. Computed tomography (CT) or MRI can be used to assess lymph nodes. Both the size and morphology of the lymph nodes are examined to determine lymph node involvement. A short-axis diameter of 8 mm or more in pelvic lymph nodes and more than 10 mm in extra-pelvic lymph nodes is usually considered to be malignant. A disadvantage of using CT or MRI is their low sensitivity for malignant lymph nodes that are smaller than these sizes and would therefore not be detected. Other imaging tests, such as prostate-specific membrane antigen positron emission tomography /computed tomography scans (PSMA PET/CT), can be used for this purpose. Multicenter trials have shown that the sensitivity of detecting lymph node involvement increases with the use of PSMA PET/CT compared with CT or MRI.

Bone scans are the gold standard for determining bone involvement. If metastases are suspected, an MRI scan may be performed to optimize the morphological assessment. (7,8,12)

1.1.3.-THERAPEUTIC MANAGEMENT

There are several ways to treat PCa. The choice of treatment is based on PSA levels, the Gleason scale and TNM classification, as well as the patient's comorbidities and expectations. Advances in the diagnosis and treatment of PCa have made it possible to stratify patients according to their risk of BCR after treatment (see Table 1.5). This is based on PSA levels, the Gleason score and TNM classifications and is divided into three groups: low risk, intermediate risk, and high risk. It also correlates with the type of cancer, whether it is localized or locally advanced.

The figure in Annex A.3 summarizes the treatment options according to disease progression. The figure shows that for patients with localized disease, the treatment options are active surveillance, radical prostatectomy, radiation in the form of external beam radiotherapy or brachytherapy.

1.1.3.1.-ACTIVE SURVEILLANCE

Active surveillance is a structured program that allows patients at low risk or with a low life expectancy to monitor their neoplastic disease and intervene when indicated. The recommendation to use active surveillance depends on the following factors: disease characteristics, life expectancy, health status, side effects and patient preferences.

1.1.3.2.-RADICAL PROSTATECTOMY

Radical prostatectomy (RP) is a treatment that aims to remove the PCa with the purpose of preserving both erectile function and urinary continence. Prostatectomy involves the full excision of the prostate gland, seminal vesicles, and the ampullary portion of the vas deferens. Followed by the establishment of a vesicourethral anastomosis.

This treatment may be considered for patients with organ-confined cancer who have a life expectancy of more than 10 years and who meet the criteria for surgery. Surgery can be open and/or laparoscopic or robotic assisted. There is no evidence that one approach is better than the other, although minimally invasive approaches result in less perioperative morbidity.

1.1.3.3.-RADIATION: EXTERNAL BEAM RADIATION THERAPY AND BRACHYTHERAPY

Radiation therapy (RT) is one of the most effective treatments for PCa. It is one of the treatments used for patients who are not candidates for surgery. Radiotherapy is a very targeted treatment, so it does not affect much normal tissue. The dose used depends on the size or volume of the prostate cancer.

There are two different techniques - external beam radiotherapy and brachytherapy. External beam radiotherapy (EBRT) is a radiotherapy technique that uses external, targeted radiation. Instead, brachytherapy uses radioactive sources that are placed in the prostate using ultrasound-guided prostate injections. There are two main types: low-dose and high-dose. Low-dose is characterized by a gradual loss of reactivity and permanent implantation. Alternatively, high-dose is a temporary implantation of high-capacity radioactive sources and is usually used in conjunction with external beam radiotherapy. (12,27–29)

1.1.4.-TUMOR RECURRENCE AND FOLLOW-UP: AFTER LOCAL TREATMENT

Post-local treatment follow-up of PCa enables evaluation of treatment compliance, control of short and long-term complications, and potential identification of necessary additional treatments. Various tests are employed to monitor PCa after local treatment.

1.1.4.1.-DIGITAL RECTAL EXAMINATION

The DRE may prove useful in specific scenarios, for instance, when detecting a local relapse after curative treatment in the absence of a concurrent elevation in PSA levels. However, usually, it is not regarded as an effective test for determining biochemical recurrence.

1.1.4.2.-PROSTATE-SPECIFIC ANTIGEN MONITORING

Assessing the importance of PSA levels is crucial as not all PSA increases are equally significant. Follow-up tests rely on PSA levels, which can differ depending on the treatment:

- PSA monitoring after RP: following RP, the PSA level is expected to be undetectable within two months of the procedure. BCR is defined as any rise in PSA after prostatectomy > 0,2ng/mL. Generally, PSA levels are monitored every six months for up to three years and then annually thereafter. However, there is limited evidence regarding a particular timeframe.
- PSA monitoring after RT: the decrease in PSA levels after radiation therapy happens at a slower rate. The Phoenix definition, proposed by the RTOG-ASTRO consensus in 2006, classifies recurrence post radiation therapy treatment as an escalation of 2 ng/mL above the post-treatment PSA nadir (corresponding to the lowest post-treatment PSA level).

Between 27% and 53% of patients who undergo radical prostatectomy or radiation therapy experience a subsequent rise in their levels of PSA, varying base of factors such as stage.

1.1.4.3.-TRANSRECTAL ULTRASOUND, BONE SCINTIGRAPHY, CT, MRI, AND PET/CT

Imaging methods are not commonly employed in the monitoring of PCa unless there was a prior elevation of PSA. Such imaging is only warranted in patients for whom the diagnostic results would significantly impact treatment decisions.

Per EAU guidelines, in instances of suspected recurrence in patients who have undergone radical prostatectomy, it is advised to employ PSMA PET-CT as a diagnostic imaging exam. For individuals who have undergone radiotherapy and are suspected of experiencing a biochemical recurrence, MRI should be the first option, and if any abnormalities are discovered, a PSMA PET-CT scan should follow. Always taking into account if the patients fit for curative salvage treatment. (12,30,31)

Recommendations	Strength rating
PSA recurrence after radical prostatectomy	
Perform PSMA PET/CT if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	*Weak*

In case PSMA PET/CT is not available, and the PSA level is > 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	*Weak*
PSA recurrence after radiotherapy	
Perform prostate MRI to localize abnormal areas and guide biopsies in patients fit for local salvage therapy.	*Weak*
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	*Strong*

Table 1.3 *Guidelines for imaging in patients with biochemical recurrence. Obtained from (12)*

In Josep Trueta Hospital and Santa Caterina Hospital, MRI imaging is often the preferred method for evaluating suspicion of local disease recurrence. This applies to patients who have undergone either radiotherapy or radical prostatectomy.

1.2.-GUIDELINES FOR PROSTATE IMAGING-RECURRENCE REPORTING (PI-RR)

As mentioned, treatments such as radical prostatectomy and radiotherapy are still used as curative intentional treatment for localized PCa. However, between 27-53% of patients experience a biochemical recurrence after treatment. (31) The recurrence of prostate cancer (PCa) hinges on the cancer's histopathological type, its stage, and the treatment implemented. The levels set by the EAU guidelines indicate the presence of biochemical recurrence depending on the type of treatment that the patient received.

After RP, biochemical recurrence is defined as the persistence of PSA levels above 0.2 ng/mL. For RT, biochemical recurrence is defined as PSA levels greater than 2 ng/mL above the PSA nadir (corresponding to the lowest post-treatment PSA level). The persistence of high PSA levels as defined above indicates the risk of persistence of tumor cells at the level of the prostate or prostate bed, or the presence of metastases. Therefore, the correct imaging study in these scenarios is very important to know which patients may benefit from local salvage therapy and to determine the best therapeutic approach. (32,33)

As indicated previously, according to the EAU guidelines, in the case of a biochemical relapse, PET-CT is used as the imaging test for the study if the patient has

received RP. There is no mention of the use of MRI in this case. On the other hand, if the patient has received RT, MRI may be used as the imaging test to detect local recurrence and PET/CT to exclude distant metastases. (12)

There is currently an expert consensus clinical practice guideline called Prostate Imaging for Recurrence Reporting (PI-RR). This guideline has been formulated using existing literature and clinical practice and has been developed to standardize the collection, interpretation, and reporting of MRI data from patients diagnosed with locoregional PCa who have been treated with curative intent and have biochemical recurrence. The PI-RR is intended to assess the probability of recurrence with various MRI imaging sequences, but has not yet undergone clinical validation. (33)

1.2.1.-TECHNICAL MRI SPECIFICATION

The preparation, equipment and protocol used to obtain multiparametric MRI images for PI-RR are like those used for PIRADS. In this case, the T2w sequence should be obtained in three anatomical planes (axial, coronal and sagittal) and contrast should always be used to obtain the DCE sequence, which is one of the most important sequences for the PI-RR score.

