Universitat de Girona
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The value of targeted MRI-US fusion biopsy in men with prior negative biopsy for prostate cancer detection

Final degree project

Author: Julen Armendariz Gayraud

Clinical tutor: Kai Vilanova Busquets

Methodological tutor: Rafel Ramos Blanes

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Contents

Abbreviation list 1

List of tables and figures 2

Tables 2

Figures 2

Abstract 3

1. Introduction 5

1.1. Prostate cancer: epidemiology 5

1.2. Prostate cancer: screening and diagnosis 6

1.2.1. Morphology of PCa 6

1.2.2. Role of the MRI 8

1.2.3. MRI-guided biopsy 13

2. Justification 17

3. Hypothesis 18

4. Objectives 18

4.1. Main objective 18

4.2. Secondary objectives 18

5. Material and methods 19

5.1. Study design 19

5.2. Participants 19

5.2.1. Inclusion criteria 19

5.2.2. Exclusion criteria 19

5.3. Sample 19

5.3.1. Sample selection 19

5.3.2. Sample size 19

5.4. Variables 20

5.4.1. Independent variable 20

5.4.2. Dependent variables 20
5.4.3. Covariates 20
5.5. Methods of measurement 21
5.5.1. MpMRI protocol and analysis 21
5.5.2. Biopsy protocol 22
5.5.3. Anatomopathological protocol 23
5.5.4. Feedback from the histological result to the PI-RADS score 23
6. Statistical analysis 24
6.1. Variables definition 24
6.2. Univariate analysis 24
6.3. Bivariate analysis 24
6.4. Multivariate analysis 25
7. Ethical and legal aspects 26
8. Limitations 27
9. Chronogram and work plan 29
9.1. Participating centres, research team staff and associated personnel 29
9.2. Study stages 29
10. Feasibility 33
11. Budget 34
11.1. Non-included costs 34
11.2. Included costs 34
11.2.1. Material costs 34
11.2.2. Personnel costs 34
11.2.3. Travels and meals costs 34
11.2.4. Divulgation costs 34
11.2.5. Overhead 35
12. Impact on the national health system 36
13. References 37

14. Annexes 42

14.1. Prostate anatomy through MRI: T2WI sequence 42

14.2. Anatomical division drawing of the prostate 45

14.3. T1-weighted sequence: prostate haemorrhage 47

14.4. PI-RADS assessment category for the peripheral zone (PZ) 48

14.4.1. PZ and TZ: PI-RADS 1 48

14.4.2. PZ: PI-RADS 2 49

14.4.3. PZ: PI-RADS 3 49

14.4.4. PZ: PI-RADS 4 49

14.4.5. PZ: PI-RADS 5 50

14.5. PI-RADS assessment category for the transition zone (TZ) 51

14.5.1. TZ: PI-RADS 2 51

14.5.2. TZ: PI-RADS 3 52

14.5.3. TZ: PI-RADS 4 52

14.5.4. TZ: PI-RADS 5 53

14.6. Sector map used in PI-RADS v2 guide 54

14.7. Informed consent sheet 55

Abbreviation list

ADC	Apparent diffusion coefficient
BPH	Benign prostatic hyperplasia
CZ	Central zone
DCE	Dynamic contrast enhanced
mpMRI	Multiparametric magnetic resonance imaging
MRGB	Magnetic resonance-guided biopsy
MRI	Magnetic resonance imaging
PCa	Prostate cancer
PSA	Prostatic specific antigen
PZ	Peripheral zone
SB	Systematic biopsy
T2WI	T2-weighted images
TRUS	Transrectal ultrasounds
TZ	Transition zone
US	Ultrasounds

List of tables and figures

Tables

Table 1. Different combinations in Gleason score 7
Table 2. PI-RADS v2 score 11
Table 3. PI-RADS v2 scoring criteria 12
Table 4. Recapitulation of dependent variables and covariates 21

Figures

Figure 1 Estimated number of new cancer cases in male in 2018 5
Figure 2. Zonal anatomy of the prostate gland in posterior lateral view 10
Figure 3. Recommendations for different PI-RADS scores 12
Figure 4. Coronal section of the prostate 42
Figure 5. Parasagittal section of the prostate 43
Figure 6. Axial section of the prostate base 44
Figure 7. Drawing of the anatomical division of the prostate by McNeal's mode in a sagittal view 46
Figure 8. Post biopsy haemorrhage area showing hyperintensity in T1-weighted sequences 47
Figure 9. PI-RADS v2 scoring for the peripheral zone (PZ) 48
Figure 10. PI-RADS 1 category in PZ and TZ 48
Figure 11. PI-RADS 2 category in PZ 49
Figure 12. PI-RADS 3 category in PZ 49
Figure 13. PI-RADS upgrading from 3 to 4 category in PZ 49
Figure 14. PI-RADS 4 category in PZ 49
Figure 15. PI-RADS 5 category in PZ 50
Figure 16. PI-RADS v2 scoring for transition zone (TZ) 51
Figure 17. PI-RADS 2 category in TZ 51
Figure 18. PI-RADS 3 category in TZ 52
Figure 19. PI-RADS upgrading from 3 to 4 category in TZ 52
Figure 20. PI-RADS 4 category in TZ 52
Figure 21. PI-RADS 5 category in TZ 53
Figure 22. Prostate segmentation model used in PI-RADS v2 54

Abstract

Background

Prostate cancer (PCa) is very prevalent among men, but with low mortality rates. This is mainly due to the high detection of indolent lesions that are more frequent than aggressive ones.

The traditional strategy for PCa detection until recently has been the blinded random biopsies of the entire gland, called systematic biopsy (SB), by transrectal ultrasounds (TRUS) guidance. Lately, multiparametric magnetic resonance imaging (mpMRI) has been becoming a clue tool in PCa detection. Nowadays, the recommendation in men with previous negative biopsy and PCa suspicion is to perform magnetic resonance-guided biopsy (MRGB), in addition to SB, as the diagnostic procedure. The application of mpMRI in men without previous biopsy is not that supported, even though is starting to grow. There are predominantly 3 MRGB techniques.

Objective

To assess whether MRGB by magnetic resonance imaging-ultrasounds (MRI-US) fusion technique improves the detection rate of clinically significant PCa over SB to improve the management of prostate cancer.

Design and methods

In this cross-sectional single centre study, both biopsy techniques (MRGB by fusion technique and SB) will be performed to patients with a PCa suspicion and a previous negative biopsy, if the MRI is suggestive of PCa. Men whose MRI results are not suggestive of PCa will not be offered biopsy. A 12-core SB guided by TRUS will be carried out firstly before the MRGB, without any information of the MRI. The results of each technique will be compared.

Key words: Prostate cancer, Magnetic Resonance Imaging, MRI-guided biopsy, Multiparametric MRI, Fusion.

1. Introduction

1.1. Prostate cancer: epidemiology

An estimated 1,2 million men worldwide have been diagnosed with Prostate cancer (PCa) in 2018 (1). This is the second nonskin cancer in frequency, after the lung cancer, in terms of numbers of new cases each year. However, if we look for prevalence rates, PCa is the most common nonskin cancer (2), probably due to differences in mortality rates between lung cancer over PCa, being present in most of men autopsies over 50 years old (3). Concerning mortality rates, PCa is the fifth leading cause of death from cancer in men (4), even if mortality rates from PCa have been in significant decline since mid-1990s as a result of early diagnosis and early treatment (5).

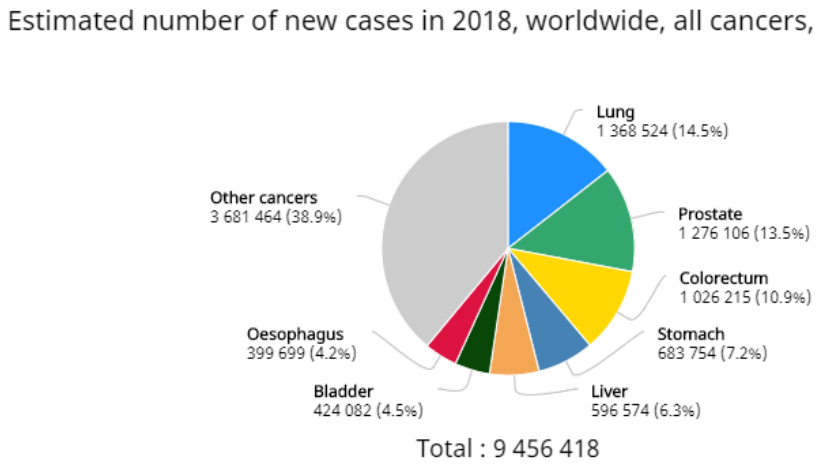

Figure 1 Estimated number of new cancer cases in male in 2018. Obtained from Global Cancer Observatory (1).

There are ethnical and geographical differences in incidence and mortality between men that suggest genetic and environmental factors in the pathogenicity of the PCa. Also, the availability and access to the health system care and screening procedures in different countries contribute to the variability of incidence and mortality rates. Oceania, followed by Northern America, Western Europe, Northern Europe and the Caribbean have among the highest PCa incidence rates in the world, while Asia and North Africa have the lowest incidence rates. Ethnically, men of African descent outside the African continent are at higher risk of developing PCa and generally have a more lethal course of the disease, suggesting a genetic predisposition, even though only a small part of them (~9%) have true hereditary PCa, with a disease onset six-seven years earlier than average (6).

Despite the high PCa rates in developed countries, the ratio between mortality and incidence is 12% for Oceania in contrast with 90% for Middle Africa. These data seem to reveal that the

relation between incidence and mortality does not show consistency and supports the continuing discussion relative to the true relative value of the prostatic specific antigen (PSA) screening (4).

Mortality rates have been decreasing in some European countries, which may be explained to the early diagnose and improved treatment (4). The reduced mortality rate seen in the USA is considered to be partly due to a widely adopted aggressive PCa screening policy. However, there is still no level 1 evidence that PSA mass screening is cost-effective in reducing PCa mortality (6).

1.2. Prostate cancer: screening and diagnosis

The aim of PCa screening is to detect PCa in early stages, so it can be managed with better results, even if the earlier stages (I and II) are found to be the most expensive in terms of diagnosis and initial treatment (7). The fact is that PCa screening has been associated with overdiagnosis, overtreatment and side effects of this treatment with no proved improvement in PCa survival but in higher incidence rates (8). For this reason, there is rejection against systematic population-based screening. Nowadays, World Health Organization has not yet developed recommendations for PCa screening using PSA because it is not a specific marker for PCa, although it is still used routinely in most of clinical practice. In the USA, the U.S. Preventive Services Task Force now recommends that patients should discuss the benefits and harms of PCa screening with their doctor and choose the best option individually (4).

The annually screening for PCa consists of: digital rectal examination and PSA levels in blood in men over 50 years old. If one or both are abnormal, PCa might be suspected. Then, the current standard diagnostic procedure is a transrectal ultrasounds (TRUS)-guided biopsy, which is a general nontargeted sampling of the entire prostate (10 to 16 biopsy cores samples) called systematic biopsy (SB), performed blinded to the possible location of a tumor. This method is blinded because most tumors are not visible at the ultrasounds (US), then it cannot get targeted biopsy with the TRUS. Hence, PCa is perhaps the only solid organ cancer that is currently diagnosed with a non-targeted random biopsy technique, thus sampling only about 0.04% of the prostate (9).

1.2.1. Morphology of PCa

PCa is a glandular malignant neoplasia (adenocarcinoma). The typical morphological features are: microglandular monolayer proliferation with absence of basal cells and irregular nuclei with large nucleoli, which are multiple in some cases. Multifocality is present in approximately 80% of patients, half of whom have more than two nodules with frequent heterogenous features (10).

Biopsy cores are sent to the pathologist. Once there, PCa grading is based on the **Gleason score** which classifies in 5 patterns based on the loss of the prostate histology and architecture (Table 1. Different combinations in Gleason score. Adapted from *(10)*.: patterns 1, 2 and 3 are discrete glandular proliferation and are united in pattern 3 category; pattern 4 has different subtypes: fused, cribriform, poorly defined and glomeruloid glands, being all them poorly defined glands; pattern 5 is no glandular differentiation with or without necrosis. Most of the PCa have different patterns, usually two or three. To classify them, Gleason score adds the number of the first pattern in frequency with the number of the second pattern. A Gleason score 3+4 means that pattern 3 is the most frequent and pattern 4 is the second most present. If there is only one single pattern, the Gleason score is the sum of twice the pattern (3+3, 4+4 or 5+5).

Table 1. Different combinations in Gleason score. Adapted from (10).

Gleason	Description
3 + 3, ≤6	Only individual discrete well-formed glands
3 + 4 = 7	Predominantly well-formed glands with a lesser component of poorly formed/fused/cribriform glands
4 + 3 = 7	Predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands
8	Only poorly formed/fused/cribriform glands or predominantly well-formed glands and lesser component lacking glands or predominantly lacking glands and lesser component of well-formed glands
9-10	Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

So, clinically significant PCa is defined as Gleason score ≥ 3 + 4 = 7, and/or >0.5 cm^3, and/or extra prostatic extension (11,12) and is the one being able to progress and metastasize. Thus, clinically insignificant tumors include: those <0.5 cm^3, confined to the prostate and with a Gleason score 3 + 3 = 6 (or just ≤ 6) without patterns 4 and 5, which are unlikely to reach a clinically significant size within a man's life (13).

SB has the main drawback: it overdetects Gleason 3 + 3 tumors that have virtually no risk of metastasis (clinically insignificant lesions). This can lead to overtreatment, as 60% of patients given a diagnosis of indolent tumor might choose aggressive treatment options like radical surgery with considerable morbidity such as bowel and erectile disfunction and urinary

incontinence (6,13). Moreover, SB can skip areas of significant cancer because is particularly poor at sampling cancers in the apical, anterior and midline locations, missing up to 47% tumors. Such is the case that 40% of SB classified as low grade or insignificant lesions were high grade or clinically significant in the surgical histologic specimens. Finally, this uncertainty associated with SB results can cause anxiety in patients and again overtreatment (2,14).

1.2.2. Role of the MRI

In the last few years, magnetic resonance imaging (MRI) has been involved in the diagnosis procedure of PCa, increasing its sensitivity and specificity. The use of **multiparametric MRI** (mpMRI) previous to the biopsy can identify suspicious regions in the prostate, well correlated with Gleason score. MpMRI incorporates anatomic (T1-weighted and T2-weighted images, T2WI) and functional imaging (diffusion weighted imaging, DWI, dynamic contrast enhanced, DCE, and MR spectroscopic imaging, MRSI) in 2-3 planes for PCa detection, localization and staging.

