Universitat de Girona
Facultat de Medicina

FINAL DEGREE PROJECT

Incidence of prostate cancer in MRI-TRUS fusion biopsy patients with a previous negative TRUS biopsy in Girona

A cross-sectional study

NOVEMBER 2023

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1 Acknowledgements

First of all, I would like to thank my tutors. To Dra. Gemma Gracia for her helpful insight on Urology and prostate cancer, for showing me this innovative technique and the protocol it is based on, and for taking her time to meet me and solve my questions. To Dra. Teresa Puig for assisting me during this hectic process and always keeping a positive view.

To the patients of prostate cancer that live and suffer from it and the researchers and health professionals around the world who are trying to find better ways to diagnose it and to treat it.
To Jose Moreno Folch, my uncle, for overcoming this cancer and being in remission for almost four years and to Manel Caballeria for living with the disease for 19 years and going through all the stages. Your loved ones remember you.

My sincere gratitude to my family, specially my parents Dr. Jeús Pérez Clausell and Dra. Vicenta Moreno Folch, for their support and being there in all the shades of colours, I truly admire the both of you. And to my friends for encouraging me to peruse my dreams and dealing with me throughout this degree. A special mention to my best friend Silvia Caballeria Lluch for celebrating with beer not only my successes and accomplishments but also my miseries and short-comings.
You are one of a kind !

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Taula de continguts

3 Abstract

Background. Prostate cancer is the second most common solid cancer in men worldwide. It is estimated that one out of nine men will suffer from it through their life span. This disease is the most deadly for men between 45 and 60 years old in the Western countries. Hence, it is essential to find competent diagnostic tools to detect the disease on early stages and treat it. At present, the most common procedure for diagnosis is a combination of medical history, physical examination, and tests, such as the prostate-specific antigen (PSA) test, digital rectal examination, and prostate biopsy. These techniques might fail to detect 50% to 80% of the tumours and also might detect non-clinically significant cancers that would not cause any harm to the patient (causing over-diagnosis and over-treatment). Nowadays, there are new techniques to guide the biopsy and improve the diagnosis. The use a previous multi-parametric magnetic resonance imaging (MRI) (where the suspicious areas are located and graded by the radiologist) and its fusion with real images from the transrectal probe might assist to target the suspicious area and improve the detection rate for prostate cancer.

Objectives. The main goal for this study is to evaluate the incidence of prostate cancer in men with a second targeted biopsy using the MRI-Ultrasound fusion software imaging.

A secondary objective is to know the incidence of clinically significant prostate cancer in these population.

Design and Methods. The study will be conducted as a cross-sectional, retrospective, descriptive, and observational analysis at the *Hospital Universitari Dr. Josep Trueta* in Girona over a period of four years. The study will involve 93 participants at least. The study will focus on participants who had previously undergone a transrectal ultrasound-guided biopsy (standard procedure nowadays) that resulted in a negative diagnosis for prostate cancer. A second biopsy will be performed guided by multi parametric MRI images and Trans-rectal Ultrasound imaging to locate the suspicious areas and obtain the cores (targetted biopsy).

These participants will be examined retrospectively (the results of the second biopsy as well as their risk factors) to assess whether the subsequent MRI-ultrasound-fusion guided biopsy provided a more efficient and accurate diagnosis.

Population. Men between 45-80 years old currently under study for prostate cancer at *Hospital Universitari Doctor Jospe Trueta*. The first prostate biopsy, which was systemic and targeted, and guided by Ultrasounds, was negative. The PSA blood levels remain high or are increasing. An MRI was performed and showed a Prostate Imaging Reporting and Data System (PIRADS) ≥ 3. A second biopsy is performed with the imaging technique MRI - ultrasound fusion- guided.

Key words. Cancer of prostate – Multiparametric MRI – Trans rectal ultrasound (TRUS) –

TRUS MRI fusion – clinically significant prostate cancer

4 Abbreviations

ACS	AAmerican Cancer Society
ADC	Aparent Diffusion Coeficent
ASR	Age-Standarised Rate
ATM	Ataxia telangiectasia mutated
BPH	Benign prostatic hyperplasia
BRCA1	Breast cancer gene
BRCA2	Breast cancer gene 2
CHEK2	Checkpoint kinase 2
DCEI	Dynamic Contrast-Enhanced Imaging (sequence in mp MRI)
DRE	Digital Rectal Examination
DWI	Diffusion-Weighted Imaging
EAU	European Association of Urology
ISUP	International Society of Urological Pathology
mpMRI	multi parametric MRI
MRI	Magnetic Resonance Imaging
PIA	Proliferative Inflammatory Atrophy
PIN	Prostatic Intra-epithelial Neoplasia
PIRADS	Prostate Imaging Reporting and Data System
PSA	Prostate Specific Antigen
TRUS	Trans Rectal Ultrasound
UTI	Urinary Tract Infections