In addition, PI-RR requires at least one large field of view sequence from the iliac crest to the pubic symphysis (either T1-weighted or DWI) to assess the presence of lymph nodes or osseous lesions suspicious for metastatic disease. (25,32,33)

1.2.2.-INTERPRETATION AND REPORTING

PI-RR is a system that classifies MRI findings into 5 stages according to the likelihood of recurrence. Stages 1 and 2 correspond to those with a very low or low probability of recurrence. Stage 3 is used when the radiological findings are uncertain. Stages 3 and 4 correspond to a high or very high risk of recurrence. Recurrences after treatment are usually in the same area where the primary tumour was diagnosed, so the criteria are based on anatomical and functional imaging findings. Functional criteria are based on DWI and DCE, which represent the cellularity and vascularity of the tissue, respectively (Annex A.4). On the other hand, T2w is not used as a functional sequence, but as a sequence to define the anatomical part of the prostate zone.

Depending on the treatment the patient has received, one sequence may be more informative than another. In the case of RP treatment, DCE is the most used sequence to determine the PI-RR score, while the DWI sequence is used in inconclusive cases (Annex A.5). On the other hand, both DWI and DCE sequences are dominant in patients treated with RT (Annex A.6).

All radiology reports should incorporate as much clinical information as possible. They should include the location of the tumour lesion, the Gleason scale, the nadir PSA, and the current PSA. The body of the report should detail the suspicious pathological findings, their location and degree of involvement in relation to other organs, and the radiopathological findings of the different sequences. The conclusion of the report should be as clear and assertive as possible and should mention the PI-RR. It is recommended that PI-RR equal to or greater than 3 should be reported adjacent to the site of suspicious findings. Suspicious findings should be described clockwise in the case of post-PR findings. In the case of RT, it is recommended to follow the same description model as for PI-RADS. (25,33)

1.2.3.-mpMRI AFTER RADICAL PROSTATECTOMY AND RADIOTHERAPY

To accurately interpret MRI scans for suspected local recurrence in treated patients, one must consider the alterations to the prostate and surrounding tissues following both radical prostatectomy and radiotherapy. The changes in anatomy are crucial to consider to ensure precision and objectivity in the interpretation of the scans.

MRI images following radical prostatectomy reveal significant post-surgical changes that require attention. As many as 20% of patients may exhibit remnants of seminal vesicle or residual glandular tissue, which may mimic recurrent disease on imaging, but typically lacks restringing diffusion of the DWI/ADC sequences or early enhancement of the DCE sequence. Shortly after surgery, there may be hyperintense signal on T2-weighted because of an inflammatory element in the surgical bed. This is a natural occurrence and should not be a cause for concern.

Following surgical intervention, tumour recurrence typically occurs at the vesicourethral anastomosis, in the retro-vesical area or at the bladder neck. It is therefore imperative that these regions are closely monitored for potential recurrence.

Post-operative local recurrences manifest as lobulated soft tissue masses, typically exhibiting hyperintensity on T2-weighted images, early contrast enhancement on DCE, high signal on DWI, and low signal on ADC maps.

At times, the assessment of DWI images can be hindered by artefacts produced by surgical clips. Therefore, it is imperative to compare results from all sequences. The DCE sequence aids in distinguishing between a suspicious lesion and fibrous tissue, as the first one will exhibit early enhancement.

Cancer recurrence in a patient who underwent radiotherapy typically occurs in the area where the primary lesion was initially identified. Radiation therapy can induce changes in the prostatic anatomy, such as reduced volume and signal density, as well as complexities in distinguishing between benign and malignant tissue. Moreover, after brachytherapy, implanted seeds might manifest as dispersed signal voids, creating an artefact that difficult accurate image interpretation.

Images taken immediately after radiotherapy can be misleading when assessing tissue vascularity. Following radiotherapy, it is typical for tissue to undergo inflammatory changes that can result in an increase in vascularization depicted by DCE sequence, resulting in a false positive result. As such, MRI image capture should occur three months post-RT.

Local recurrence following radiotherapy presents as an abnormality with slightly lower T2w intensity in comparison to atrophic prostatic tissue. It exhibits a hyperintense signal on DWI coinciding with a hypodense area on ADC maps, and an early contrast enhancement on DCE images. (29,32)

Another aim of the PI-RR since its establishment has been to minimize inconsistencies in radiological interpretation. Hence, validation for its application is imperative.

2.-JUSTIFICATION

Treatment with curative intent is a favorable recommendation for patients diagnosed with localized prostate cancer. However, there is a substantial likelihood of biochemical relapse among 27-53% of individuals, which increases according to their cancer staging.

Prostate-specific antigen (PSA) levels serve as an essential prognostic indicator for predicting the likelihood of recurrence following treatment. As per the clinical practice guideline of European Association of Urology (EAU), patients who have undergone radiotherapy (RT) will be considered to have a biochemical recurrence if their PSA level at nadir PSA is more than 2 ng/mL. For patients who have undergone radical prostatectomy (RP) and have a PSA higher than 0.2 ng/mL, imaging is recommended to detect suspected recurrence. Therefore, to confirm or rule out tumour recurrence, an imaging method is always necessary.

The EAU recommends using positron emission tomography/computed tomography scans (PET-CT), preferably prostate-specific membrane antigen PET/CT (PSMA PET-CT), to detect suspected recurrences in patients treated with RP, and magnetic resonance imaging (MRI) to detect those treated with RT. This makes the role of MRI as the preferred imaging technique for assessing local recurrences controversial. In 2021, Prostate Imaging for Recurrence Reporting (PI-RR) was established to standardize the acquisition and reporting of local recurrence in biochemical recurrence (BCR) patients using multiparametric-magnetic resonance imaging (mpMRI).

Ciccarese et al and Bergaglio et al have conducted studies to validate the PI-RR. Despite their expert radiologist evaluation of individual cases, these studies are limited to a single center and require further validation. (31,34)

Therefore, the main objective of this study is to validate the PI-RR by evaluating the accuracy of mpMRI in identifying localized recurrence of PCa. This will involve calculating sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and likelihood ratio. The study's second purpose is to establish if PI-RR bears equal validity in patients treated by RT and RP and to evaluate the interobserver agreement between experts with diverse levels of expertise.

3.-HYPOTHESIS

The PI-RR is an effective system for scoring MRI in the evaluation of patients with locoregional PCa, treated with radical prostatectomy or radiotherapy and who have biochemical recurrence according to PSA levels described in the European Association of Urology (EAU) guidelines. This will improve diagnosis and therefore patient management by individualizing treatment.

4.-OBJECTIVES

4.1.-MAIN OBJECTIVE

The aim of the study is to validate the PI-RR scoring system to assess the diagnostic accuracy of MRI in the local detection of PCa recurrence in patients treated with radical prostatectomy or radiotherapy, who present biochemical recurrence according to the PSA levels described in the European Association of Urology (EAU) guidelines.

4.2.-SECONDARY OBJECTIVES

To determine whether the use of the PI-RR system is equally valid in patients treated with RT and those treated with RP, as the radiological anatomy is altered after these treatments and radiological assessment may be different.

To determine whether the use of PI-RR can reduce the variability in the delivery of a radiological result between radiologists with different levels of expertise.

5.-MATERIAL AND METHODS

5.1.-DESIGN OF THE STUDY

This will be a retrospective descriptive bicentric study. A sample will be selected based on the inclusion and exclusion criteria listed below from two main institutions: Josep Trueta Hospital and Santa Caterina Hospital. The sample will correspond to patients diagnosed with localized PCa who had biochemical recurrence after treatment (radiotherapy or radical prostatectomy) and underwent a mpMRI study. The PSA levels used by EAU as an indicator of recurrence are different for each treatment, so the selection of the sample will be stratified into two main groups. However, the images from both groups will be analyzed, interpreted, and reported together.