T2WI sequence reflects tissue water content and defines the prostate's zonal anatomy due to its high spatial resolution, in peripheral, central and transition zones (Annex 14.1). T2WI also contributes to the cancer staging by facilitating evaluation of extra-prostatic extension and invasion of other structures such as seminal vesicles or the neurovascular bundle. Ultimately, T2WI sequence plays a part in significant PCa detection within the transition zone (TZ).

DWI sequence assesses the diffusion of water molecules within different tissues. Therefore, normal prostate glandular tissue has a higher water diffusion rate than cancer tissue due to restricted diffusion in tightly packed cancer cells (15). DWI should include an apparent diffusion coefficient (ADC) map on a high b-value images:

- ADC map is a display of ADC values for each voxel in a parametric image. Most clinically significant cancers have restricted diffusion compared to normal tissues and thus appear hypointense in grey-scale ADC maps. Although ADC values have been reported to correlate inversely with histologic grades, there is considerable overlap between benign prostatic hyperplasia (BPH), low grade cancers and high grade cancers (16). ADC values are measured as mm^2/s.
- High b-value images should be ≥1400 s/mm^2. The b-value is the power of the sequence, thus the sequence has to be performed on high power, getting high b values.

DCE sequence consists of serial rapid sequences obtained after a bolus of intravenous contrast (gadolinium). Because of the vessel formation and capillary permeability of PCa, it can be easily seen as a rapid enhancement area compared with normal prostate tissue and, usually, a more

rapid washout of contrast, being useful for PCa detection in the peripheral zone. Although, other entities could have this pattern, thus limiting the utility of DCE findings in isolation (15).

1.2.2.1. Anatomy and microanatomy of the prostate gland through MRI (5,10,17)

Classically described as inverted walnut or chestnut-shaped, it is conical shaped and surrounds the urethra as it exits from the bladder. It can be classified in thirds: the apex is the lower ⅓, the midprostate is the middle ⅓ and the base is the upper ⅓.

Histologically, it is composed of glandular and stromal elements inside a pseudo-capsule made of smooth muscle in the inner layer and collagen in the outer, covered by the peri-prostatic fascia. The vasculo-nervous elements pass along an interfascial space delimited by the peri-prostatic and the endopelvic fascia (18). The cells that form the gland are arranged in two layers: basal and luminal or secretory cells.

Intrinsically, it is divided into 4 zones using **McNeal's model** (19) (Annex 14.2)

- Peripheral zone (PZ): comprises the 70% of the glandular tissue, extending from the base to the apex along the posterior surface and surrounding the distal prostatic urethra. Here, PCa and chronic prostatitis are more common. Characterized by a loose stromal tissue with a high water content, resulting in a high signal intensity on T2WI. About 70% of all PCa arise from PZ and here, it can be easily detected due to the typically round or oval foci of low T2WI signal intensity presentation of the PCa and the posterior location, closer to the biopsy needles. The intensity of the T2WI signal is inversely proportional to the Gleason score (15). Nevertheless, other entities can mimic PCa in T2WI by appearing hypointense as chronic prostatitis, haemorrhage, post-irradiation or hormonal treatment effects, scar tissue, atrophy or prostate intraepithelial neoplasia.
- Central zone (CZ): accounts for approximately 25% of the glandular tissue, situated between the transition zone and PZ and crossed by the ejaculatory ducts. The stroma is compact and has thick muscular bundles with less water content than in PZ, resulting in hypointense images on T2WI sequence. Only 5-10% of PCa are found here but they are usually aggressive because a higher Gleason score, an extracapsular extension and seminal vesicle invasion are more frequent (20).
- Transition zone (TZ): only 5% of the glandular tissue, surrounds the proximal prostatic urethra. This is the part enlarging when benign prostatic hyperplasia (BPH) occurs. BPH has variable proliferation of glandular and fibromuscular stromal components, exhibiting heterogenous signal intensity: glandular hyperplasia contains more ductal and acinar elements and secretions, resulting in a high signal intensity in T2WI.

Contrarily, stromal hyperplasia, with muscular and fibrous elements, may appear as a well-defined hypointense nodule in T2WI (20). Here we find 10-25% of PCa, which are more challenging to detect because of the densely packed stroma and BPH nodules overlapping with PCa, and the anterior location, farther from the biopsy cores.

- Anterior fibromuscular stroma: represents approximately 33% of the volume of the prostate, forms the anterior convexity and is composed of collagen and spindle-shaped smooth muscle cells without any glandular tissue. Thus, it is relatively low in T2WI signal intensity. In a few surgical specimens, cancer have been found here too.

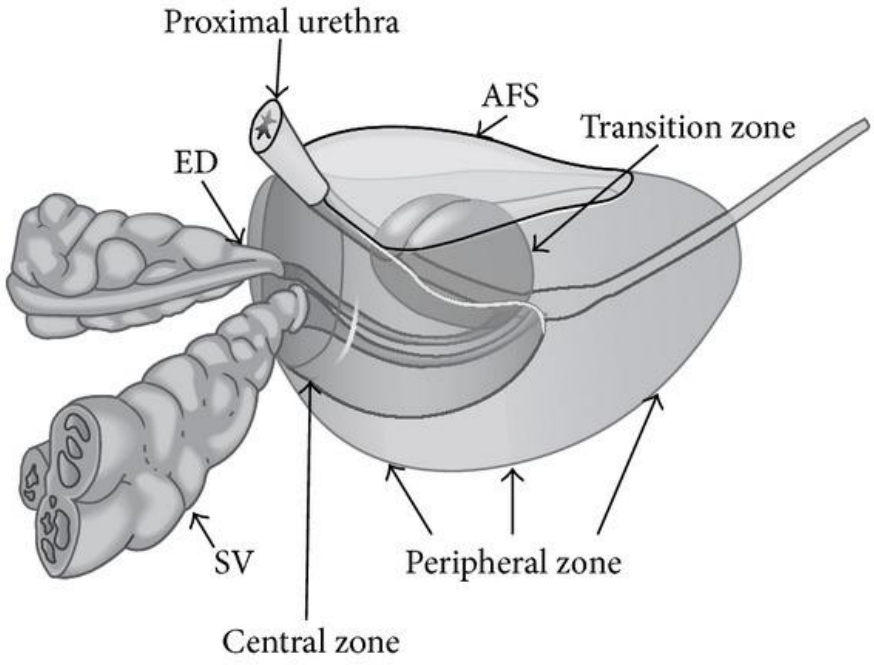

Figure 2. Zonal anatomy of the prostate gland in posterior lateral view. ED ejaculatory ducts, SV seminal vesicles, AFS anterior fibromuscular stroma. Obtained from (5).

Because the mpMRI image is dependent upon the cellular distribution and the mobility of the water molecules, it can be easily understood that certain non-neoplastic pathologies may be confused for a tumor lesion when they are characterized by sufficient large accumulations of isolated cells on a liquid medium or by necrosis, especially when they raise PSA levels, as occurs in inflammatory processes like prostatitis or cystic glandular atrophy.

Usually, when prostatitis is symptomatic or PSA levels response to antibiotics, imaging techniques are not necessary for diagnosis. However, in cases of asymptomatic prostatitis with elevated PSA, the mpMRI diagnosis can be challenging for the radiologist, even more when prostatitis shows inflammatory changes in the peri-prostatic fat or enlarged reactive lymph nodes, simulating a higher PCa stage. Usually, both acute and chronic prostatitis appear

hypointense on T2WI sequence, more diffuse than in PCa, with hyperintense DWI signal and contrast enhancement (20).

As haemorrhage can simulate PCa too, T1-weighted sequence should always be analysed before the initial evaluation of the different sequences, to rule out the presence of blood post-biopsy (being it hyperintense on T1-weighted sequence), thus avoiding false-positive diagnosis of PCa (12,20) (Annex 14.3).

1.2.2.2. MpMRI interpretation

MpMRI analysis and reporting has been showing variable accuracy related to different learning curve of the technique and lack of standardization. In order to improve mpMRI results, a reporting standardized system has been developed, the Prostate Imaging Reporting and Data System version 2 (**PI-RADS v2**) (3).

PI-RADS v2 classification scores from 1 to 5, showing the probability of having clinically significant PCa in the mpMRI.

Table 2. PI-RADS v2 score. Adapted from (2).

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

PI-RADS Prostate Imaging Reporting and Data System.

DWI is the dominant sequence in PZ that will determine the overall suspicious score. So that, for a detected PZ lesion, if DWI score is 4 and T2WI score is 3, the PI-RADS assessment category should be 4. DCE sequence has a secondary role in equivocal cases (PI-RADS 3), where a positive DCE (fast and early focal contrast uptake corresponding with suspicious findings on T2WI and/or DWI) score can upgrade the lesion to a PI-RADS 4 (12) (Annex 14.4).

T2WI is the dominant sequence in TZ that will determine the overall suspicion score. DWI has a secondary role in TZ for equivocal cases (PI-RADS 3), where a large corresponding abnormality (PI-RADS 5, >1.5 cm) can upgrade the lesion to a PI-RADS 4 (12) (Annex 14.5). These criteria can be also applied into the CZ and anterior fibromuscular stroma.

Table 3. PI-RADS v2 scoring criteria. Adapted from (15).

PI-RADS score	Peripheral zone			Transition zone		
	DWI	T2WI	DCE	DWI	T2WI	DCE
1	1	Any	Any	Any	1	Any
2	2	Any	Any	Any	2	Any
3	3	Any	(-)	≤4	3	Any
4	3	Any	(+)	5	3	Any
	4	Any	Any	Any	4	Any
5	5	Any	Any	Any	5	Any

PI-RADS Prostate Imaging Reporting and Data System, DWI diffusion weighted imaging, T2WI T2-weighted images, DCE dynamic contrast enhanced.

The PI-RADS v2 guide recommends to perform a targeted biopsy with a mpMRI score of 4 or 5, and avoid to perform biopsy with PI-RADS 1 or 2. The individual risk profile may help to decide the management in PI-RADS 3 category, taking into account some other clinical factors (PSA kinetics, previous biopsy results, tumor size, age, comorbidity, life expectancy and patient's preferences), because no clear management recommendations for monitoring or repeat biopsy in these undetermined lesions have yet been defined (2,3,11,21).

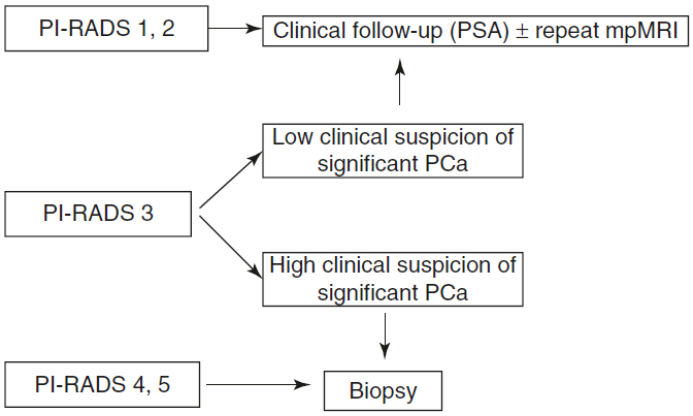

Figure 3. Recommendations for different PI-RADS scores. PI-RADS Prostate Imaging Reporting and Data System, PSA prostatic specific antigen, mpMRI multiparametric MRI, PCa prostate cancer. Obtained from (12).

Assignment of the PI-RADS category is based on mpMRI findings only. Nevertheless, patient's management should always combine the results of mpMRI with PI-RADS assessment and the clinical factors like PSA determinations, family history, digital rectal examinations findings and previous biopsy results (12).

1.2.2.3. MpMRI application

As mpMRI has a low false negative rate of 5-15% for clinically significant cancer, some authors affirm that MRI could be used as a triage test, and if the results were negative, avoid to perform

a biopsy, asserting that a negative result on mpMRI is more reassuring to the patients and clinicals than a negative result on the SB (22). Then it could be followed up with the PSA levels. In the same way, the negative predictive value, is found to increase with MRI reporting experience, until rates approaching 90% (14). Others do not accept this triage technique, as it might not be sufficient to discard SB (23) because some small cancers (<0.5mL) can escape its detection by mpMRI (MRI-silent tumors) (2,11,24,25).

Another application of the mpMRI is as an active surveillance tool, when a low-risk and localized PCa (insignificant PCa) is diagnosed, in order to delay prostatectomy, because a PSA follow-up do not reliably predict progression and biopsy follow-up carries morbidity (26).

But then, there is hesitation to add MRI into practice guidelines for PCa detection because it is perceived to be an expensive technology. Although, Pahwa *et al.* showed that using MRI targeted biopsies techniques in patients with clinical suspicion of PCa is cost-effective, mainly because the ability to not detect insignificant lesions and the avoidance of unnecessary biopsies and treatments carrying complications (13).

Although the recent advances in mpMRI have improved its sensitivity in PCa diagnosis, some other factors can affect the diagnosis such as technical issues acquisition of the mpMRI images, the expertise of the radiologist reporting images, the threshold used to define a lesion in the mpMRI and the definition of clinically significant PCa (27). In this way, Gaziev *et al.* demonstrated an improvement in PCa detection for MRI reporting over time, suggesting a learning curve for the technique (14).

In order to implement the technique as a cost effective and available tool, it is being recommended to perform a biparametric MRI, using only T2WI and diffusion (DWI) sequences avoiding the use of intravenous contrast for DCE sequence. Studies have shown similarly efficacy, allowing less costs and MRI examination time, with no contrast exposure (3). In a study, of those with negative biparametric MRI findings, DCE did not in isolation find any clinically significant PCa, concluding that both MRI techniques (biparametric and multiparametric) shown similar PCa detection rates (28).

1.2.3. MRI-guided biopsy

MRI-guided biopsy (MRGB) consists of using an MR image to localize the suspected area detected on the MRI to perform a targeted biopsy (neither random nor blinded). This method tries to improve the detection rate of significant cancer, mainly because MRI is able to detect PCa in locations not biopsied on the blinded SB and moreover identify lesions with higher

Gleason scores, achieving this goal with less samples of biopsy cores. Avoiding systematic biopsy could decrease the detection rate of clinically insignificant cancer, as well (22).