5 Introduction

5.1 Prostate

The prostate is a gland that belongs to the male reproductive system. Its shape is that of an inverted cone and is located within the pelvis: inferior to the urine bladder, posterior to the pubic symphysis and anterior to the rectum. The first 3 to 4 cm of the urethra, also known as prostatic urethra, go through this gland. During development, the prostate originated from 30 to 40 autonomous glands that grow from the urethral epithelium. Each single gland will preserve its autonomy and flow into the urethra. A fibrous capsule encloses the gland, from which the nerves and vascular plexus branch off [1].

The main function of the gland is contributing to the synthesis of semen [1 2]. The prostate generates around 25% of the volume of semen, about 0.5 mL of the ejaculate. The prostatic fluid is thin and milky. It contains compounds responsible for liquefaction that occurs 15 to 30 min after ejaculation and triggers the activation of sperm [3]. The fluid also contains supportive proteins and enzymes that provide nourishment to sperm. The prostatic secretion is alkaline and will help to neutralise the acidity of the vagina. In addition, during ejaculation, the smooth muscle in the capsule and stroma contract, and the prostatic fluid is squeezed into the urethra assisting with the expulsion of semen [2].

Anatomically, the prostate is divided into five lobes: anterior, posterior, median and two lateral lobes. Histologically three different zones can be differentiated: peripheral, central and transitional (Figure 1). The peripheral zone is the largest (70% of volume) and encompasses most of the central zone and also the distal portion of the prostatic urethra. The central zone corresponds to a 25% of the gland and surrounds the ejaculatory ducts. The transitional zone occupies the remaining 5% and surrounds a portion of the urethra.

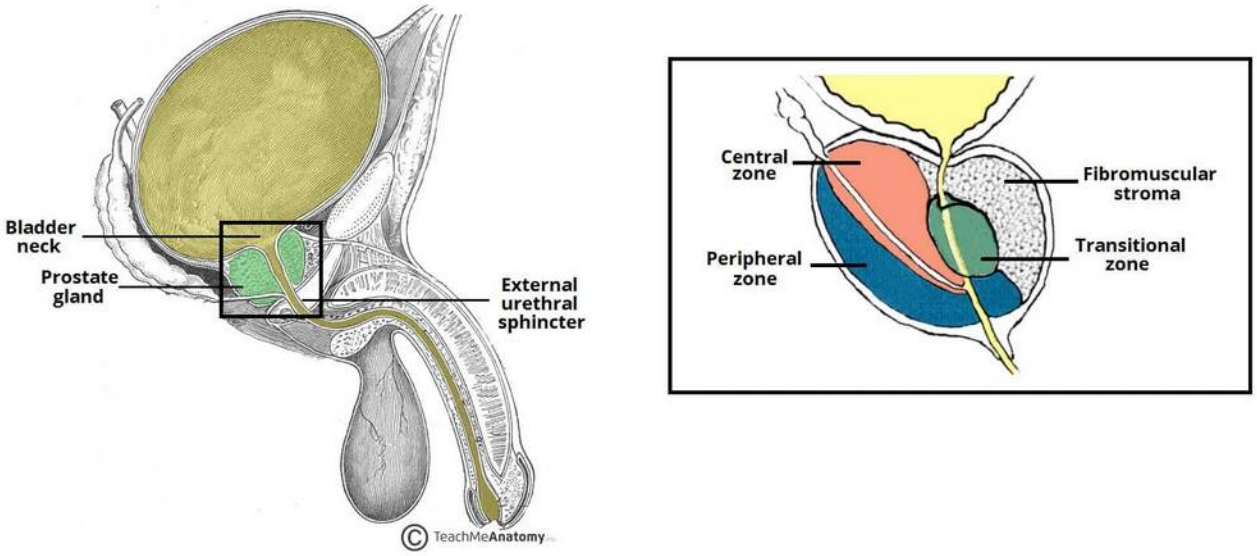


Figure 1. Left The sagittal plane of a man's pelvis showing the male reproductive organs and the lower urinary system. Right Diagram of the different zones of the prostate and its location with respect to other structures such as the bladder and ejaculatory ducts [4].

The prostate contains an area that is not glandular and contains muscular and fibrous tissue. This area is called the anterior fibromuscular stroma and surrounds an inferior portion in the prostate called the apex.