The images will be analyzed independently by professional radiologists with varying levels of expertise. Each radiologist will assess the different MRI sequences, specifically Tw2, DWI/ADC and DCE, using the PI-RR criteria. Afterward, a report will be produced by each radiologist detailing their PI-RR score.

The results will be validated using diverse resources, with only one of them needing fulfillment.

The criteria for confirming a true positive result:
- PET-CT confirms the presence of the lesion. - Reducing PSA levels after applying salvage treatment. - Obtaining a positive biopsy of PCa after mpMRI.
The criteria for determining a true negative result:
- PET-CT positive at a site other than the initial site of the primary tumour (bone or lymph node metastases), the first to be treated will lower the PSA. - Spontaneous PSA declines without treatment. - Obtaining a negative biopsy of PCa after mpMRI.

Table 1.4 *Reference standard definition. Obtained from (31,34)*

5.2.-STUDY POPULATION

The research sample will comprise men who have experienced biochemical recurrence based on the PSA level and meet the EAU criteria, and have additionally completed an mpMRI assessment. Participants will be selected from two hospitals: Hospital Josep Trueta and Hospital Santa Caterina.

5.2.1.-INCLUSION CRITERIA

Inclusion criteria will be:

- Patients who have undergone complete follow-up at the above institutions with an MRI examination: Josep Trueta Hospital and the Santa Caterina Hospital.
- Patients diagnosed with localized cancer. Localized cancer is defined as:

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL GS < 7 (ISUP grade 1) And cT1-T2a*	PSA 10-20 ng/mL GS 7 (ISUP grade 2/3) Or cT2b*	PSA > 20 ng/mL GS > 7 (ISUP grade 4/5) Or cT2c*	Any PSA Any GD (any ISUP grade) cT3-4* or cN**
Localized			**Locally advanced**

GS: Gleason Score; ISUP: International Society of Urological Pathology, PSA: prostate-specific antigen.

***Based on digital rectal examination.**

****Based on CT/bone scan**

***Table 1.5** EAU risk groups for biochemical recurrence in localized cancer and locally advanced prostate cancer. Obtained from (12)*

- Patients diagnosed with localized PCa treated with radiotherapy and suspected of biochemical recurrence: PSA levels greater than 2 ng/mL above PSA nadir.
- Patients diagnosed with localized PCa treated with prostatectomy and suspected of biochemical recurrence: persistence of PSA levels above 0.2 ng/mL.

5.2.2.-EXCLUSION CRITERIA

Exclusion criteria will be:

- Patients who have been diagnosed with locally advanced prostate cancer, which is defined as: cT3-T4 cN+ (based on digital rectal examination and CT/bone scan) with any PSA value and Gleason score. See Table 1.5.
- Patients who missed their follow-up appointments at the center or who had an inadequate MRI scan that did not conform to the proposed PI-RR imaging protocol.
- Patients who have undergone MRI imaging within three months of their last radiotherapy session.
- Patients who have received salvage therapy before imaging.
- Evidence of recurrence outside the prostate bed on mpMRI images: systemic recurrence or intrapelvic lymph node involvement.

5.3.-SAMPLE

The sample will be obtained through a descriptive and retrospective non-probabilistic sampling technique. Patients who underwent mpMRI for BCR suspicion after undergoing RT and RP and met the inclusion and exclusion criteria will be selected from the Institut Diagnòstic Imatge (IDI) database. The sample will be taken from the primary institutions, specifically the Josep Trueta Hospital and Santa Caterina Hospital, during the period of 12th September 2013 to 14th November 2023.

The sample size was determined using Clin-Calc's sample size and power calculator (version 2023), resulting in an anticipated sample size of 153 patients with an accepted alpha risk of 0.05 and a power of contrast of 80%.

5.4.-VARIABLES

5.4.1.-STUDY VARIABLES

5.4.1.1.-PRINCIPAL OUTCOME VARIABLES

The primary variable study is the occurrence of local recurrence in patients with BCR treated through RP or RT. The presence or absence of this effect will be assessed by the participating radiologists through studying the mpMRI images and utilizing the PI-RR guide.

To establish the validity of the results obtained using PI-RR, they will be compared to the corresponding reference standards, which include PET-CT reports, biopsy reports or PSA levels after salvage treatment or not, as described in Table 1.4. This will enable the calculation of sensitivity, specificity, NPV, PPV and likelihood ratio.

The variable will be measured as a dichotomous qualitative variable: a score of PI-RR < 2 will be considered a negative outcome, while a score of PI-RR ≥ 3 will be considered a positive outcome.

5.4.1.2.-SECONDARY OUTCOME VARIABLES

The secondary results of the corresponding analyses will be:

- Previous treatment: determining whether there is a discrepancy in the accuracy and efficacy of the PI-RR system in detecting recurrence using mpMRI among patients who underwent RT or RP.
- Concordance among readers: will be determined if there is an inter-reader agreement.

5.4.1.3.-COVARIATES

The identified variables have the potential to act as interaction factors in determining the probability of local PCa recurrence in BCR patients using the PI-RR system. As a result, they will be considered during the statistical analysis:

- Age: the mean and SD will be calculated for the patient's age in years.
- Biochemical recurrence risk group: Table 1.5 will be used to determine the patient's risk classification based on PSA values, Gleason score, and TNM staging according to the EAU.
- PSA levels of biochemical recurrence: the mean and SD will be calculated for the patient's PSA levels before MRI.

- Previous treatment: it corresponds to a categorical qualitative variable, which is described as either RP or RT.

	Variable	Type	Categories Of Value
Independent	Local recurrence determinate by PI-RR score.	Dichotomic qualitative	Positive Negative
Dependent	PET-TAC report	Dichotomic qualitative	Positive Negative
	Biopsy report	Dichotomic qualitative	Positive Negative
	PSA values following mpMRI	Dichotomic qualitative	Positive Negative
	Concordance among readers	Dichotomic qualitative	Yes No
Covariates	Age	Discrete quantitative	Numerical (years)
	Biochemical recurrence risk group	Categorical qualitative	Low risk Intermediate risk High risk
	PSA levels of biochemical recurrence	Continuous	
	Previous treatment	Categorical qualitative	RP treatment RT treatment

Table 1.6 *Description of variables included in the study.*

5.5.-METHODS OF MEASURING

5.5.1.-DATA COLLECTION

The project will require various highly skilled professionals, among them an administrator who will function as a data coder, responsible for collecting and coding the essential information for the project.

MRI images of patients participating in the study will be acquired from the IDI databases of two institutions - Hospital Josep Trueta and Hospital Santa Caterina. Verification of image acquisition will be based on the criteria outlined in the PI-RR system protocol. Images not meeting the acquisition protocol will be excluded based on the specified exclusion criteria.

The images to be collected from the database shall be T2w sequences in axial, coronal, and sagittal planes, as well as axial images from DWI/ADC sequences and axial images from DCE sequences with contrast (3ml/s of intravenous contrast). These images must have been obtained using scanners with a minimum power of 1.5T. The sequences should cover the entire prostate gland or vesicourethral anastomosis, seminal vesicles if present, and pelvic nodes. To achieve a match, all sequences must have been obtained in the same plane.

The technical parameters to be met for each mpMRI sequence are as follows:

- T2w: should have been acquired with a slice thickness of 3 mm no GAP, and a field of view of 1-20 cm.
- DWI: should have been obtained with a slice thickness $\leq$ 4 mm no GAP, with a field of view of 16-22 cm. It is crucial to verify the presence of sequences acquired via multiple b-values ranging from 50 to 1000 s/mm^2. Furthermore, it is imperative to recollect a sequence with a high value, at least $\geq$ 1400 s/mm^2. The ADC map should have been determinate using multiple b-value that are less than 1000 s/mm^2.
- DCE: images should have been acquired both before and during contrast administration. The administration of gadolinium contrast ought should have been at a 3 s/mL rate. To visualize early tumour uptake, a high temporal resolution of less than 15 seconds it is needed. The images should have been obtained in slice of 3 mm no GAP, and should have been performed three months from the last RT.