Primary biopsy or biopsy-naïve is the first biopsy performed in the patient, being MRGB or just SB. Some studies with MRGB are focused only on men with a raised PSA or abnormal digital rectal examination (primary biopsy) while others only perform MRGB on those with a previous biopsy (repeated biopsy). Nevertheless, a MRBG also has to include additionally a SB from the whole gland, as it has been shown several limitations:

False negative results might be due to technical issues. Cash *et al.* found two main causes for targeted biopsy failure: an error in sampling by prostate or patient movement and incorrect image registration, and a falsely high PI-RADS score due to the inter-reader variation, leading to a negative anatomopathological result. Some of these over-graded lesions were reclassified as PI-RADS ≤2 in an MRI rereading. Among the other causes for over-grading, the main is the ratio of MRI false positives. Sheridan *et al.* found, in patients with a PI-RADS score of 5, 18% of benign prostates and 10% of clinically insignificant PCa. The reasons of this false positives were, in decreasing order: nodules of BPH, inflammatory changes, discordance between anatomopathological and imaging findings and normal anatomic structures. Prostatitis, due to a low signal intensity on T2WI and early enhancement with contrast, and stromal hyperplasia can mimic PCa too (29,30). Moreover, if performed after the SB, the efficacy of the mpMRI may be reduced due to bleeding and swelling artefacts in the gland. For this reason, it is recommended to delay the MRI until at least 4 to 6 weeks after a prostate biopsy (5,31).

The following three MRGB techniques are most commonly used:

- cognitive biopsy, also called visual registration, when the radiologist correlates mentally a previous MRI image with the real time transrectal ultrasounds (TRUS) to target the suspicious area. The radiologist has to define clearly the anatomic area of the lesion using standardized anatomic localization maps from PI-RADS (Annex 14.6). While some have found betters PCa detection rates that in SB, others have shown same rates of cancer detection as in SB in primary biopsy (biopsy-naïve), but with a higher proportion of positive cores as the 10-16 systemic cores are not performed. The main limitation is the variability depending on the skills of the operator in order to cognitively transfer the visual information from one format to another, MRI to the real time ultrasounds (US) (2,27).
- in-gantry MRGB, is the most unavailable technique, as core samples are obtained directly from the MRI guidance, which entails more problems such as a wide availability

of the MRI machine, additional training for the radiologist and MRI compatible needles. The main advantage of performing the biopsy in gantry is the improved targeting of the lesion, allowing to ensure that the designated lesion is well sampled by taking only a few targeted cores. Some studies have found that in gantry MRI reduces the detection of low risk or insignificant PCa while improving the detection of clinically significant PCa, in comparison with SB (2,27).

- MRI-US fusion guided biopsy, software-fused, combining previously taken mpMRI images with real-time TRUS images displayed on the US screen, thus getting fused MRI-US images to allow the operator to target the lesions identified on mpMRI. Registration and fusion MRI-US images can be done with either rigid or elastic method. The drawbacks with this technique are the presence of a learning curve, the costs for the investment in the fusion technology and the quality of the fusion between MRI and ultrasounds that can lead to error. For that, it is suggested to take at least 2 cores from each target lesion (2,32).

A meta-analysis did not find significant differences in PCa detection in primary biopsy (biopsy-naïve) between the two most performed techniques, cognitive and MRI-US fusion biopsy (33).

To execute the biopsies, different anatomical approaches can be used: transrectal, transperineal and transgluteal. The transperineal technique has shown greater significant PCa detection of the anterior lobe as it can be biopsied more easily and has shown less infection rates than the transrectal because the needle does not go through the rectum. Despite some countries adopted it as the standard way, it is usually reserved for patients with either limited or no rectal access because it requires more time and moderate sedation due to the percutaneous puncture (27). Antimicrobial prophylaxis is mandatory for transrectal way, remaining highly recommended for transperineal and transgluteal. Usually, fluoroquinolones are used, but due to growing resistance, a second antimicrobial should be also added (2).

Currently there is no consensus on which of the three MRGB techniques is more effective in PCa detection, basically because there have been substantial differences in methodology among the comparative studies, although cognitive biopsy seems to be the cheapest, but these three have shown the potential to overcome the drawbacks of the TRUS-SB (27).

As previously described, primary biopsy or biopsy-naïve is the first biopsy performed to the patient. The current procedure is to perform SB, and nowadays it is being recommended to include MRGB together (33) when a previous MRI has been performed, as some studies have found better PCa detection performing both SB and MRGB together (23,33).

As the cancer detection rate decreases from primary to repeated biopsies (9) due to the reduced prevalence of higher volume disease in patients with a prior negative biopsy (34), the targeting becomes even more logical in repeated biopsies.

Therefore, after a negative primary biopsy, patients are followed for PSA levels, PSA velocity and PSA density and the recommendation is to perform a mpMRI after a previous negative biopsy and a PSA level rising (35). Whenever a suspicious lesion is detected on mpMRI, a second SB of all the prostate plus an extra MRGB of the suspicious lesion is performed, that is the repeated biopsy. Some studies observed that the number of sample cores with PCa, this is positive cores, was significantly higher in the cognitive and fusion MRGB group than in the SB group in repeated biopsies, as they go targeted (36,37). In some other cases, the MRI does not show any lesions, so, because of the high negative predictive value of a first negative biopsy with a negative mpMRI, for some authors, a vigilance procedure can be considered instead to repeat the biopsy (11).

In primary biopsy many tumors will be detected on both SB and MRGB, but when re-biopsying after a negative primary biopsy (this is repeated biopsy), the tumors are mostly detected on MRGB rather than SB (27). This suggests that targeting improves the detection rate from systematic errors in SB such as missing lesions in midline, anterior, apical and extreme basal tumors (23,27,38). For this reason, both European Association of Urology and American Urology Association recommend performing an mpMRI in patients suspecting a PCa and a negative primary biopsy, before repeating biopsy (27).

The goal of this MRI previous to repeat the biopsy is to avoid an unnecessary biopsy if the MRI does not show any suspicion lesion and target the biopsy of the lesion if present, thus improving significant PCa detection while especially decreasing insignificant PCa detection. Nevertheless, both biopsies (SB and MRGB) are still performed, keeping all the side effects of sampling the entire prostate (blood in the urine or in semen, hematoma and pain in the puncture zone, infection, acute urine retention, erectile dysfunction, urethrorrhagia and rectal bleeding (39)) and mostly the risk to still detect insignificant cancer. Certainly, the question is, can we avoid the SB in patients with repeated biopsy indication (PCa suspicion) and apply a single MRGB as the unique procedure?

2. Justification

The high negative predictive value of multiparametric MRI (mpMRI) for detecting significant cancer has led to recommend this technique previous to a repeated biopsy in patients with risk of prostate cancer for a rising prostatic specific antigen (PSA) level, to shun unnecessary procedures when it does not show irregular areas. Whether a suspicious lesion is detected on mpMRI, it has been demonstrated that targeted biopsy, is superior to standard transrectal ultrasounds (TRUS)-guided systematic biopsy (SB) in identifying more clinically significant cancers, detecting less clinically insignificant cancer and obtaining fewer biopsy cores. However, other studies have not shown the superiority of this magnetic resonance-guided biopsy (MRGB) alone over SB, suggesting both techniques should be still performed together to improve prostate cancer (PCa) detection and that MRGB does not avoid the need for SB (33,40). Despite the addition of MRGB to the SB in primary biopsy that has improved significant PCa detection, it has also increased the detection of insignificant PCa as more cores are added (40), which could induce over-treatment, and has increased the risk of side effects within the procedure. Thus, currently the recommendation is to perform biopsies of the prostate gland with targeting the lesion but not to avoid all the systematic biopsies whether a suspected lesion is seen on MRI.

It could be reasonable to avoid detecting clinically insignificant cancer on patients that have had a previous negative biopsy and have suspected lesions on an MRI. For this purpose, it could be necessary to perform a unique target biopsy to the lesions found, without performing a systematic biopsy, reducing the prostate wound and insignificant cancer diagnostics.

For this reason, it should be compared whether MRI-US fusion guided biopsy technique (with a software fusion image in real time) shows similar or better accuracy than SB in men with an increasing PSA level after a first negative SB, for detecting clinically significant PCa.

3. Hypothesis

Magnetic resonance-guided biopsy (MRGB), by MRI-ultrasounds (US) fusion technique, demonstrates a higher efficacy in terms of clinically significant prostate cancer (PCa) detection with more proportion of positive cores, more quantity of tumor per core and less clinically insignificant PCa detection over systematic biopsy (SB) in patients with repeated biopsies indication due to persistent suspected PCa. In those patients SB may be avoided and could be performed a unique targeted MRGB.

4. Objectives

4.1. Main objective

The aim of the study is to assess if MRI-US fusion targeted biopsy technique detects more clinically significant PCa in comparison with SB in patients with a repeated biopsy indication for a suspected prostate cancer.

4.2. Secondary objectives

Other objectives are:

- To prove if MRI-US fusion targeted biopsy technique detects less clinically insignificant PCa in comparison with the SB in patients with a repeated biopsy indication.
- To determine the different sampling efficiency between MRGB and SB. This is the number of positive cores (cores with significant PCa) when performing MRI-US fusion targeted biopsy technique in comparison with SB technique.
- To calculate the differences of maximum cancer core length between MRGB and SB.
- To evaluate the anatomic location differences of significant PCa from each technique.
- To evaluate the accuracy of Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) score in mpMRI for significant PCa detection in MRGB technique.
- Evaluate the differences of clinical and epidemiological data (age, prostate volume, PSA levels, PSA velocity and PSA density, number of previous negative biopsies) from significant cancer and insignificant cancer.
- Evaluate the differences on overall PCa detection in each technique.

5. Material and methods

5.1. Study design

This is a descriptive cross-sectional study.

5.2. Participants

Participants in this study will be men with prostate cancer (PCa) suspicion admitted in Hospital Universitari de Girona Doctor Josep Trueta and Hospital de Santa Caterina who have indications for repeated biopsy with a suspicious lesion seen by MRI, by meeting the following criteria:

5.2.1. Inclusion criteria

- A negative primary prostate biopsy by systematic biopsy (SB) technique.
- Prostatic specific antigen (PSA) > 4 ng/mL and a PSA velocity > 0.75 ng/mL/year.
- A suspicious lesion on the multiparametric MRI (mpMRI), defined as PI-RADS 3, 4 or 5.

5.2.2. Exclusion criteria

- Patients who had received hormonal, surgical or irradiation therapy.
- Patients undergoing medical treatment for benign prostate hyperplasia (BPH).

5.3. Sample

5.3.1. Sample selection

A non-probabilistic consecutive sampling method will be used. Patients admitted in Hospital Universitari Doctor Josep Trueta (Girona, Spain) and Hospital de Santa Caterina (Salt, Spain) fulfilling the inclusion and exclusion criteria will be accepted for the study.

5.3.2. Sample size

The sample size has been calculated with the sample size and power calculator: “Calculadora de Grandària Mostral GRANMO versió 7.12” (41).

Using data from other papers, the clinically significant PCa detection rates in both techniques for repeated biopsies is estimated to be: 47,9% (9), for MRI-ultrasounds (US) fusion biopsy technique and 30,7% (9) for SB, showing significative differences between both techniques.

It has been accepted an alpha risk (α) of 0.05, a beta risk (β) of 0.2 and a drop-out rate of 10%.

With all this, GRANMO showed a sample size of 143 participants.

5.4. Variables

5.4.1. Independent variable

Biopsy technique: systematic biopsy (SB) and magnetic resonance imaging-guided biopsy (MRGB) by fusion technique. Both by transrectal ultrasounds (TRUS) guidance.

5.4.2. Dependent variables

Main outcome:

- Detection of clinically significant prostate cancer (PCa), defined as the presence of a single biopsy core indicating disease of Gleason score 3+4 =7 or greater. Expressed by the percentage of clinically significant PCa biopsies per total biopsies performed.

Secondary outcomes:

- Detection of clinically insignificant PCa, defined by a Gleason score 3+3 without any higher Gleason score. Expressed by percentage of clinically insignificant PCa biopsies per total biopsies performed.
- Sampling efficiency, defined as precision of the technique in sampling by the ratio of positive biopsy cores (cores with significant PCa) among the total cores obtained in each biopsy. Expressing the average percentage and standard deviation (SD).
- Maximum cancer core length in each biopsy, measuring in millimetres its mean and SD.
- PCa localization. Calculating the percentage of clinically significant PCa in peripheral zone (PZ) and transition zone (TZ) among all the clinically significant PCa been detected.
- Accuracy of PI-RADS v2 score in mpMRI. Calculating the proportion of clinically significant PCa in each 3, 4 and 5 PI-RADS stratus biopsied group.
- Percentage of PCa detection, adding all cancers (significant and insignificant) detected and dividing them by the biopsies performed.

5.4.3. Covariates

The following covariates might act as interaction variables between the biopsy technique efficacy and the clinically significant or insignificant PCa detection, so they will be determined in each group (biopsy technique and significant or insignificant PCa detection):

- Age: in years, calculating the mean and SD.
- Prostate volume: by mpMRI following PI-RADS v2 directions, multiplying 3 axes on T2-weighted images (T2WI) sequence: maximum transversal and antero-posterior axes on the axial view and oblique cranio-caudal axis on the sagittal view; and multiplying the

result by 0.52 (16). Calculating the mean and SD, in cm^3. Prostate volume will be used to calculate PSA density, too.

- Prostatic specific antigen (PSA) levels, PSA velocity and PSA density: from the blood samples taken before, calculating the mean and SD, in ng/mL, ng/mL/year and ng/mL^2, respectively.
- Number of previous biopsies, calculating the median and interquartile ranges.

Table 4. Recapitulation of dependent variables and covariates.

Main outcome
Significant PCa detection
Secondary outcomes
Insignificant PCa detection
Sampling efficiency
Cancer length
PCa localization
PI-RADS v2 score accuracy
PCa detection
Covariates
Age
Prostate volume
PSA, PSA density, PSA velocity
Previous biopsies

PCa prostate cancer, PI-RADS v2 Prostate Imaging Reporting and Data System version 2, PSA prostatic specific antigen

5.5. Methods of measurement

5.5.1. MpMRI protocol and analysis

All patients with a repeated biopsy indication will undergo a 1.5T prostate MRI (General Electric, Signa for Hospital de Santa Caterina; Philips, Ingenia and Philips, Achieva dStream for Hospital Universitari de Girona Doctor Josep Trueta) without an endorectal coil before the repeated biopsy. MRI protocol will include an axial T1-weighted sequence from the pelvis, an axial and sagittal T2WI sequence from the prostate and an axial diffusion-weighted imaging (DWI) sequence. DCE sequence will not be included to reduce patient disturbances, time and costs.

Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) will be used to evaluate prostate lesions following the below criteria:

- DWI will be the dominant sequence in the peripheral zone (PZ) (Annex 14.4, but with no contrast infusion, DCE, thus biopsying every PI-RADS 3 category) and T2WI in the transition zone (TZ) (Annex 14.5). The axial and sagittal views in T2WI will be used to estimate the prostate volume. The written report of the cancer's anatomic location will be described as it is on PI-RADS v2 guide (Annex 14.6).

Two experienced radiologists will be in charge of evaluate the MRI studies:

- The radiologist (with more than 2 years of experience in prostate MRI), before the biopsy, will report mpMRI images following the PI-RADS v2 criteria. A positive MRI study will be defined as presence of PI-RADS 3, 4 or 5 lesions, this being the target lesion. Only participants with a positive mpMRI can be biopsied in the study (included participants).
- The genitourinary radiologist (with 5 years of experience in MRGB), during the biopsy procedure and after performing the SB, will perform the MRGB by fusion technique.

5.5.2. Biopsy protocol

The genitourinary radiologist with 5 years of expertise in MRGB will carry out the biopsies initially blinded to the MRI images, with less than 4 weeks after the MRI. The biopsy procedure includes:

- A correct coagulation assessment must be done by visiting the haematologist 1 week before the biopsy procedure.
- Antimicrobial prophylaxis with oral Cefuroxime 500mg 2 hours prior to the biopsy procedure.
- A cleansing enema will be administered the day before the examination.
- Left lateral decubitus as the position to perform the biopsies.
- A previous digital rectal examination with an anaesthetic and lubricant cream.

First, a 12-cores systematic biopsy (SB) will be taken by TRUS guidance, without any information from the previous MRI, with the following succession: 2 cores directed towards the medial segments of the PZ, 2 cores towards the lateral segments of the PZ and 2 cores towards the TZ for each lobe of the prostate (Annex 14.6). Then, if visible by TRUS, 1 core towards the suspicious lesion will be added, if the SB does not include it.

5.5.2.1. Software fusion protocol

The mpMRI images previously reported by the first radiologist in each hospital, will be now imported to the US machine of Hospital Universitari de Girona Doctor Josep Trueta, and then,

fused with the real time TRUS image by Toshiba/Canon software platform and rigid registration method.

After that, with the fused images displayed on the US screen and knowing the reporting of the MRI lesion made by the first radiologist, 2 cores of each targeted lesion by MRI-US fusion software technique will be taken by the same genitourinary radiologist who performed the SB.

So, the first biopsy procedure (SB) will include 12±1 cores, while the second procedure (MRI-US fusion technique) will include 2 cores per lesion located.

The biopsy cores will be sent to the anatomopathological department.

5.5.3. Anatomopathological protocol

Biopsies from each technique will be reviewed by a single uropathologist of Hospital Universitari de Girona Doctor Josep Trueta with at least 2 years of experience in urologic cancer reporting. If cancer is detected, cancer length will be measured in millimetres and histologic grading will be accorded following Gleason score.

The cases of PCa will be recorded in number and divided into the following categories: significant PCa (as Gleason ≥7) and insignificant PCa (as Gleason ≤6).

Locations of PCa within the zonal anatomy of the prostate will also be divided in 2 groups: peripheral zone (PZ) and transition zone (TZ), here including central zone (CZ) and anterior fibromuscular tumors too.

5.5.4. Feedback from the histological result to the PI-RADS score

Every clinically significant PCa result will be matched with its previously assigned PI-RADS v2 category: 3, 4 or 5.

6. Statistical analysis

For all analysis, a p value <0.05 will be defined as statistically significant.

6.1. Variables definition

To perform the statistical analysis of the data, first, the variables have been classified in 2 categories:

- Qualitative or categorical:
    - Independent variable: the technique of biopsy is considered as a nominal variable.
    - Outcomes: significant prostate cancer (PCa) detection, insignificant PCa detection, PCa localization and PCa detection as nominal variables. To get the outcome "Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) accuracy", the main outcome "significant PCa detection" will be stratified in PI-RADS categories 3, 4 and 5.
- Quantitative or numeric:
    - Outcomes: sampling efficiency and cancer length as continuous variables.
    - Covariates: age, prostatic specific antigen (PSA) levels, PSA velocity, PSA density and prostate volume as continuous variables; previous biopsies as a discrete variable.

6.2. Univariate analysis

A descriptive analysis of the variables will be performed.

Categorical variables will be expressed as proportions (%) for each category assessed and will be shown with bar charts.

With continuous numeric variables, the mean and standard deviation (SD) will be calculated. For the discrete numeric variable, the median and interquartile ranges (IQR) will be used. Quantitative variables will be shown as box-plot charts.

6.3. Bivariate analysis

It will be stratified for significant and insignificant cancer to do simple inference in relation with the main objective. In particular, it will be compared the proportions of the independent variable and the mean or median of the covariates with the groups defined by significant and insignificant cancer, by performing a Chi-square test (X^2) or Fisher's F exact test when the expected

frequencies be less than 5 for the difference of proportions, Student's t test to compare means and Mann-Whitney U test for median comparisons.

The same analysis will be performed stratifying for significant PCa localization and PI-RADS stratus 3, 4 and 5 of significant PCa.

6.4. Multivariate analysis

Several logistic regressions will be carried out, with the main independent variable of interest being the biopsy guidance technique used (ultrasounds or fusion), adjusting for covariates (age, prostate volume, PSA, PSA density, PSA velocity and previous biopsies) and the following dependent variables:

- Significant PCa or insignificant PCa
- PCa localization (PZ or TZ)

Furthermore, several lineal regressions with the same independent variable and the same covariates will be carried out with the dependent variables:

- Sampling efficiency
- Cancer length
- PCa detection

In all cases the interactions between the techniques and covariates to detect significant cancer will be evaluated.

7. Ethical and legal aspects

The study will be performed following the "Ethical Principles for Medical Research involving Human Subjects" established by the World Medial Association in Declaration of Helsinki (1964, lately revised in 2013) (42) and "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research" (43).

Before starting the study, the protocol will be sent to the Clinical Research Ethics Committee (CEIC) of Hospital Universitari de Girona Doctor Josep Trueta, and its advices will be followed to get its approval.

This study will be carried out respecting the biomedical research regulation described in "Ley 14/2007, de 3 de julio, de Investigación Biomédica" and "Real Decreto 1716/2011, de 18 de noviembre" for invasive procedures and use of biological samples in biomedical research, and "Real Decreto Legislativo 1/2015, de 24 de julio".

The patients fulfilling the inclusion criteria of the study will be appropriately informed about it and a written consent will be asked for (Annex 14.7) prior to the biopsies, where it is collected the information about the biopsy procedure and the study (name, objectives and methods). It is mandatory to have signed the informed consent to participate in the study.

To guarantee and protect confidentiality of all participants, as well as their personal data, the study will be performed according to "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales". Patient information will remain confidential, it will only be used for the purpose of the research and data will be analysed anonymously.

The research team will assert that all the results will be published with transparency and clarity, avoiding any unfavourable data exclusion.

A no conflict declaration will be declared by all the investigators participating in the study. The authors will declare that the ultimate goal of this research is to build better knowledge to improve human health and quality of life.

8. Limitations

Some limitations should be considered:

- I am aware of this is not a common comparative study between a diagnostic technique and the Gold Standard (GS), because there is not a GS described for prostate cancer (PCa) detection. Ideally, all results should be compared to prostatectomy specimen, in order to be fully able to define the real presence of clinically significant PCa and confirm the localization of the index tumor.
- This study will use a non-probabilistic sampling method, which means that the subjects of the study population will not have the same chance to be elected to constitute the sample, which could lead to a non-representative sample. Although, we will use the consecutive method as is one of the non-probabilistic methods that induces less bias, as theoretically guarantees a free-of-choice selection. Even so, it could be possible that in the task of participants recruitment, the radiologists may not perform the study at every potential candidate fulfilling the inclusion and exclusion criteria, generating a selection bias.
- Multiple effect modifiers may influence the association between dependent and independent variables. It will be tried to detect these interactions through a multivariate analysis.
- Even if there is a small risk of sample loss as the study has been designed as a cross-sectional study, a few losses will occur mainly due to the right of not signing or revoking the informed consent among included patients. For this reason, it will be anticipated with a drop-out rate of 10%.
- As we will use the multiparametric magnetic resonance imaging (mpMRI) for selecting men at risk, we will not include scores Prostate Imaging Reporting and Data System (PI-RADS) 1 and 2 in the study, which can enhance the performance of systematic biopsy (SB) that, otherwise, it would re-biopsy every PCa suspicion (including those low-probably cancer patients).
- Also, as these men with negative mpMRI (PI-RADS ≤2) will not be enrolled in the study, it will not be possible to compare PCa detection rates between those with negative and those with positive mpMRI (PI-RADS ≥3), what would be interesting to complete the outcome “PI-RADS v2 score accuracy”. However, these men will have at least one previous negative biopsy, which provides added justification for excluding men with negative mpMRI from the present study. Additionally, mpMRI has been reported to have a high negative predictive value (>90%).

- The PI-RADS v2 guide suggest a dynamic contrast enhanced (DCE) sequence for those equivocal cases (PI-RADS 3) in peripheral zone (PZ), in order to better classify them into category 3 or 4. It will not be applied, in this study, the contrast sequence as it has not shown additional significant PCa detection and, additionally, so as to save time, costs and avoid patients exposure to gadolinium. Thus, biparametric MRI will be the technique used.
- The results of a biopsy by the fusion technique rely on various factors, including the strength of the MRI magnet, the quality of the MR images, the experience of the radiologists interpreting the MR images and the experience of the genitourinary radiologist performing the fusion biopsy, that may increase by a learning curve within the technique. These factors should be considered when evaluating the results of any study and when counselling patients for prostate MRI and fusion biopsy.
- For some, insignificant PCa is defined as Gleason ≤6, <0.5cm³ and confined to the prostate, but this still remains without total accord. For that reason and the fact that is not easy to measure the tumor volume, only the Gleason score will be consider to classify insignificant tumors.
- It will be tried to strongly avoid the information bias by blinding the genitourinary radiologist who perform the biopsies, from the MRI images. Nevertheless, there will exist a lack of blinding within the anatomopathological study as the uropathologist can receive both 12 biopsy cores and 2 biopsy cores, knowing that the 12-cores biopsy belongs to the SB and the 2-cores biopsy from the magnetic resonance-guided biopsy (MRGB), thus falling into an information bias.
- By performing part of the study in two different centres, there can be disparity in data collection from the mpMRI, especially with the experience of the radiologist using the PI-RADS score. Anyway, we will try to minimize it by choosing radiologists with more than 2 years of prostate MRI reporting and similar years of experience between them. Furthermore, there are planned some days for mpMRI protocol coordination and data collection checking between both radiologists.
- So, by selecting participants in 2 coordinated centres and with an MRI reporting standardized system, plus the fact that both biopsy techniques are performed to the same patients and both radiologists will have similar years of experience, result in a high intern validity of the study. However, by accomplishing it in one single study population, may limit the ecological validity, making complicated to generalize the findings.

9. Chronogram and work plan

9.1. Participating centres, research team staff and associated personnel

2 hospitals will participate in the study:

- Hospital Universitari Doctor Josep Trueta (Girona)
- Hospital de Santa Caterina (Salt)

With the following research team staff involved:

- 2 radiologists (RD1 and RD2): both with more than 2 years of experience in prostate MRI.
    - RD1 will be the radiologist from Hospital Universitari de Girona Doctor Josep Trueta, this being the principal researcher (PR).
    - RD2 will be the radiologist from Hospital de Santa Caterina.
- 1 genitourinary radiologist (GUR): with 5 years of experience in prostate magnetic resonance-guided biopsy (MRGB).
- 1 Uropathologist (UP): with at least 2 years of experience in urologic cancer reporting.

Both GUR and UP will be from Hospital Universitari de Girona Doctor Josep Trueta.

Other out of the study but implicated personnel are:

- A qualified statistician (St) from Institut d'Investigació Biomèdica de Girona (IdibGi) will carry out the statistical analysis.
- An expert radiologist with 2 years of experience in fusion technique will implement the MRI-US fusion training for the GUR.
- MRI technicians (MRIt) of both hospitals, to perform the multiparametric MRI (mpMRI) following the MRI protocol.

9.2. Study stages

The estimated duration to perform the study will be approximately 24 months, including the following stages:

- Stage 1: centres request, protocol elaboration and ethical evaluation (5 months).
    - Bibliography research: by the principal researcher (PR) (1 month).
    - Proposal to centres: to request both centres to participate in the study, by the PR (1 month).
    - Protocol elaboration: written by the PR (2 months).

- Protocol consent: modification and approval of the protocol after the advices of Clinical Research Ethics Committee (CEIC) (1 month).

- Stage 2: coordination and formation of the research team staff (1 month).
  - Coordination within the research team: by 2 meetings involving every member of both participant centres (RD1, RD2, GUR, UP). The PR will explain the aims of the study, the inclusion and exclusion criteria and the methods to perform and report the MRI, the MRGB and the data collection (1 week).
  - MRI technician's protocol explanation: RD1 and RD2 will show the MRI protocol to the MRI technicians of their hospital (1 week).
  - MRGB fusion technique training: the GUR will assist to a fusion software 4-day formation imparted in Hospital Universitari de Girona Doctor Josep Trueta by an expert radiologist with at least 2 year of MRI-US fusion technique experience (1 week, 3h/day).
  - Data collection explanation: the UP will receive an explanation, by the PR, of how to gather and group data together, after interpreting them, into the different categories: significant, insignificant or total prostate cancer (PCa) detected (1 week).
- Stage 3: participant's enrolment and data collection (13 months).
  - MpMRI acquisition: all patients with a repeated biopsy indication will undergo a 1.5T prostate MRI in both centres, by following the MRI protocol.
  - Participant's recruitment and informed consent (IC): after starting reporting mpMRI images following the PI-RADS v2 criteria, both RD will also apply the inclusion and exclusion criteria to enrol patients until the sample size will have been covered, asking for the informed consent to include them (Annex 14.7).
  - Covariates record: both RD will be in charge of collect clinical and epidemiological data from each patient (PSA levels, PSA velocity and PSA density, prostate volume, age, number of previous negative biopsies) after the mpMRI, during participant's enrolment.
  - Biopsies: GUR will perform both biopsies to each registered patient who has consent, starting as soon as the firsts participants are included by the RD.
  - Data collection: data from each biopsy group will be compiled by the UP, starting to review simultaneously with the biopsy procedures.