The prostate is encompassed by a fibrous layer, the capsule, as mentioned before.

5.2 Prostate cancer

5.2.1 Epidemiology

Prostate cancer is the second most common solid cancer in men worldwide [5] [6]. In 2020, it was estimated that 1.41 million new cases were diagnosed globally (EAU, 2023). The incidence for prostate cancer is not distributed evenly[7] [5]. There are factors that influence the epidemiological differences across the world such as: family history or genetic predisposition, ethnicity, geographic distribution and multiple risk factors related to the individual, the environment and work.

Variability in incidence and mortality can also be explained by the different health systems in each country and their approach to prostate cancer diagnosis, and the socio-economic status of the country [5] [7] [8].

In addition, the incidence of prostate cancer may be influenced by the use of different diagnostic strategies [5] [8]. At present, there is no unanimity in the diagnosis of prostate cancer. For this reason, some countries opt for PSA screening of their population, resulting in a greater incidence in these countries. Another strategy is "selective" screening of individuals with risk factors. Hence, countries with a strategy that systematically test their population for prostate cancer are more likely to detect it and have a higher incidence.

In contrast, countries without screening or “selective” diagnosis strategies will have a very low incidence. Even though the incidence of the disease might be high in the region, if there is no health plan to diagnose the disease, the value will be wrongly low. It is not the real incidence but is conditioned by the diagnostic system of each region.

At present, the highest incidences are found in Australia/New Zealand, North America, and Western and Northern Europe with incidence values greater than 85 cases per 100,000 men. The lowest values can be found in Asia, particularly South and South-Central Asia (Table 1) [7] [8]

Table 1. Incidence of prostate cancer (cases per 100,000 men with age-standarised rated ASR) in certain geographic areas. Data based on [8].

Geographical Area	Incidence of prostate cancer per 100,000 men
Australia and New Zealand	111, 6
Northen America	97,2
Western Europe	94,9
Northen Europe	85
Eastern Asia	10,5
South-Central Asia	4,5

The richer countries in the globe appear to be the geographical areas where the incidence in prostate cancer is higher (Figure 2).