The rest of clinical data will be collected using the IDI and SAP database. Some of the data will be used as a reference standard for the study:

- Primary tumor location.
- Stage and Gleason score of the primary tumour.
- PSA levels: nadir PSA level, biochemical recurrence PSA level, post mpMRI PSA level.
- PET-CT reports (including choline PET-CT, PSMA PET-CT fluciclovine PET-CT). It will be dichotomized as either negative or positive depending on the clinical report.
- Transrectal biopsy reports for the lesion that have been acquired less than three months following mpMRI. The biopsy results will be categorized as either positive or negative, based on the conclusions from the report.

After data collection, it will be stored in an initial database. Subsequently, an additional database will be created by the administrator to contain patient information coded for anonymity. Access to this database will be restricted to researchers exclusively, ensuring participant confidentiality.

The examination of mpMRI images will be conducted independently by two resident radiologists in their second (reader 1) and fourth year of residency (reader 2) and two assistant radiologists with five (reader 3) and ten years of experience (reader 4), respectively. They will not be blinded to following clinical and pathological data: the initial tumor location, stage, Gleason score, nadir PSA levels, PSA levels of biochemical recurrence and type of treatment have been used in the patient. They will not have access to the rest of the data to ensure the outcome of the study.

5.5.2.-mpMRI INTERPRETATION AND OBTAINING THE PI-RR SCORE

The PI-RR system will evaluate, clarify, and summarize findings found in MRI scans. A score from 1 to 5 will be given, with a higher score indicating a higher probability of recurrence:

- Lesions scoring 1 to 2 will be classified as having a very low or low chance of recurrence, correspondingly.
- Uncertain lesions indicative of recurrence will receive a score of 3.
- Scoring 4 to 5 will be assigned to lesions with high or very high chance of recurrence, respectively.

The T2-w sequence will not be utilized for determining PI-RR. Instead, it will be employed to provide anatomical information on the suspected area. The DWI/ADC and DCE sequences shall be utilized for assessment purposes. The scoring criteria is presented in Annex A.4 and applies to both RP and RT.

The variation in obtaining the PI-RR scores between RP and RT will be dependent on the sequencing application. For RP, the dominant sequence will be DCE and DWI will be used in specific cases. Conversely, for RT, both DCE and DWI will be used as the dominant sequences. See Annex A.5 and Annex A.6.

If two lesion areas coincide, only the lesion with the higher PI-RR score will be taken into consideration.

5.5.3.-REPORTING ACCORDING TO PI-RR

Each MRI of the prostate examined by every radiological professional must be reported following the PI-RR criteria. As stated in the Interpretation and Reporting section, it is imperative to provide maximum clinical information in reports. This includes the primary tumour's location, Gleason score, stage of the primary tumour, type of treatment, nadir PSA levels, and PSA levels of biochemical recurrence.

The report will present the findings uncovered from various sequences, along with the corresponding PI-RR score. The position of the suspicious area, its relation to the remaining parenchyma, adjacent organs and their dimensions will be described. Furthermore, any absence of suspicious lesions on MRI or extra prostatic involvement will be stated.

Lastly, the report's conclusion will provide the location of detection and the PI-RR score. The description of the watch face shall be employed to determine the location of post-RP suspected lesions, and the PIRADS guideline recommendation will be used for post-RT findings. An example of a template to be used for the report can be found in Annex 1.7 to avoid missing information.

6.- STATISTICAL ANALYSIS

A professional statistician from our team group will conduct the statistical analysis using the Statistical Package for the Social Sciences (SPSS) software. Significance will be determined using a p-value of less than 0.05 for all analyses, and a 95% confidence interval will be applied.

6.1.- UNIVARIATE ANALYSIS

First, a descriptive analysis of the variables will be carried out and presented in a table. The study will utilize mainly qualitative and categorical variables, and percentages will accordingly be employed. For continuous variables, measures such as mean$\pm$standard deviations will be utilized.

6.2.- BIVARIATE ANALYSIS

In the bivariate analysis, it is crucial to meet all three objectives of this study.

The primary goal is to validate the diagnostic system that corresponds to the PI-RR system. To achieve this, we will calculate sensitivity, specificity, NPV, and PPV. The primary outcome variable is a dichotomous qualitative variable that can be classified as either positive recurrence or negative recurrence. A PI-RR score of less than 2 will indicate negative recurrence results while a score of 3 or above will indicate positive results. A table can be created to categorize the data into four groups: true positive, true negative, false positive, and false negative. Using these groups, sensitivity, specificity, PPV, and NPV can be calculated.

This table displays the results obtained with the use of the PI-RR score in the columns and the results of the reference tests in the rows.

PI-RR final score	Standard reference test	
	Positive for recurrence	Negative for recurrence
Positive for recurrence	True positive	False positive
Negative for recurrence	False negative	True negative

Table 1.7 *Statistical analysis: Table*

$$\boldsymbol{Sensitivity} = \frac{True\ positive}{(True\ positive + False\ negative)}\ x\ 100$$

$$\boldsymbol{Specificity} = \frac{True\ negative}{(False\ positive + True\ negative)}\ x\ 100$$

$$\boldsymbol{Positive\ predictive\ value\ (PPV)} = \frac{True\ positive}{(True\ positive + Flase\ positive)}\ x\ 100$$

$$\boldsymbol{Negative\ predictive\ value\ (NPV)} = \frac{True\ negative}{(False\ negative + True\ negative)}\ x\ 100$$

Finally, to fulfill the main objective, the calculation of the likelihood ratio will be carried out. This measures how much more likely a particular result is (positive or negative) depending on the presence or absence of disease. We will proceed to calculate:

$$\boldsymbol{Positive\ likelihood\ ratio} = \frac{Sensitivity}{(1 - Specificity)}$$

$$\boldsymbol{Negative\ likelihood\ ratio} = \frac{(1 - Sensitivity)}{Specificity}$$

With likelihood ratio and a nomogram, it will be possible to calculate the post-test probability, given a pretest probability.

One of the secondary objectives is to assess the equivalence of PI-RR usage in patients who have had surgery versus those who have undergone radiotherapy. Therefore, a subgroup analysis will be conducted considering the therapeutic interventions previously undertaken, to determine sensitivity, specificity, PPV, and NPV for each one of them. For this purpose, the same type of data tables used in the previous analysis will be redone.

As a last objective to be fulfilled, the agreement of readers will be evaluated through the Gwet kappa statistical analysis, and only for the final PI-RR score.

Stratification by covariables will be applied to identify any potential interference that could modify the result.

7.-ETHICAL ASPECTS

Before starting the research, we will submit this protocol to the "Comitè d'Ètica i Investigació Clínica" (CEIC) of the Josep Trueta Hospital for review and approval. The committee's suggestions will be duly considered. Once approved, the project will start.

This study will adhere to the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (2013 version) and the ethical principles of Beauchamp and Childress. All ethical principles will be strictly followed throughout the research process:

- **Autonomy:** the required information for this project will be extracted from the IDI database. Informed consent will not be obtained in this case due to the significant burden it may place on the research study. However, pseudo-anonymization will be carried out to process the data. One administrative staff member from the health sector in our research team will act as data coder and create an initial database that includes patient information. The next step involves coding each person's data separately into a different database. The trial researchers will access the second database while ensuring confidentiality and data security. Participants' information will be stored securely without any re-identification, unless it poses a potential threat to the patient's health.

- **Beneficence:** the inclusion criteria have been described with the intention of including the patients who will benefit most from the study. The study has substantial potential for producing valuable data that could enhance the care of patients with biochemical recurrence of prostate cancer. Improvements in the diagnosis of PCa recurrence could result in personalized treatment as a benefit for those patients.

- **No maleficence:** patients who meet the exclusion criteria will be excluded from the project as they would not benefit from the study.

- **Justice:** all patients who meet the inclusion and exclusion criteria will receive equal consideration for participation in the study, guaranteeing fairness and impartiality among individuals.