    - Radiologists first meeting: both RD will gather to solve practical problems, test mpMRI protocol coordination and check data collection in the midst of the process (1 day).
- Stage 4: statistical analysis, accomplished by a qualified statistician from IdibGi (1 month).
- Stage 5: interpretation of the results (1 month).
    - The research team staff will meet to analyse, interpret and discuss the results obtained (twice in 1 week).
    - Radiologists second meeting: both RD will put in common their discussions and interpretations (1 week).
    - The PR will write a final report with the most relevant aspects of the study (2 weeks).
- Stage 6: publication and dissemination of the results (3 months).
    - Article publication: the PR will write a journal article with the findings and will apply for its publication (1 month).
    - The PR will attend to congresses to present the conclusions of the study (2 months, once a week).

			2019				2020			
	Tasks	**Person**	**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	Bibliography research	PR								
	Proposal to centres	PR								
	Protocol elaboration	PR								
	Protocol consent	CEIC/PR								
stage 2	Research team coordination	All								
	MRI technician's explanation	RD1/RD2								
	MRGB fusion technique training	GUR								
	Data collection explanation	PR/UP								
stage 3	MpMRI acquisition	MRIt								
	Participant's recruitment and IC	RD1/RD2								
	Covariates record	RD1/RD2								
	Biopsies	GUR								
	Data collection	UP								
	Radiologists first meeting	RD1/RD2								
s4	Statistical analysis	St								
stage 5	Research team meeting	All								
	Radiologists second meeting	RD1/RD2								
	Writing final report	PR								
s6	Article publication	PR								
	Result dissemination	PR								

10. Feasibility

Both hospitals have already available means to conduct the study.

In the context of performing the study in 2 years, multiparametric MRI (mpMRI) and biopsies will last 11 months each (around 220 effective days). The rhythm needed to apply the timing of the chronogram is approximately 200 mpMRI scans (estimation to get the sample size) in 220 days in 2 hospitals, and 143 biopsies (sample size) in 220 days to complete the sample. These proportions show an easily affordable rate of less than 0.5 mpMRI scans per day and less than 1 biopsy performed and examined per day.

Magnetic resonance imaging-ultrasounds (MRI-US) fusion software is not still applied in most hospitals. Although the radiologists of Hospital Universitari de Girona Doctor Josep Trueta are experimented in the field of cognitive magnetic resonance-guided biopsy (MRGB), the fusion MRGB technique is unknown for most of the radiologists, by now. To solve this lack of knowledge, there is a 12-hour fusion training programmed, imparted by an experienced radiologist in fusion technique. The rest of the research team staff, uropathologists and radiologists of Hospital Universitari de Girona Doctor Josep Trueta and radiologists of Hospital de Santa Caterina, have broad experience in prostate cancer diagnosis procedure, and the principal researcher has already been involved in other prostate MRI publications.

11. Budget

11.1. Non-included costs

- Staff: the personnel involved in the study who work in the hospital will not be reimbursed.
- Materials: the magnetic resonance imaging (MRI) acquisition is not included in the budget as it is part of the currently diagnosis in Hospital Universitari de Girona Doctor Josep Trueta for patients with repeated biopsy indication (cognitive MRGB+SB). In the same way, Hospital Universitari de Girona Doctor Josep Trueta has already the equipment to perform the biopsies, as it is the same as currently used to perform the SB. The hospital already has the fusion software gadgets attached to its ultrasounds (US) equipment, too.

11.2. Included costs

11.2.1. Material costs

- Informed consent sheet: for a sample size of 143 people we will print 160 informed consent double-sided sheets at 0.08€ per copy, 12.80€

11.2.2. Personnel costs

- Expert radiologist with fusion experience: who will impart a 12-hour fusion formation in 4 days to the genitourinary radiologist. The training will be paid for 50€/h, with a final cost of 600€.
- Qualified statistician from Institut d'Investigació Biomèdica de Girona (IdibGi): who will accomplish the statistical analysis. For 25€/h and working approximately 64h in a month, it will cost 1,600€.

11.2.3. Travels and meals costs

- The travel, lodge and meals for the radiologist who impart the fusion formation: 4 days and 3 nights in an hotel, costing 400€ in total

11.2.4. Divulgation costs

- Publication fees: It will be assumed 1,000€ to publish a journal article.
- Inscriptions to congresses: to divulge the results through national and international urology congresses: 750€ for national congresses attendance and 1,500€ for international congresses attendance.

11.2.5. Overhead

The overhead costs for hospitals will be assumed as 10% of the total cost.

The overall cost assumed for the study is 6,449.08€.

Table 5. Detailed costs of the study

	Item	Cost	TOTAL
Non-included costs	Research staff and materials	0€	0€
Materials	Informed consent sheet	0.08€/copy	12.80€
Personnel	Radiologist imparting fusion training	50€/h	600€
	Statistician	25€/h	1,600€
Travels and meals	4 days radiologist travel, lodge and meals	100€/day	400€
Divulgation	Publication fees	1,000€	1,000€
	Inscriptions to congresses	750€ for national	750€
		1,500€ for international	1,500€
Overhead	Hospitals overhead	10% of total cost	586.28€
			6,449.08€

12. Impact on the national health system

Prostate cancer is the most common non-skin cancer in men, achieving the fifth position in cancer-related deaths among men. For these reasons, a suitable diagnosis procedure must be done.

As previously discussed, prostate biopsy has some drawbacks such as hematoma and pain in the puncture zone, haematuria, hematospermia, infection, difficulties with urination, acute urine retention, erectile dysfunction, urethrorrhagia and rectal bleeding (39), and more specifically systematic biopsy (SB), has the weakness of over-detecting clinically insignificant prostate cancer (PCa) while under-detecting clinically significant disease. This uncertainty with the results of SB leads to increase patient anxiety, compelling patients to elect unnecessary therapies with associated morbidity, decreased quality of life and increased costs of care (2).

If the hypothesis of this study is validated by the results, it would be reasonable to contemplate a change in the currently procedure of repeated biopsy, moving from a double SB plus magnetic resonance-guided biopsy (MRGB) to a single MRGB by fusion technique.

Hence, with favourable results, patients could benefit from a new technique with less side effects, less iatrogenic effects associated with the low insignificant PCa detection rate, and more accuracy in significant PCa detection, thus preserving a higher quality of life. Concisely, hospitals could decrease costs in PCa detection with better quality of care.

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14. Annexes

14.1. Prostate anatomy through MRI: T2WI sequence

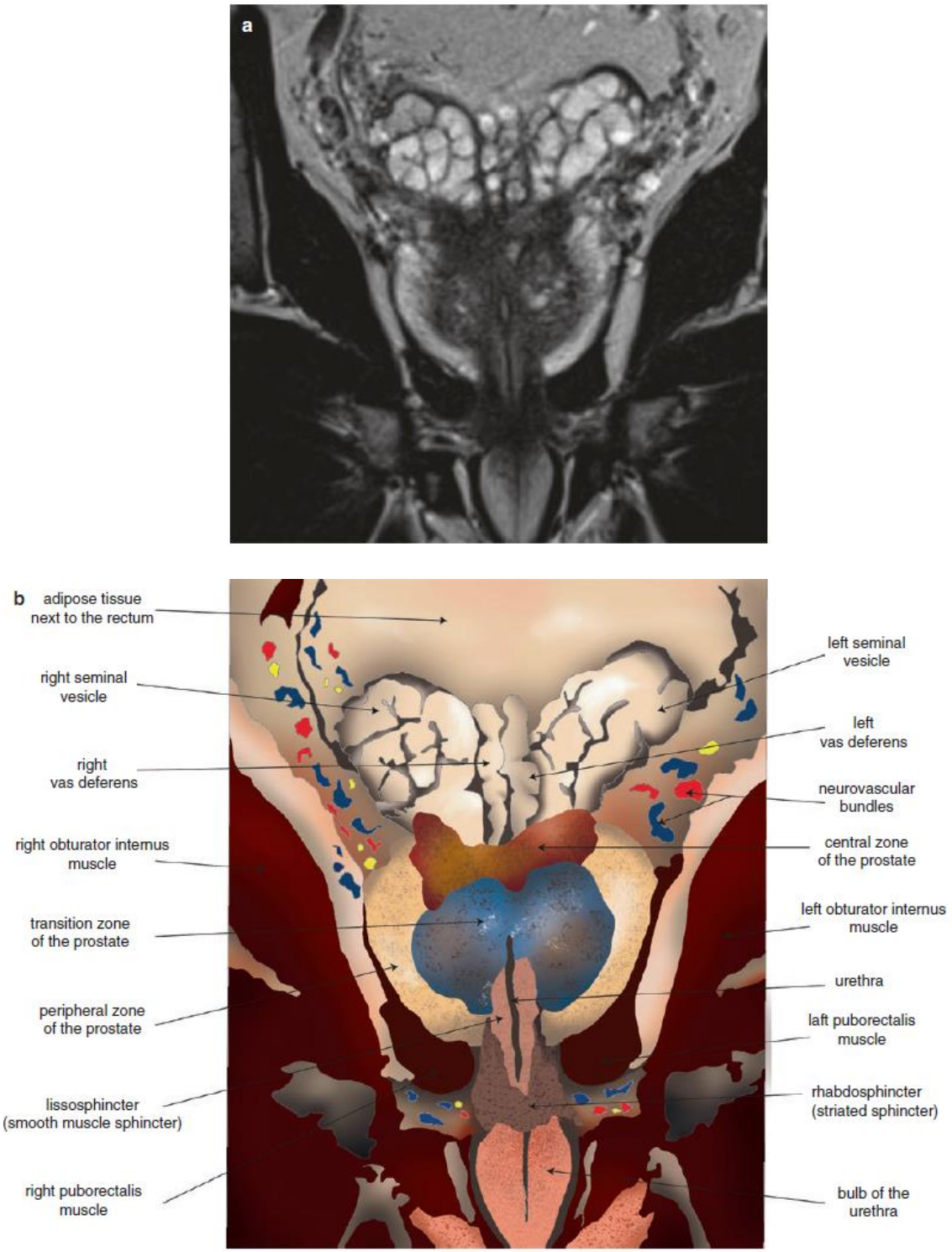


Figure 4. Coronal section of the prostate. (a) Appearance on T2WI sequence. (b) Anatomical drawing of the same location as shown in (a). Obtained from (17).

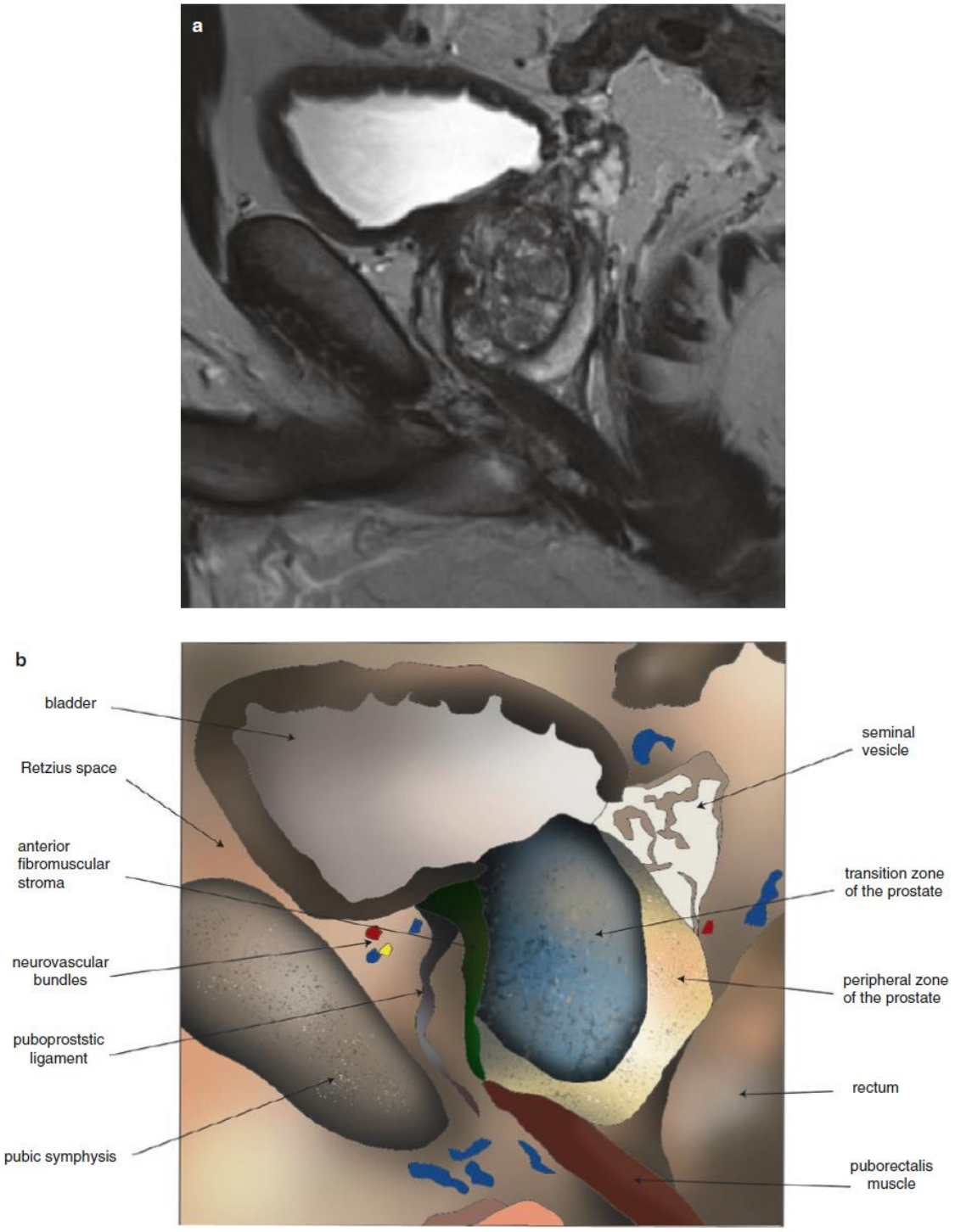


Figure 5. Parasagittal section of the prostate. (a) Appearance on T2WI sequence. (b) Anatomical drawing of the same location as shown in (a). Obtained from (17).