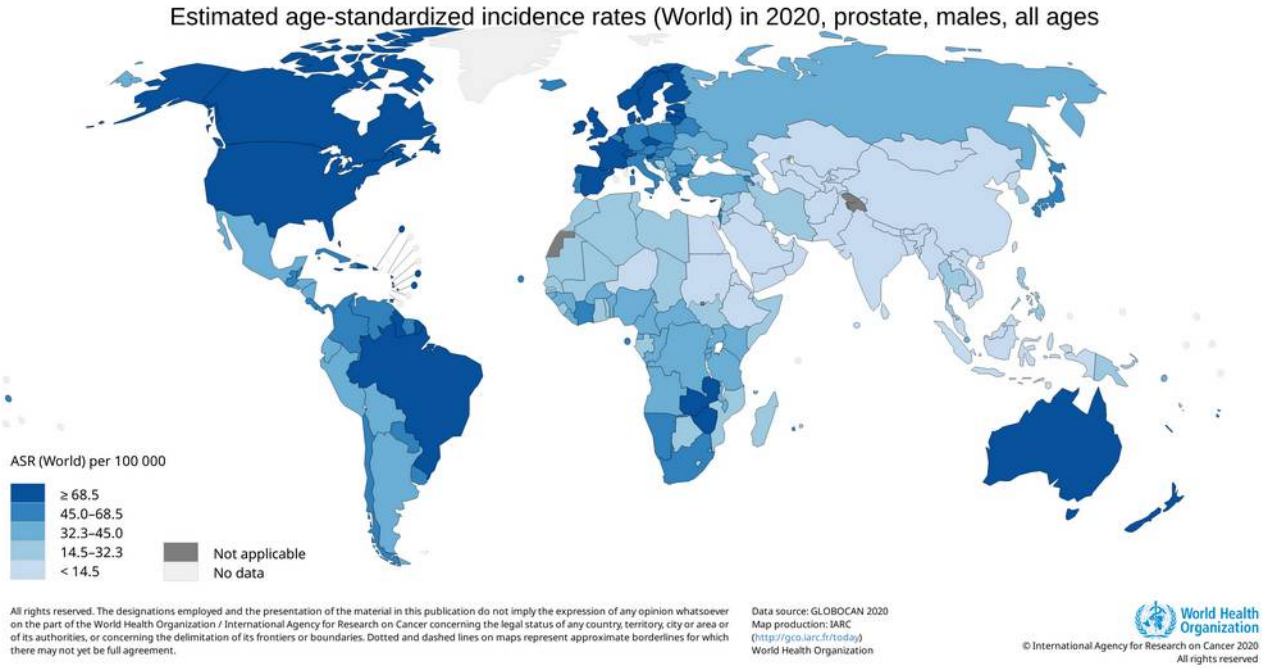


Figure 2. Estimated age-standarised incidence rates, worldwide, in 2020 for prostate cancer in men from all ages. The darker shade of blue indicates an incidence higher than 68,5 cases per 100,000 men and can be found in North America and some countries from South America (Brazil, French Guiana and Guyana), Australia/New Zealand area, North and South-West of Europe. Lower values are marked as light blue and correspond to the entire Asian continent [7].

Age is strongly related to the prevalence of prostate cancer. The prevalence of prostate cancer in autopsy studies showed that, there is a prevalence of 5% under 30 years old, with an increasing odds ratio of 1,7 per decade. At the age over 79 years old, the prevalence reaches a 59% [9].

Those findings in the autopsies were incidental. Patients might not-show any sings nor symptoms at the time of their death. The cancers diagnosed might be clinically significant (it may cause morbidity or death) or clinically insignificant (it will not cause any harm) [8]. All prostate cancers diagnosed during autopsies were not clinically significant and may have never caused any symptom nor harm to the patient. Diagnosing a condition that will never cause an illness nor death during the individuals lifespan is called over-diagnosis and is not the goal. The aim is to diagnose only those diseases that will impact the persons life and cause them harm. The study on prevalence in corpses might have over-diagnosed the disease.

Mortality rates are more homogeneous worldwide (Table 2) [5] . The most affected areas are Africa and Latin America & Caribbean. Mortality seems to be greater in populations of African descent (Figure 3) [5 7 8]. Surprisingly, these areas are not at peak for their incidence. The areas where the incidence is higher does not correspond with higher rates of mortality. These might be because the

diagnostic strategy and early detection of the disease allows the patient to be treated and never reach the final stages,in which the disease would have spread untreatable and leading to death.

Table 2. Incidence and mortality rate per 100,000 men in each continent with Age-Standarised Rate [5].

Geographical Area	Incidence ASR/100,000	Mortality ASR 100,000
North America	73	8.3
Oceania	70	11
Europe	63	11
Latin America and Caribbean	59	14
Africa	30	16
Asia	14	4.4