This study will be conducted in accordance with the following laws:

- "**Reial decret legislatiu 1/2015 de 24 de juliol, pel qual s'aprova el text refós de la Llei de garanties i ús racional dels medicaments i productes sanitaris**."
- "**Llei Orgànica 3/2028 de 5 de desembre, de Protecció de Dades Personals i garantia dels drets digitals**."

The purpose of this investigation is to provide new knowledge that can enhance human wellbeing and quality of living. The study will be registered, and, upon completion, the findings will be transparently and clearly published. Unfavorable data will not be excluded. All researchers who participated in the project will declare that they have no conflict of interest.

In this study we will not proceed to contract an insurance company as it corresponds to a study with a low level of intervention.

8.-STUDY LIMITATIONS

The design of this study may have the following limitations:

- This study, based on a retrospective analysis, has limitation in obtaining a standard reference test to validate the images. Therefore, a selection of heterogeneous parameters, including post-imaging PSA levels, PET-CT reports, or biopsy reports, listed in Table 1.4, will be used as a standard reference. To be more precise, all mpMRI analysis results should be compared with PSMA PET-CT results, but not all patients will have these reports available, and this may affect the sample size, which could be smaller. It was determined that conducting a prospective study comprising of PSMA-PEC/CT imaging examinations was not feasible due to the high financial costs associated with the investigation and the difficulty of obtaining the sample, given that it would take time to recruit.

- Another limitation of the study is the potential for selection bias due to also its retrospective nature. The selection will be made using non probabilistic method, which will not be randomized and will have strict inclusion and exclusion criteria. This could limit the generalizability of the findings to the wider population and may limit the ecological validity. Furthermore, it is important to note that the sample will be taken from an IDI database, which may not provide an equal representation of patients treated with radiotherapy and those treated with radical prostatectomy.

- An effort will be made to prevent information bias by blinding the radiologists involved in the study. Nevertheless, they will receive data on the initial tumour location, Gleason score, stage of the primary tumour and PSA levels (PSA nadir and PSA levels of biochemical recurrence). It will also aim to prevent any loss of information in the image report that will be made after evaluation of the mpMRI, through the implementation of a standardized reporting system.

9.-WORKING PLAN AND CHRONOLOGY

9.1.-RESEARCH GROUP AND ASSOCIATED STAFF

This study will be conducted through our research group, consisting of:

- General coordinators (GC): Kai Vilanova and Kaouthar Aknaf will supervise and direct the team throughout various research stages, ensure deadlines are met, and facilitate proper communication between all professionals involved.
- Four radiologists will be affiliated with Hospital Santa Caterina and Hospital Josep Trueta, consisting of two resident radiologists (RR) and two expert radiologists (ER).

The staff to be recruited from outside the research group comprise:

- One health administrator (ADM) will collect the data samples and code each participating patient, serving as our data coder.
- A professional statistician (ST) who will conduct statistical analysis.

9.2.-STUDY STAGES

This study will comprise five stages, scheduled to occur within a 26-month time frame:

PHASE 1: COORDINATION, PROTOCOL DESIGN AND ETHICAL APPROVAL

This phase will last 5 months, from November 2023 to March 2024.

A thorough bibliographic search will be carried out to determine the main hypotheses and objectives, from which the protocol will be constructed and shaped. This procedure will occur during the initial one month and will be executed by the GCs.

The selected reference hospital will be contacted to submit the protocol to the “Comitè d'Ètica i Investigació Clínica” (CEIC) for review and approval. During this process, any suggestions will be considered and, if necessary, the protocol will be re-evaluated and revised for approval. This process may take up to three months.

In the final month of this phase, meeting will take place with the entire team, including radiologists (ER, RR), administrative (ADM) and statistical (ST) staff, to determine individual responsibilities and synchronize the study. During these meetings, the study's objectives, inclusion and exclusion criteria, selection of the sample,

completion of the two databases, and, most importantly, interpreting the mpMRI sequences and reporting according to PI-RR will be elucidated. They will receive regular supervision throughout the research process to evaluate the study's progress in scheduled meetings.

PHASE 2: DATA COLLECTION AND CODIFICATION

This phase will last 5 months, from April 2024 to August 2024.

Patients who meet the inclusion and exclusion criteria will be chosen from the Institut Diagnostic Imatge database. A retrospective search of patients will cover the past decade, from 12 September 2013 to 14 November 2023. The selection will be made with assistance from healthcare administrator, while GC will provide guidance throughout the process.

After selecting the sample, ADM will collect the clinical information necessary for the study under the supervision of the GC. The gathered data will be stored in a primary database which will be encoded in a secondary database to ensure anonymity. Once complete, the GC will be granted access to the second database. Radiologists will only have access to mpMRI images and clinical data, which includes the initial tumor location, stage, Gleason score, nadir PSA levels, PSA levels of biochemical recurrence and the treatment have been used in the patient. They will be blinded to any other information to ensure the validity of the results. The statistician will be granted access to all the data from the second database to conduct the analytical study.

PHASE 3: EVALUATION, INTERPRETATION AND REPORT ISSUANCE

This phase will last 9 months, from September 2024 to May 2025.

This phase of the study is crucial. The first month involve initial meetings with ER and RR to provide guidance on the application of the PI-RR system. The sequences to be utilized will depend on the patient's previous medical treatment, such as prostatectomy or radiotherapy, and will be explained in detail including how to obtain an accurate score through interpretation. Finally, the most significant aspect of the training will be how to craft the final report in accordance with PI-RR guidelines. Throughout the entire phase, there will be supervision in addition to the scheduled meetings.

The interpretation and reporting phase will span over an extended period of 9 months.

PHASE 4: STATISTICAL ANALYSIS AND INTERPRETATION OF THE RESULTS
This phase will last 4 months, from June 2025 to September 2025.

Statistical analysis will be carried out by the ST over a period of one month. Upon completion of the analyses, a meeting will be scheduled between the ST and the GC to interpret the results. This process is expected to take one month. The research team, consisting of the GC, ER and RR, will then discuss the outcome of the analysis and write the final report. The report will detail the results and conclusions of the study. This process will take two months.

PHASE 5: PUBLICATION AND PUBLICATION OF THE RESULTS
This phase will last 3 months, from October 2025 to December 2025.

The results of the clinical trial will be made public after the study is concluded. They will be submitted to a range of medical journals and magazines for publication, and the ultimate report will be presented at National Congress conferences. This phase will be carried out mainly by GC, ER and RR.

STAGES	STAFF	2023		2024												2025											
		N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
STAGE 1: COORDINATION, PROTOCOL DESIGN AND ETHICAL APPROVAL																											
Protocol design	GC																										
Ethical approval	GC, CEIC																										
Coordination	GC, ER, RR, ADM, ST																										
STAGE 2: DATA COLLECTION AND CODIFICATION																											
Sample recruitment	GC, ADM																										
Baseline data collection	ADM																										
Code generation	ADM																										
STAGE 3: EVALUATION INTERPRETATION I REPORT ISSUANCE																											
Training on PI-RR guidelines	GC, ER, RR																										
Evaluation, interpretation of mpMRI and report	ER, RR																										
STAGE 4: STATISTICAL ANALYSIS AND INTERPRETATION OF THE RESULTS																											
Statistical analysis	ST																										
Interpretation of the results	ST, GC																										
Final report elaboration	ST, GC, ER, RR																										
STAGE 5: PUBLICATION AND PUBLICATION OF THE RESULTS																											
Paper publication	GC, ER, RR																										
Diffusion	GC, ER, RR																										

***Table 1.8** Study chronogram.*

GC: General coordinators / **ER:** Expert radiologists / **RR:** Resident radiologists / **ADM:** Administrator / **ST:** Statistician

Research team meetings General coordinators meeting

10.-BUDGET

10.1.-NON-INCLUDED BUDGET

The research group will conduct their research during regular hospital hours and will not receive any financial compensation.

The data collected for this study will be retrospective, with tests having been previously performed, obviating the need for instrumentation. Therefore, the materials section does not include any costs associated with clinical tests, which are minor expenses for the study.

10.2.-INCLUDED BUDGET

To gather the required sample and clinical data for the project, one administrative staff member from the health sector will be employed. This task is estimated to take 160 hours and each hour will cost 40€. Lastly, a statistical analyst will be hired for roughly 70 hours, with each hour costing 40€.