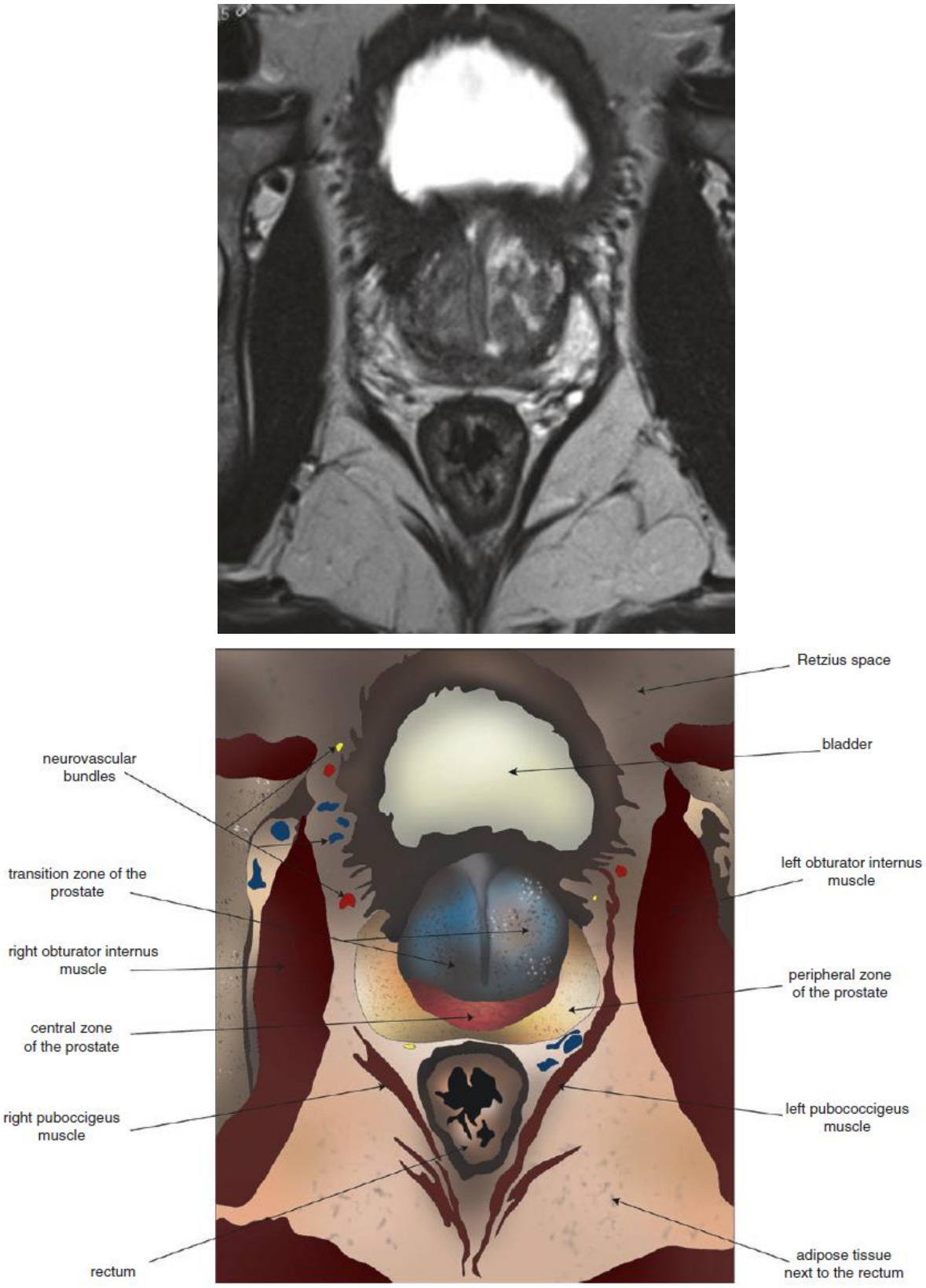
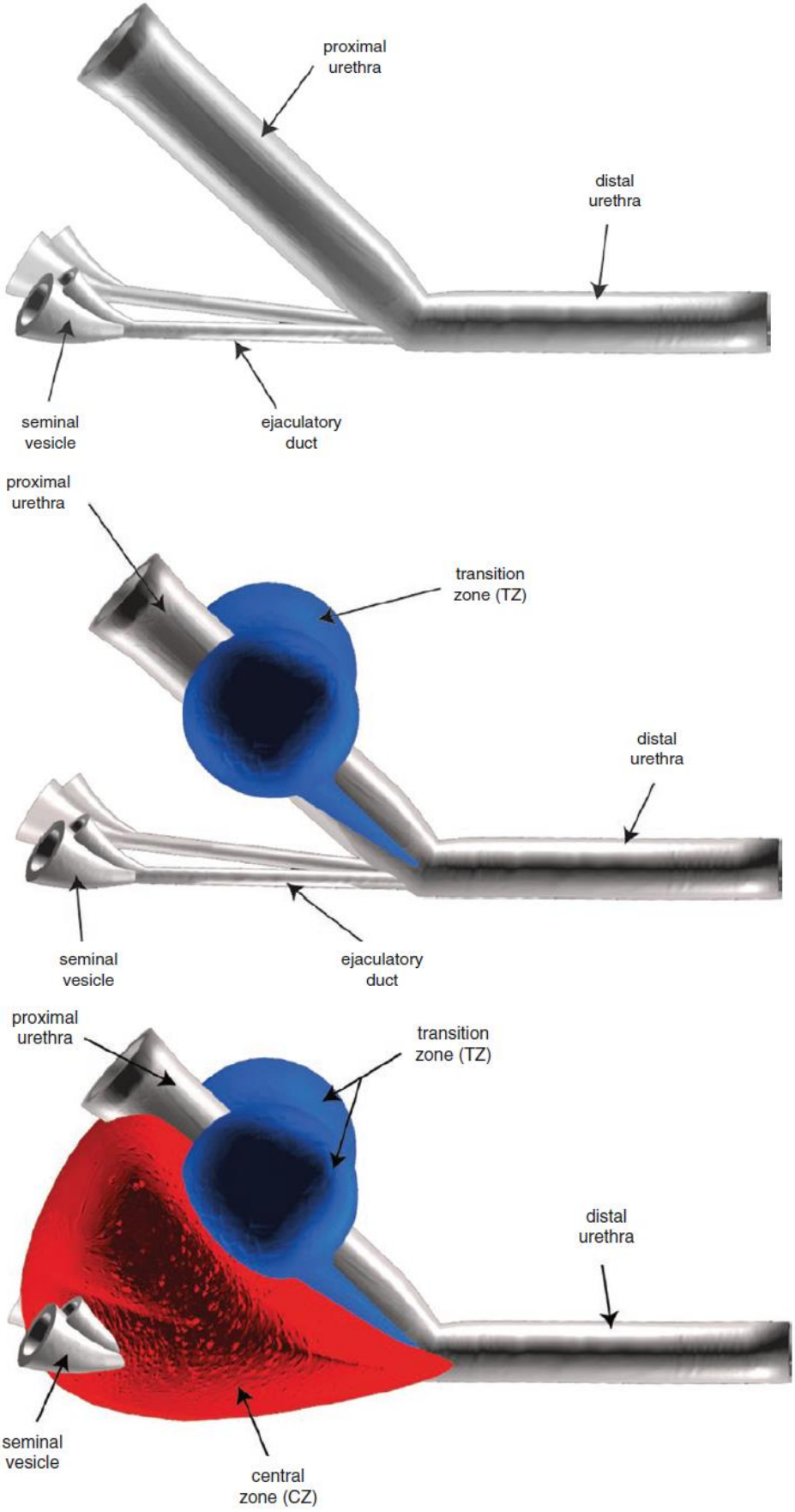


Figure 6. First, axial section of the prostate base on T2WI. Second, the anatomical drawing of the same location as shown in the first image. Obtained from (17).

14.2. Anatomical division drawing of the prostate



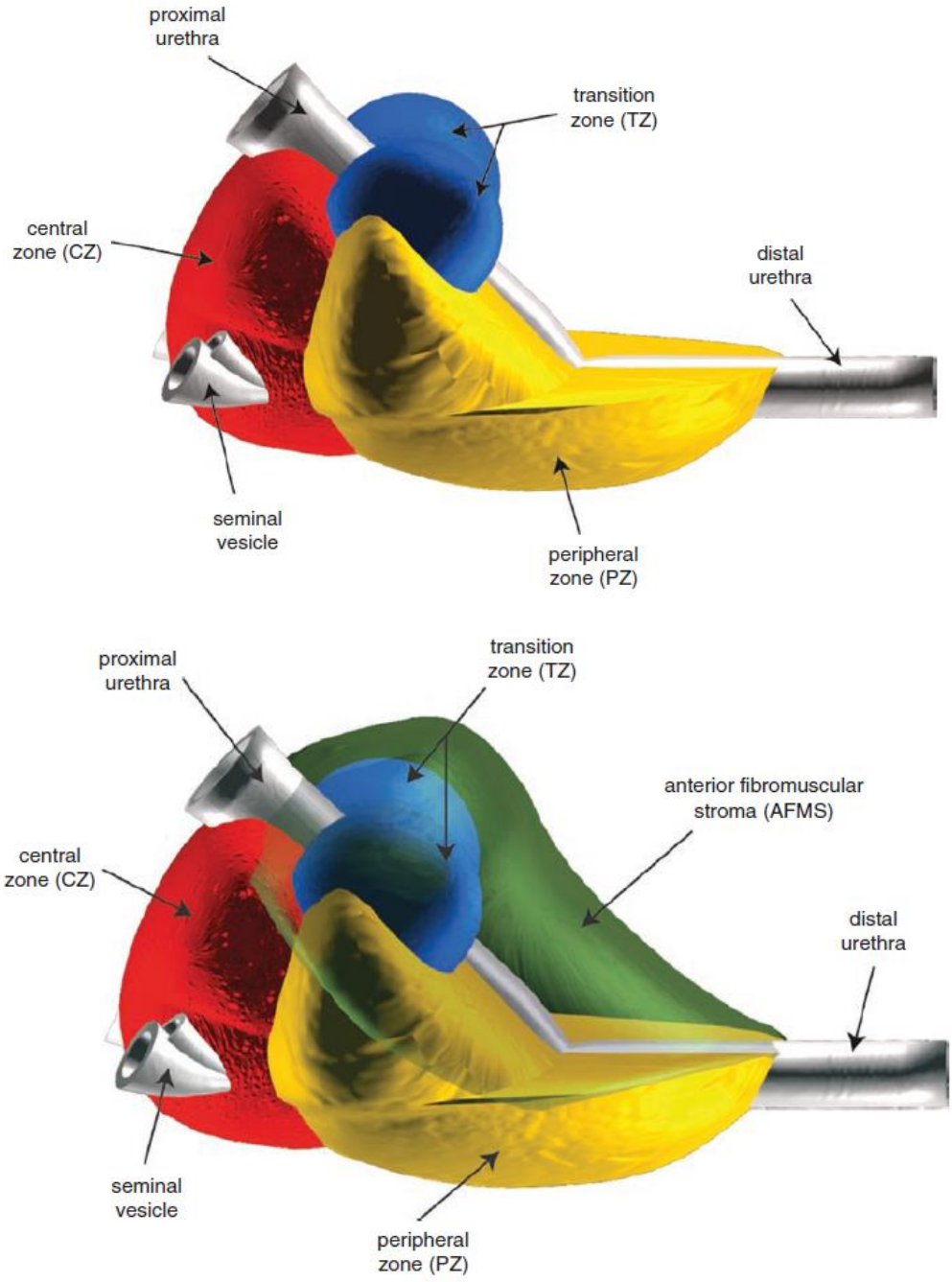


Figure 7. Drawing of the anatomical division of the prostate by McNeal's mode in a sagittal view. Obtained from (17).

14.3. T1-weighted sequence: prostate haemorrhage

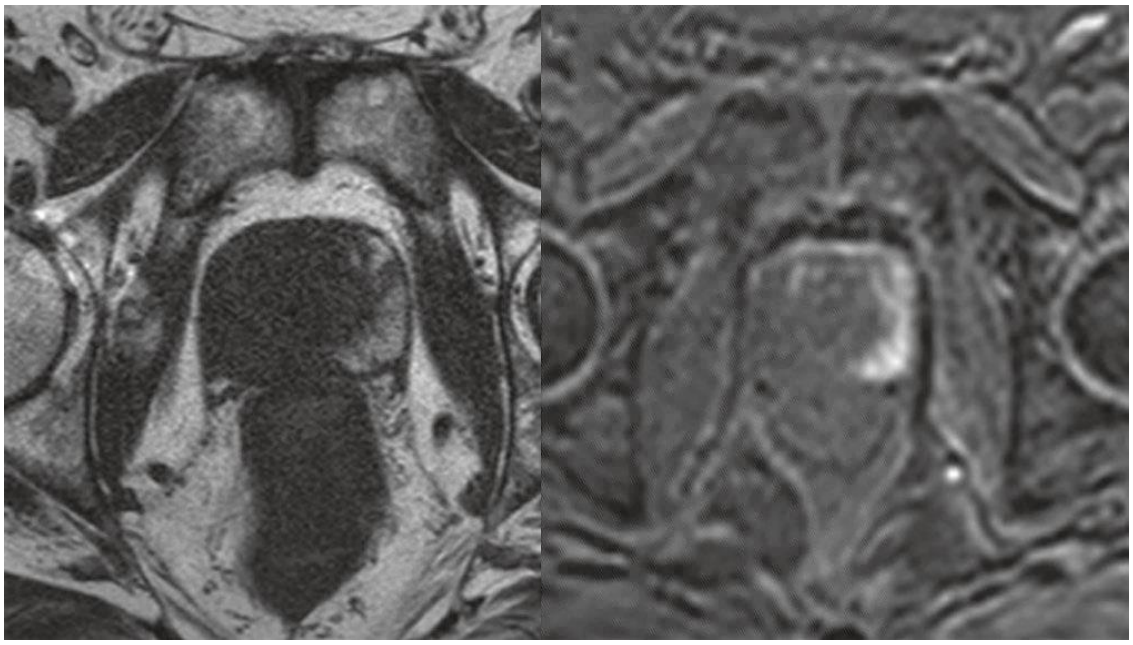


Figure 8. Post biopsy haemorrhage area showing hyperintensity in T1-weighted sequences in the left peripheral zone. First, axial turbo spin-echo T1-weighted sequence. Second, precontrast fat-supressed fast-field-echo T1 weighted sequence. Obtained from (8).

14.4. PI-RADS assessment category for the peripheral zone (PZ)

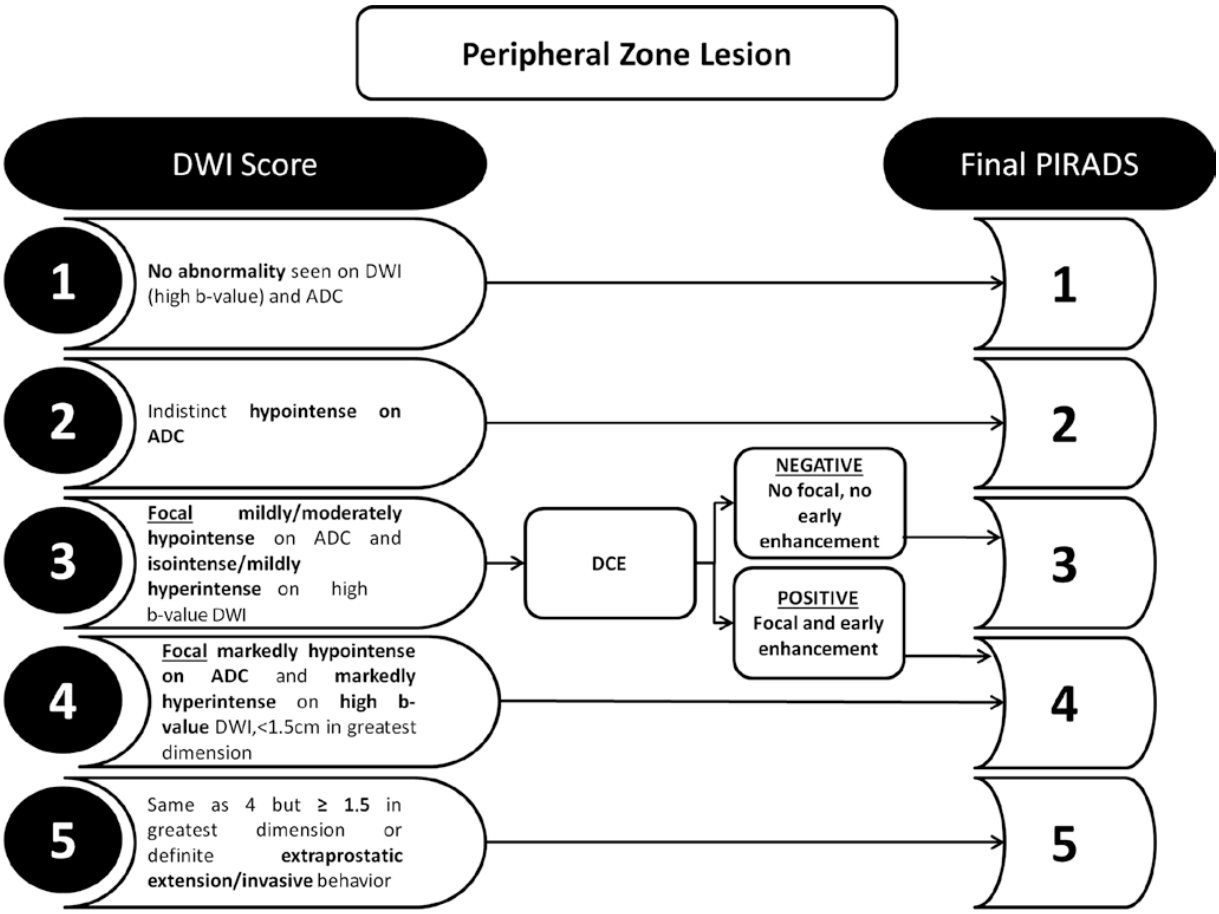


Figure 9. PI-RADS v2 scoring for the peripheral zone (PZ). ADC apparent diffusion coefficient, DWI diffusion weighted imaging, DCE dynamic contrast enhancement, PIRADS Prostate Imaging Reporting and Data System. Obtained from (10).

14.4.1. PZ and TZ: PI-RADS 1

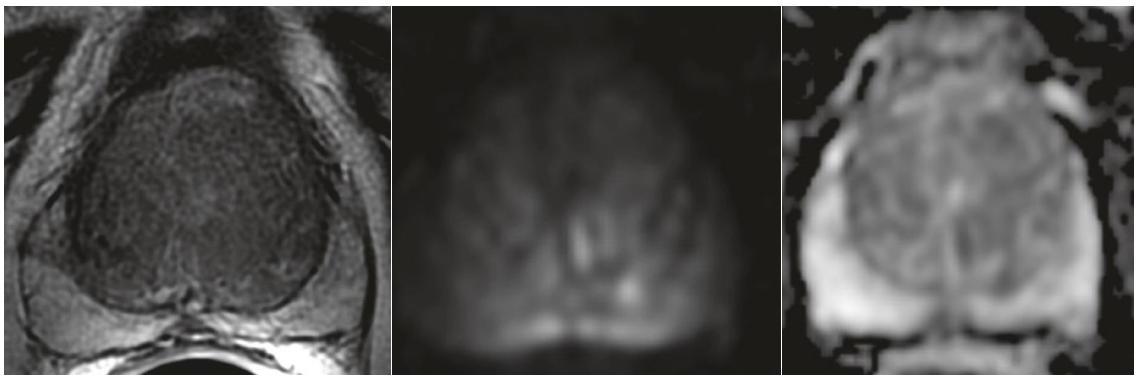


Figure 10. PI-RADS 1 category in PZ and TZ. First, axial T2WI. Second, b1400 DWI. Third, ADC map, without any abnormality on DWI/ADC map in the PZ and homogenous intermediate signal intensity of the TZ on T2WI. Obtained from (12).

14.4.2. PZ: PI-RADS 2

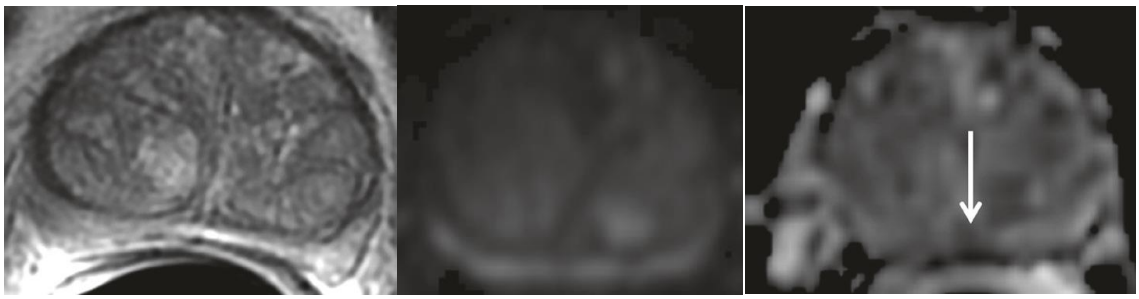


Figure 11. PI-RADS 2 category in PZ. First, T2WI. Second, b1400 DWI. Third, ADC map, without any focal lesion on DWI and a mild low signal intensity on ADC map (arrow) in the PZ. Obtained from (12).

14.4.3. PZ: PI-RADS 3

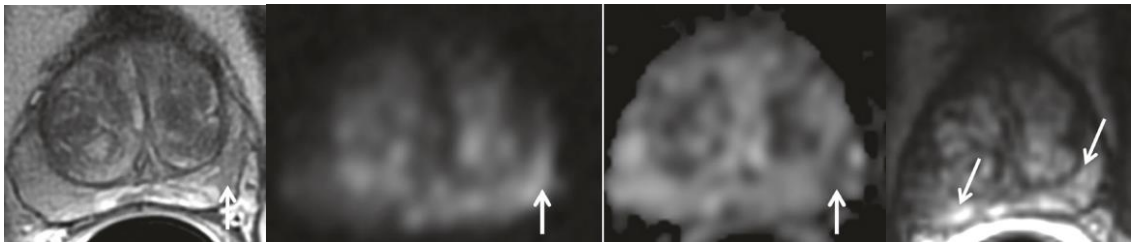


Figure 12. PI-RADS 3 category in PZ. First, axial T2WI. Second, b1400 DWI. Third, ADC map. Fourth, DCE at 10 seconds. Shows a mildly focal high signal area on DWI and mildly hypointense on ADC (arrows) in the left PZ, corresponding to an intermediate signal intensity on T2WI. DCE shows early diffuse uptake of the PZ bilateral (arrows), indicating negative contrast assessment. Obtained from (12).

14.4.4. PZ: PI-RADS 4

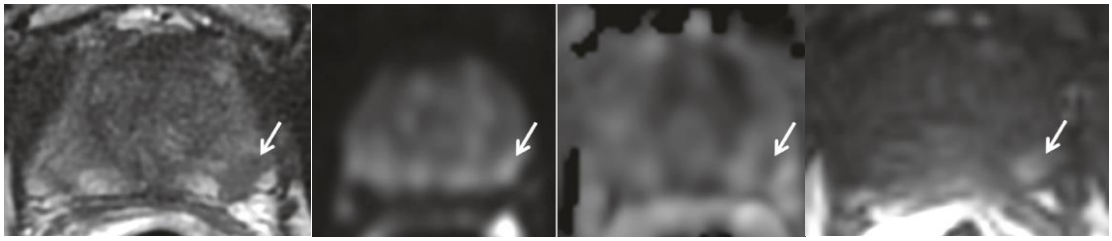


Figure 13. PI-RADS upgrading from 3 to 4 category in PZ. First, axial T2WI. Second, b1400 DWI. Third, ADC map. Fourth, DCE at 10 seconds. Shows a mildly focal high signal area on DWI and mildly hypointense on ADC (arrows), corresponding to a low signal intensity on T2WI (arrows). DCE shows early focal uptake at the same location (arrows), indicating positive contrast assessment. Obtained from (12).

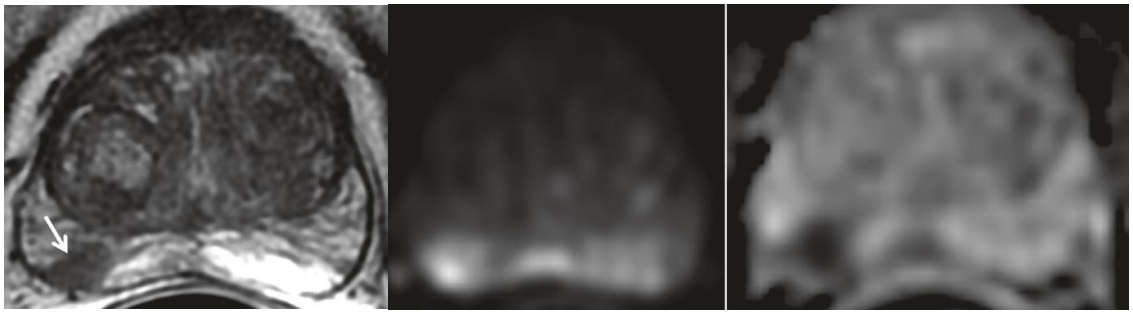


Figure 14. PI-RADS 4 category in PZ. First, axial T2WI. Second, b1400 DWI. Third, ADC map. Shows focal low signal lesion in the right PZ (arrow) on T2WI, with markedly hyperintense signal on DWI and markedly hypointense signal on ADC, <1.5 cm. Obtained from (12).

14.4.5. PZ: PI-RADS 5

Figure 15. PI-RADS 5 category in PZ. First, axial T2WI. Second, b1400 DWI. Third, ADC map. Shows focal low signal lesion in the right PZ (arrow), with markedly hyperintense signal on DWI and marked hypointense signal on ADC, with features of extraprostatic extension. Obtained from (12).

14.5. PI-RADS assessment category for the transition zone (TZ)

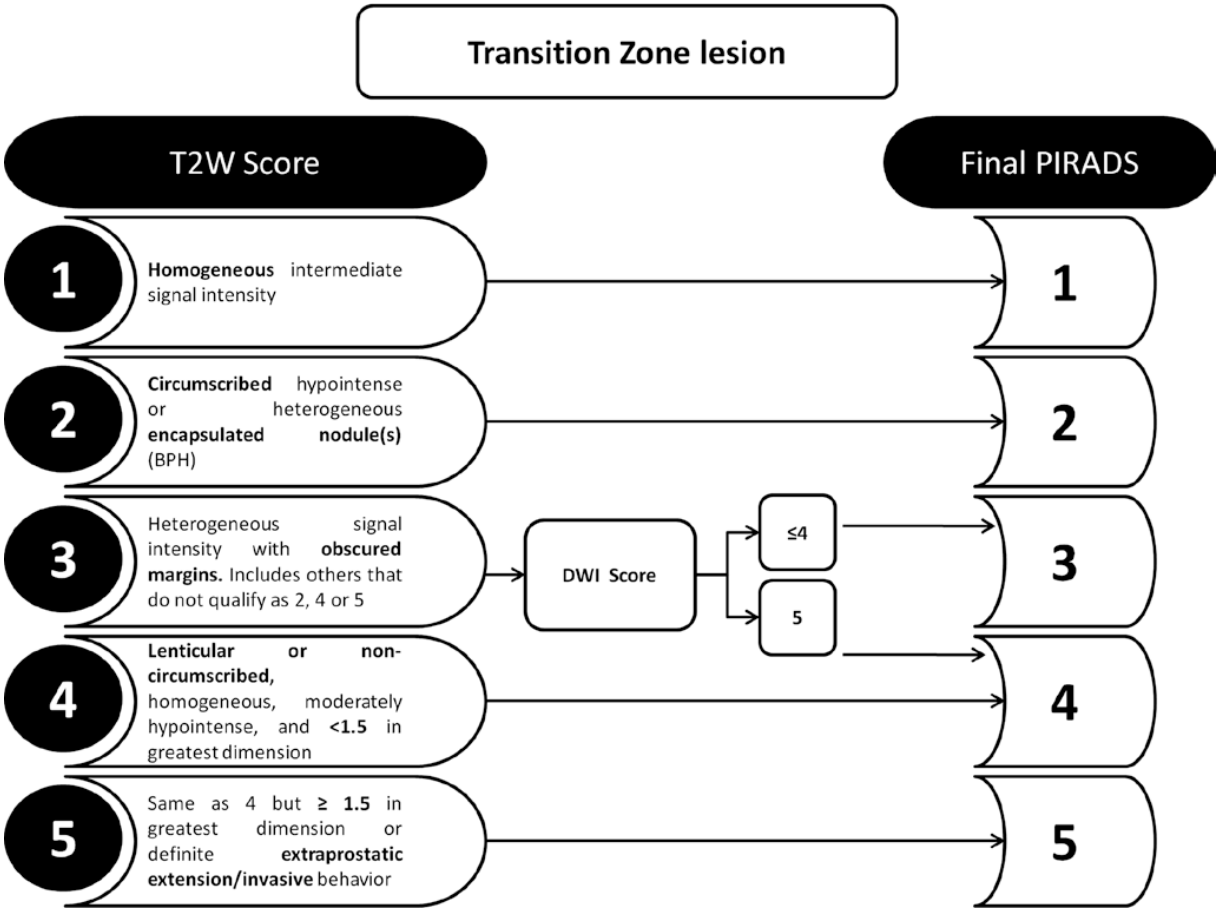


Figure 16. PI-RADS v2 scoring for transition zone (TZ). T2W, T2 weighted, DWI diffusion weighted imaging, BPH benign prostatic hyperplasia, PIRADS Prostate Imaging Reporting and Data System. Obtained from (12).