Finally, it is essential to consider the expenses of the meetings scheduled for the project. The total number of meetings scheduled is three, with a projected cost of 300€.

Once the study is completed, the results will be published in three scientific journals, each of which will charge a fee of 1000€ for publication. Following publication, the two responsible GCs will attend national and international conferences for dissemination purposes. The estimated cost for these conferences is 6000€.

Item	Amount	Price	Subtotal
Staff costs			
Main investigators	-	0€	0€
Radiologists	-	0€	0€
One healthcare administrator	160 hours	40€/hour	6400€
Statistical analyst	70 hours	40€/hour	2800€
Transportation, accommodation, and other expenses	-	-	300€
Publishing expenses			
Journals and magazines	Three	1000€	3000€
Presentation expenses			
Inscriptions to congresses, travel costs, accommodation, and meals	Main investigators (two attendants)	National congress: 1000€ International congress: 2000€	6000€
Total			**18.500€**

Table 1.9 *Budget.*

11.-CLINICAL IMPACT

Recurrence of prostate cancer in patients who underwent curative treatment for localized cancer is estimated to range from 27-53%. The variability of this estimate is dependent on the stage of the tumor and the type of treatment used, specifically radiotherapy or radical prostatectomy. Currently, clinical practice guidelines recommend the use of PET-CT for diagnosing recurrent cancer in patients treated with radical prostatectomy, and the use of MRI for patients treated with radiotherapy, followed by PET-CT. However, no clear indication for imaging is provided.

The lack of standardized indications for determining local recurrence after treatment can result in postponed salvage therapy, and consequently an increased risk of disease progression and diminished treatment effectiveness. Therefore, validating the PI-RR system, it can be implemented as a standard clinical tool for the management of these patients. The earlier the diagnosis of recurrent cancer is made, the faster the treatment can be implemented, reducing treatment failure, and increasing survival in these patients. In conclusion, the implementation of PI-RR can greatly influence treatment and patient outcomes. (29)

Finally, it is important to note that the implementation of the PI-RR system will have a significant economic impact on reducing healthcare costs. This is because the system will promote the use of mpMRI over PET-CT scans, which are much more expensive.

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A.-ANNEXES

A.1.- GENERAL ANATOMY OF THE PROSTATE WITH T2W SEQUENCES

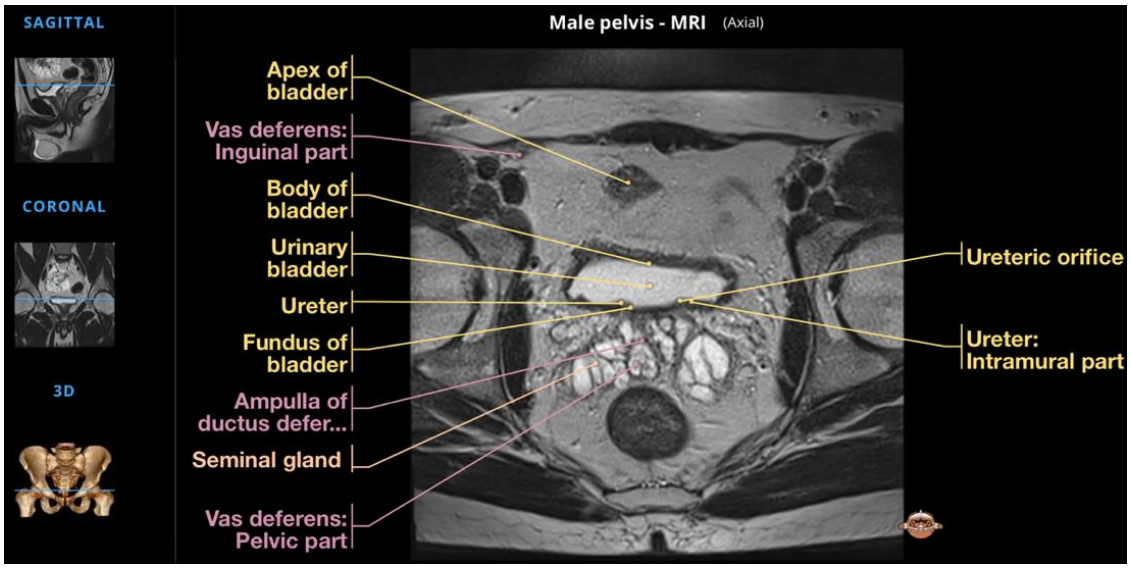


Figure 1.4 *A standard male pelvic region is displayed in an axial plane image captured via magnetic resonance imaging using a T2-weighted sequence. The illustration emphasizes the bright structures, which denote the seminal vesicles and urinary bladder, components of the urinary tract. Additionally, the vas deferens can be identified in its inguinal and pelvic sections in a cross-sectional view. Obtained from (20).*

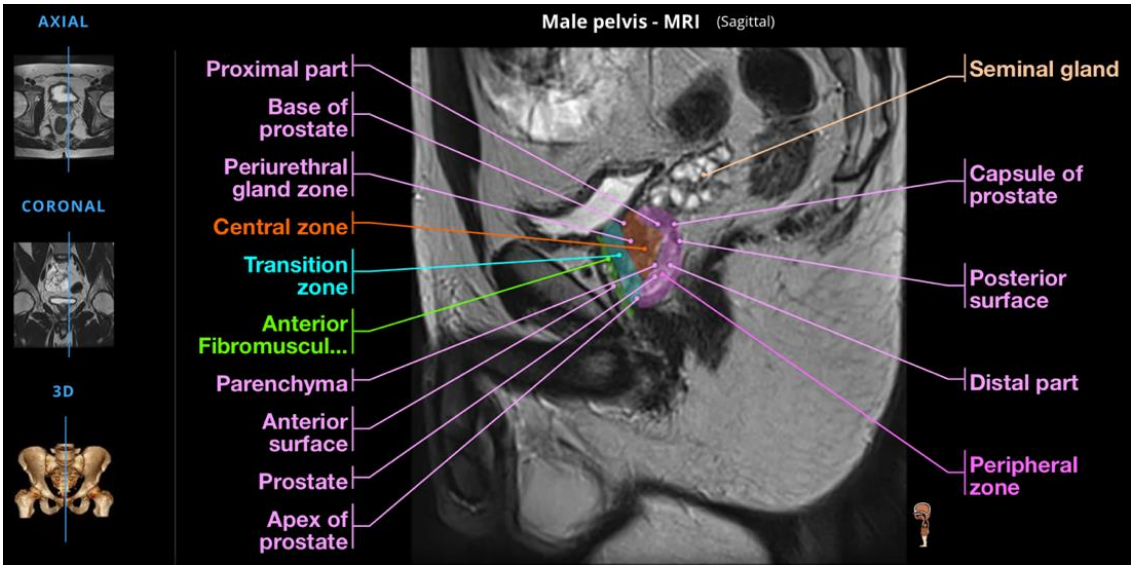


Figure 1.5 *Sagittal T2-weighted MRI of a typical male pelvis illustrates the anatomy of the prostate and its zones. The superior portion of the prostate gland is visible with its connection to the seminal vesicle and their topographical relationship. Obtained from (20).*

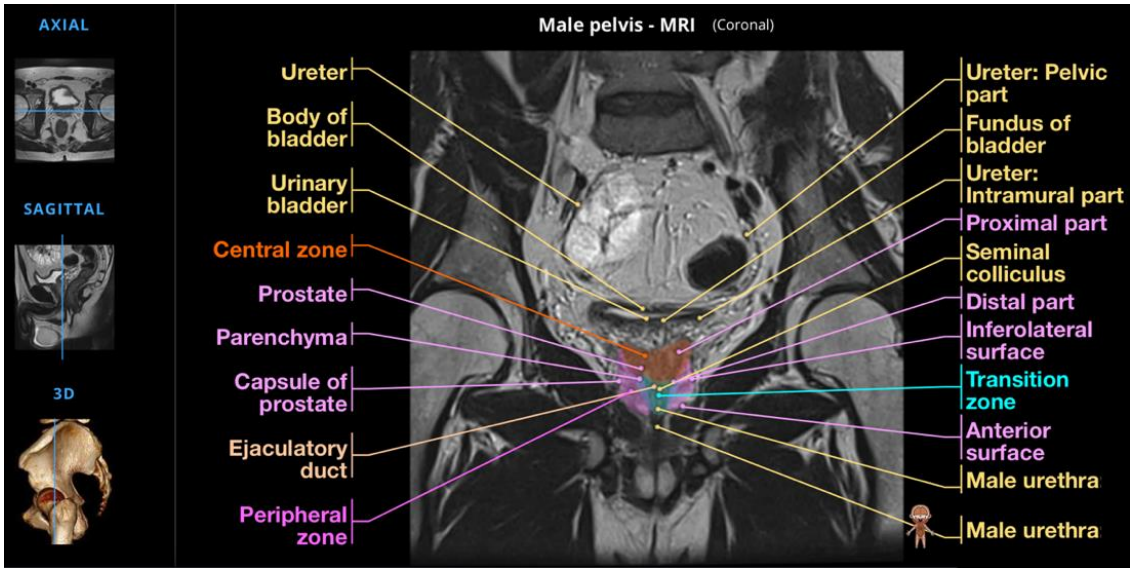


Figure 1.6 *A T2-weighted MRI scan of a typical male pelvis provides visualization of the anatomy and zones of the prostate, urinary system including the bladder, ureter, and urethra. The scan also displays the ejaculatory duct. Obtained from (20).*

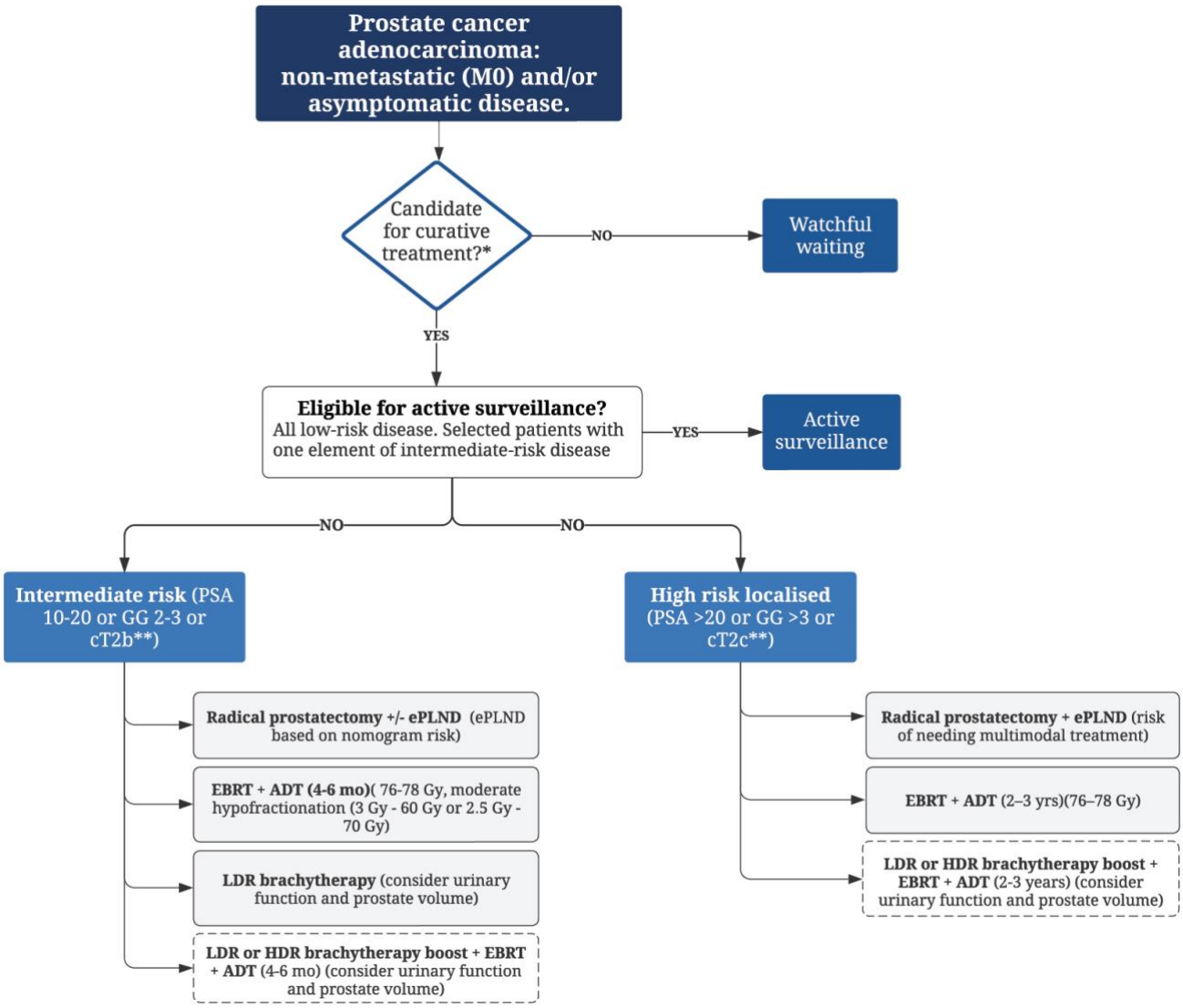
A.2.- TNM AND STAGING TABLES

T - Primary Tumour (stage based on digital rectal examination [DRE] only)	
TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1	Clinically inapparent tumour that is **not palpable.**
	T1a Tumour incidental histological finding in 5% or less of tissue resected.
	T1b Tumour incidental histological finding in more than 5% of tissue resected.
	T1c Tumour identified by needle biopsy (e.g., because of elevated PSA).
T2	Tumour that is palpable and confined within the prostate.
	T2a Tumour involves one half of one lobe or less.
	T2b Tumour involves more than half of one lobe, but not both lobes.
	T2c Tumour involves both lobes.
T3	Tumour extends **palpably** through the prostatic capsule.
	T3a Extracapsular extension (unilateral or bilateral).
	T3b Tumour invades seminal vesicle(s).
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles:
	external sphincter, rectum, levator muscles, and/or pelvic wall.
N - Regional (pelvic) Lymph Nodes[1]	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Regional lymph node metastasis.
M - Distant Metastasis[2]	
M0	No distant metastasis.
M1	Distant metastasis.
	M1a Non-regional lymph node(s).
	M1b Bone(s).
	M1c Other site(s).

1 Metastasis no larger than 0.2 cm can be designated pNmi.
2 When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

Table 1.10 *Clinical Tumour Node Metastasis (TNM) classification of prostate cancer. Obtained from (12).*

A.3.- TREATMENT OF LOCALIZED PROSTATE CANCER



**** Rule of thumb: Life expectancy 10 years.***
*****Recommendation based on clinical staging using digital rectal examination, not imaging.***
: weak recommendation.

GG: grade group.
ePLND: extended pelvic lymph node dissection.
EBRT: external beam radiotherapy.
ADT: androgen deprivation therapy.
LDR: low-dose rate.
HDR: high-dose rate.

Figure 1.7 *Treatment non-metastasized (M0) – asymptomatic disease. Adapted from (12).*

A.4.- PI-RR SCORING CRITERIA FOR APPARENT DWI/ADC IMAGING, AND DCE SEQUENCES.