14.5.1. TZ: PI-RADS 2

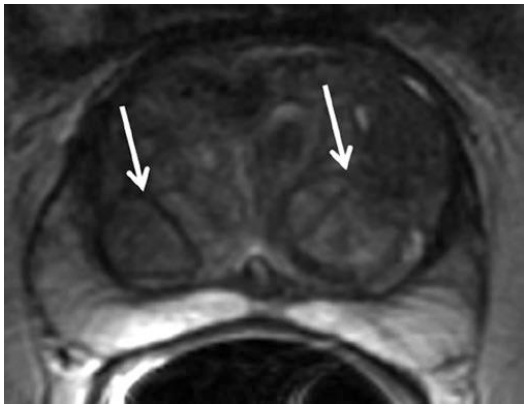


Figure 17. PI-RADS 2 category in TZ. Axial T2WI showing different encapsulated and round nodules in the TZ (arrows). Obtained from (12).

14.5.2. TZ: PI-RADS 3

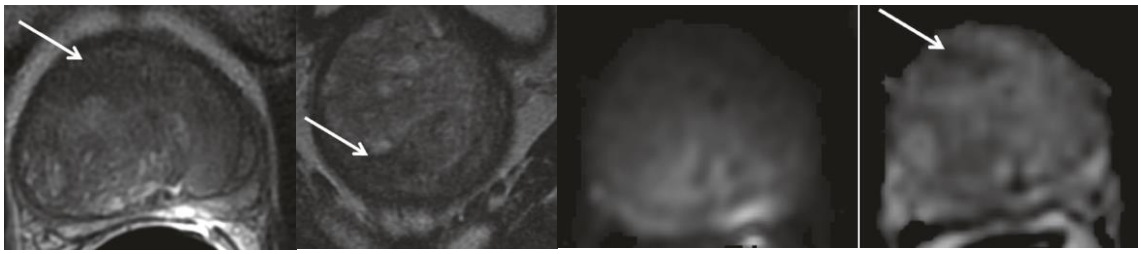


Figure 18. PI-RADS 3 category in TZ. First, axial T2WI. Second, coronal T2WI. Third, b1400 DWI. Fourth, ADC map. There is a heterogenous low signal intensity area in the right TZ with obscured margins without restriction. The DWI score is <4. Obtained from (12).

14.5.3. TZ: PI-RADS 4

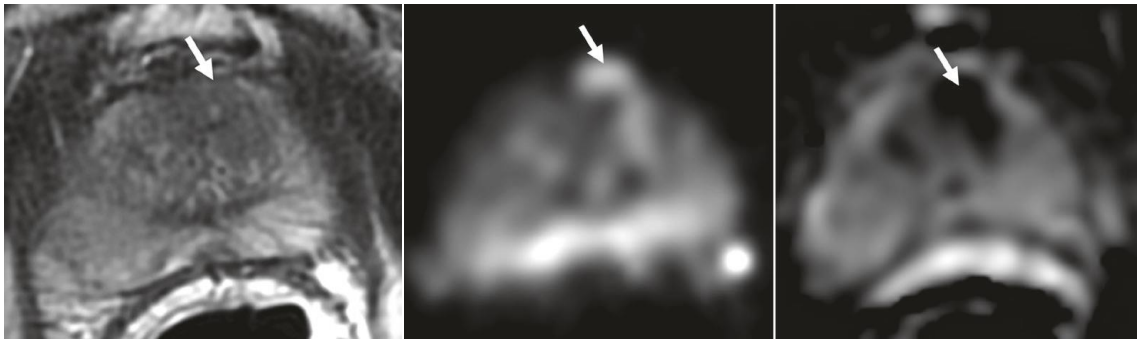


Figure 19. PI-RADS upgrading from 3 to 4 category in TZ. First, axial T2WI. Second, axial b1400 DWI. Third, ADC map. There is a heterogenous signal intensity area in the left anterior TZ with obscured margins (arrows). The focal lesion shows high signal on DWI and low signal in ADC with longest diameter ≥1.5 cm consistent with a DWI component score of 5. Obtained from (12).

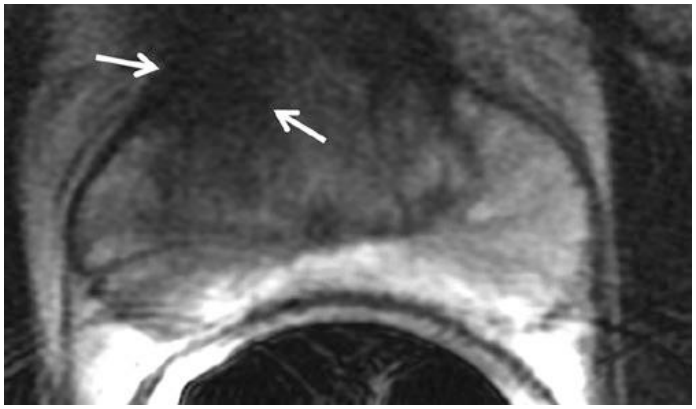


Figure 20. PI-RADS 4 category in TZ. Axial T2WI showing a non-circumscribed homogenous lesion (arrows) on the anterior right TZ, <1.5 cm. Obtained from (12).

14.5.4. TZ: PI-RADS 5

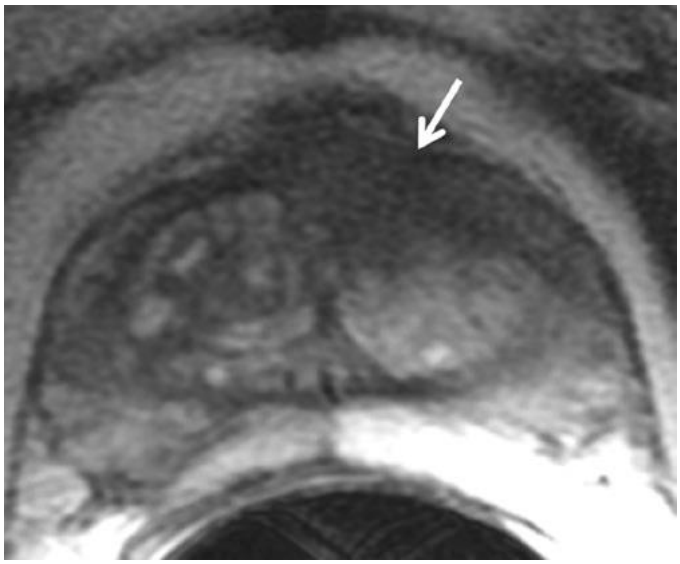


Figure 21. PI-RADS 5 category in TZ. Axial T2WI showing a lenticular non-circumscribed homogenous lesion (arrow) on the anterior left TZ, >1.5 cm. Obtained from (12).

14.6. Sector map used in PI-RADS v2 guide

This map will be used by the first radiologist to report the lesions that will appear on the mpMRI, and also by the genitourinary radiologist when performing the SB on the zones described before.

The segmentation model used in PI-RADS v2 employs thirty-nine sectors/regions: thirty-six for the prostate, two for the seminal vesicles and one for the external urethral sphincter.

The sector map illustrates an idealized "normal prostate". In patients and their corresponding MRI images, many prostates have components that are enlarged or atrophied, and the PZ may be obscured by an enlarged TZ. In such instances, in addition to the written report, a sector map which clearly indicates the location of the findings will be especially useful for localization (16).

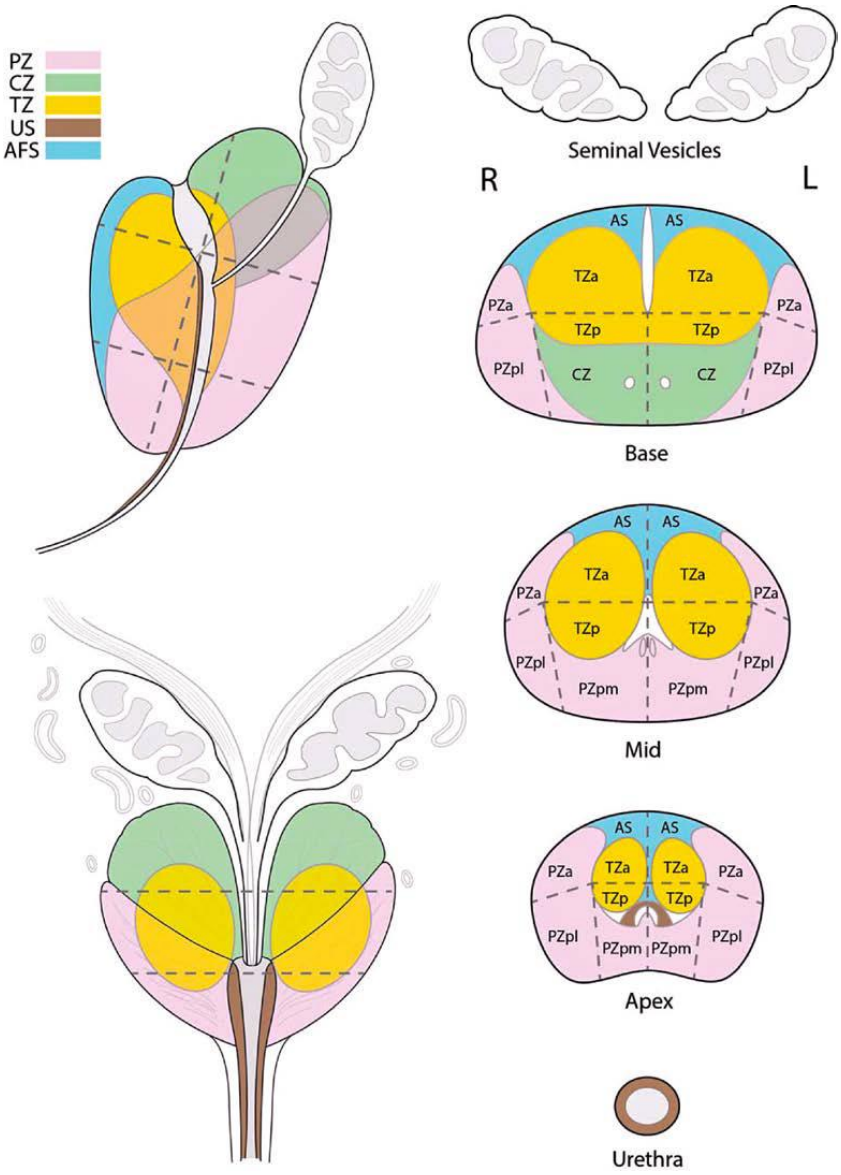


Figure 22. Prostate segmentation model used in PI-RADS v2. PZ peripheral zone, CZ central zone, TZ transition zone, US urethral sphincter, AFS (AS) anterior fibromuscular stroma, a anterior, p posterior, l lateral, m medial. Obtained from (16).

14.7. Informed consent sheet

Name:	Last names:	Birthdate:
National identity document:	Personal identification code (health card):	
Clinic history number:		

Procedure information

Name of the procedure: Prostate biopsy guided by transrectal ultrasounds.

What does it consist of? Through this procedure, we want to differentiate between benign and malign lesions, that is to say the presence or not of cancer.

The procedure may need local anaesthetic administration by injection at prostate nerves, to diminish the pain. The procedure starts with the transrectal ultrasounds probe introduction through the rectum, and then, the prostate is punctured with a thin needle biopsy to get multiple tissue samples, by ultrasounds guidance. Patients use to feel uncomfortable during the ultrasounds probe introduction. Discomfort or pain during the punctures can be felt as well. The total procedure lasts around 15 minutes.

The procedure may be filmed for scientific and didactic purposes. The data of the procedure and the results obtained in samples will be registered in a database for a posterior analysis, together with the data and results from other patients. The confidentiality will be always preserved.

Possible side effects: Even with a correct realization of the procedure, side effects can happen, systemic or local. Among the firsts, apart from the anaesthetic local reactions, a sepsis or generalized infection can occur. Within the locals, it can produce hematoma in the puncture zone, haematuria or blood in the urine, infection, difficulties with urination, acute urine retention, urethrorrhagia or blood into urethral orifice and rectal bleeding. These complications habitually resolve with medical treatment (drugs, serum…) but they can need an urgent reintervention. There exists an exceptional risk of mortality.

If one of the following health problems is present, it must be notified: drug allergies, coagulation alterations, cardiopulmonary diseases, presence of prothesis, pacemakers or actual drugs intake.

Study information

Name of the study: "The value of targeted MRI-US fusion biopsy in men with prior negative biopsy for prostate cancer detection".

Purpose of the study: Its main objective is to assess the differences in cancer detection between 2 biopsy techniques: fusion technique, guided by magnetic resonance + ultrasounds and systematic biopsy technique guided by ultrasounds. To compare the results of both techniques, they will be performed to patients with a suspicion lesion on the MRI. It consists of: first, a systematic biopsy procedure, and then, 2 more samples of the target lesion by fusion technique.

We think that fusion technique will detect better the cancer and reduce unnecessary invasive procedures by getting less uncertain results, and if the results are positives, a change in the current procedure may be done.

There is not an added risk or side effects with the biopsy procedure, as it is almost the same as the currently used. By entering in the study, you only have to attend to the biopsy procedure. It is not provided, in this study, an economical compensation for the participants. If you have any question or doubt, do not hesitate to contact with Dr. Kai Vilanova, email: kvilanova@comg.cat.

Every information obtained from the procedure will remain strictly confidential, as said on "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".

Alternative: the current procedure is biopsy guided by ultrasounds, with no fusion technology.

Informed consent

I have understood with an easy vocabulary all the explanations and my doubts have been answered.

I participate voluntarily, and I understand that I can revoke this consent at any time, with no need for explanations and no clinical attendance repercussions.

I manifest that I am satisfied with the information I have received, and I know the risks of the procedure. In these conditions, I CONSENT for undergoing a PROSTATE BIOPSY GUIDED BY TRANSRECTAL ULTRASOUNDS and I give my authorization to PARTICIPATE IN THE STUDY.

This consent is developed following: "Ley 21/2000, del 29 de diciembre" about health information rights, patient's autonomy and clinical documentation.

Professional informing: **Identification number:**

Signature of the patient	**Signature of the professional**	**Date**

- **Accept**
- **Do not accept**

Hospital Universitari de Girona Doctor Josep Trueta