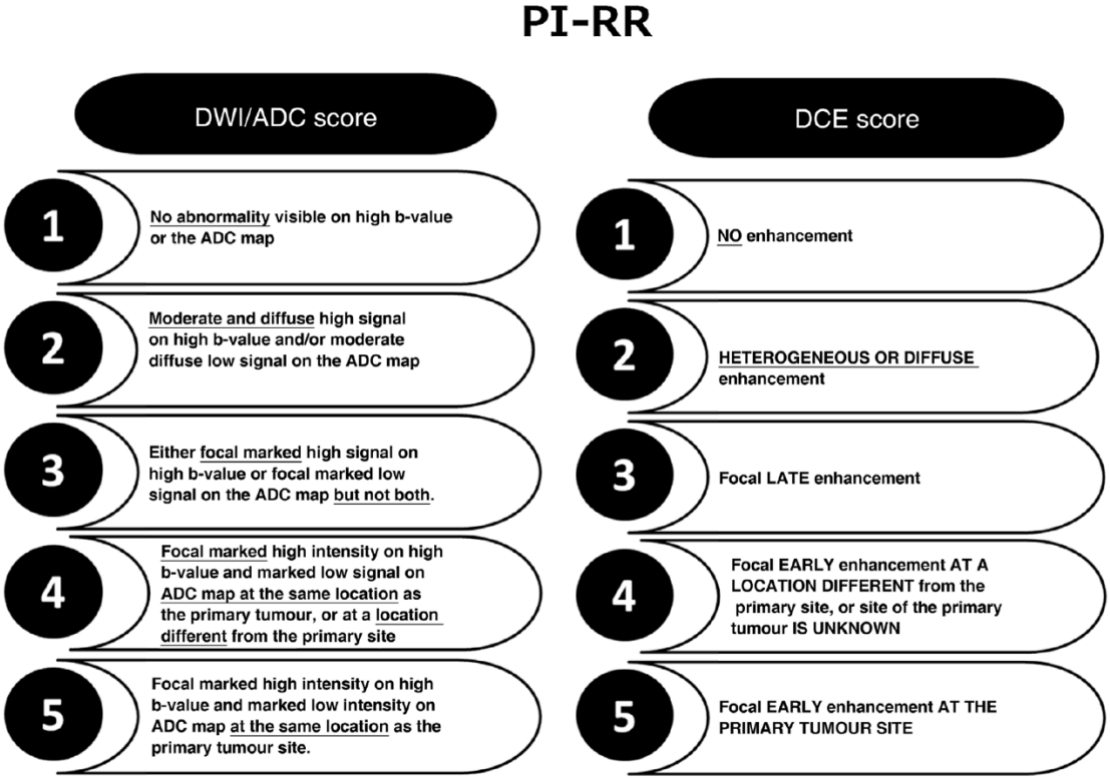


Figure 1.8 *Scoring criteria for DWI/ADC and DCE sequences in accordance with PI-RR. Obtained from (25).*

A.5.- SCORING CATEGORIES FOLLOWING RADICAL PROSTATECTOMY.

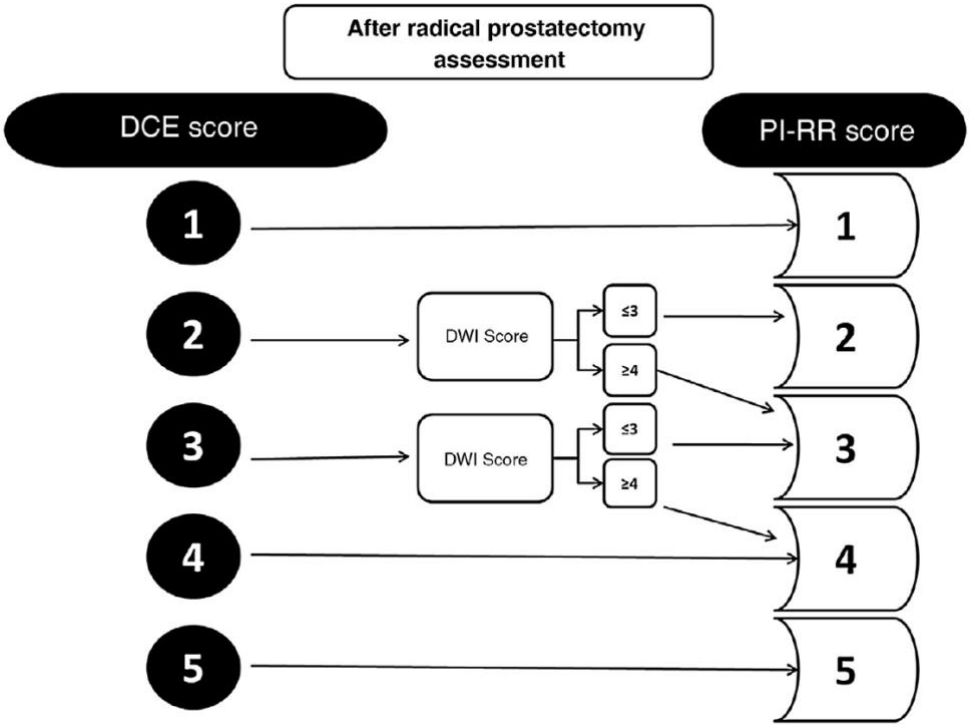


Figure 1.9 *PI-RR scoring criteria for patients treated with radical prostatectomy with DCE sequence as dominant. Obtained from (25).*

A.6.- SCORING CATEGORIES FOLLOWING RADIATION THERAPY.

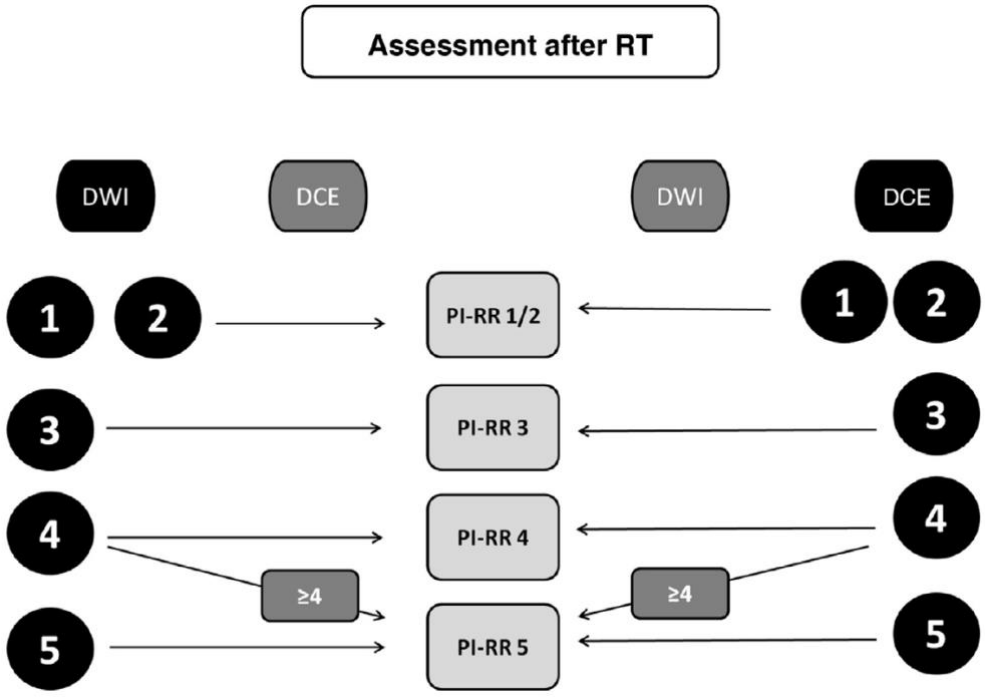


Figure 1.10 *PI-RR scoring criteria to assess patients who received radiotherapy treatment. Obtained from (25).*

A.7.- PI-RR REPORT TEMPLATE

Title of study	Validation of the MRI prostate imaging for recurrence reporting assessment score - PI-RR.
Radiologist in charge	☐ Reader 1 ☐ Reader 3 ☐ Reader 2 ☐ Reader 4
Patient identification number	

INDICATION:

Nadir PSA levels:

PSA levels of biochemical recurrence:

Primary tumour localization:

Stage of the primary tumour:

Gleason score of the primary tumour:

Prior therapy:

☐ Radical prostatectomy

☐ Radiotherapy

TECHNIQUE: Multiplanar and multi-sequence imaging of the pelvis according to PI-RR recommendations before and after intravenous contrast administration at 3.0 ml/sec at 1.5 or 3.0 T. T2w, DWI/ADC and DCE sequences will be analyzed.

FINDINGS:

Lesion nº1	Location: Size: T2: DWI/ADC: DCE:
Lesion nº2	Location: Size: T2: DWI/ADC: DCE:
Other information	

CONCLUSION: (Overall, PI-RR category)