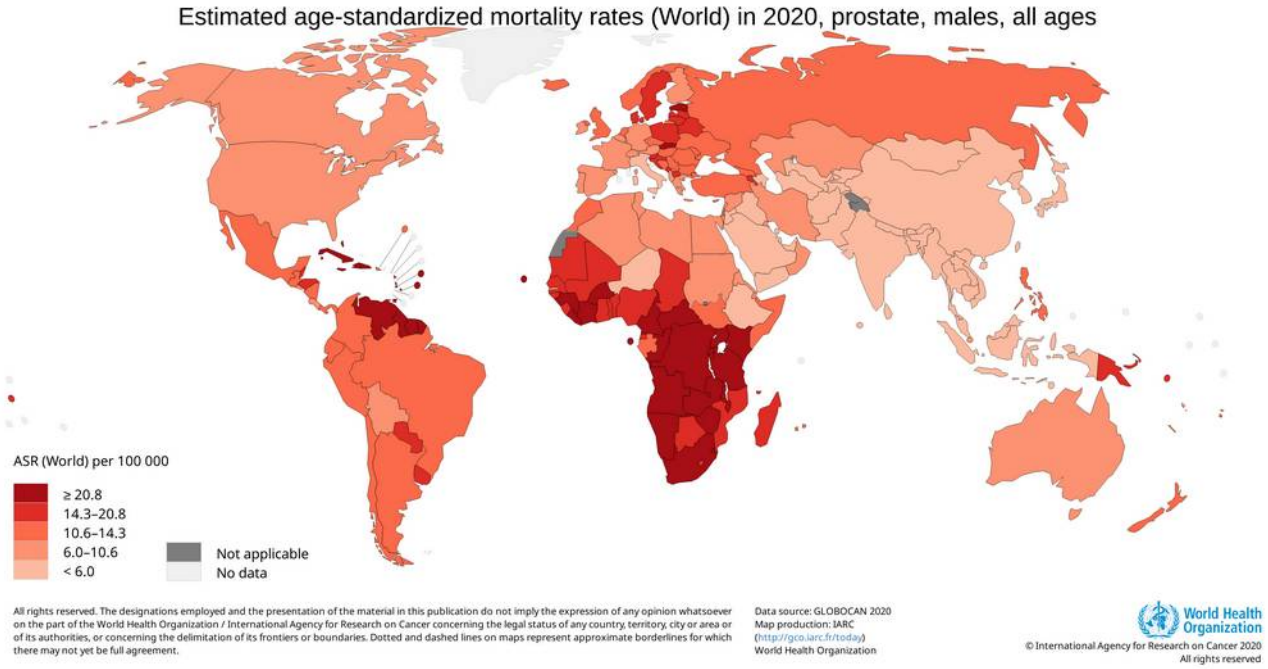


Figure 3. Word map where the estimated mortality rate in 2020 of men at all ages and age-standardised rate. Darker shades of red indicate a mortality rate 20.8 or greater for 100,000 men. Countries on the Caribbean and Southern Africa have the highest mortality rate around the globe [7].

In Europe, there are some remarkable differences. The lowest incidence rates can be found in the South: in Italy (5,9) and Spain (7,3). The higher rates can be found in Estonia (21,8) and Slovakia (20,9). This differences might occur due to different health systems and their strategies to fight prostate cancer.

In summary, prostate cancer is predominant worldwide. A man out of nine men will suffer from it through their life [7 10] . The incidence is not distributed evenly and can be influenced by many factors such as genetic predisposition, environment, work, age, or ethnicity.

At present, the higher incidence can be found on those countries with a powerful health system, enabled by a strong economy, that have an strategy for the diagnosis. Despite the greater incidence

the mortality rate remains stable. The implementation of diagnostic strategies allows the detection of the disease in treatable phases, allowing for a better life expectancy and reducing mortality.

Studies on autopsies show that the prevalence of the disease is much higher. However, they detect clinically significant tumours as well as non-significant ones. In practice, there is only a need to detect only those cancers that will cause harm to the patient and treat them (despite the side effects of the treatment). The clinically insignificant ones should never be treated since it will never harm/threaten the patient's life. Therefore, it is necessary to find a diagnostic technique capable to detect only the clinically significant cancers, and then implement the strategy worldwide. The suitability of one of these methods, MRI-TRUS fusion guided biopsy will be addressed in the present study (See Objectives).

5.2.2 Anatomical pathology evaluation

A 95% of prostate cancers are adenocarcinomas and originate from the secretory cells at the acinar epithelium or the proximal ductal epithelium. There are other types of tumours with reduced incidence: sarcomas, transitional cell carcinomas, small cell carcinoma and mucinous carcinomas.

In stages previous to prostate cancer, pre-neoplasic lesions usually appear: Proliferative Inflammatory Atrophy (PIA) and Prostatic Intra-epithelial Neoplasia (PIN)[3 6 11].

Pre-neoplasic and cancer lesions will be described briefly.

Proliferative inflamatory Atrophy (PIA) is a benign condition where there are areas of atrophy (cells look smaller or even shrinking) and there are signs of inflammation. It is not cancerous but it is considered that it might lead to high grade PIN (see below) or even cancer [6].

Prostatic Intra-Epithelial Neoplasia (PIN) is a pathology where ducts and acini are affected. There are two types depending on the changes observed under the microscope (cellular stratification, increased nuclear size, chromatin pattern, pleomorphism and appearance of nucleoli). There are low grade PIN and high grade PIN. The last one is considered a precursor lesion of cancer and if found, a second biopsy is requested [6 11].

Adenocarcinoma

The most of these tumours are located in the peripheral zone. Macroscopically it has a yellow colour, or whitish grey [3 11]. In order to grade the aggressiveness of the prostate cancer, the Gleason system (see below) evaluates the histology from the cores obtained during the biopsy.

5.2.2.1 Evaluation

The Gleason system. The Gleason score is one of the most established grading systems for prostate cancer. It was developed by Dr. Donald Gleason and introduced in the 1960s.The Gleason score is determined through the examination of prostate tissue obtained from a biopsy. Pathologists assign a Gleason score based on the pattern and appearance of cancer cells in the biopsy samples. The rates each pattern vary from 1 to 5, from (1) the most differentiated cells similar to healthy prostate tissue to (5) at least differentiated cells have suffered multiple changes and barely resemble to normal tissue (Table 3) [11].

Table 3. Grades of Gleason for each predominant area ranging from 1 to 5.

Gleason Score	Description of the pathologist
1	Uniform, single glands with little stroma between them. No infiltration is observed tration.
2	Similar Gleason 1, the glands present some variability in size and shape, presenting stroma between the cells.
3	The tumor infiltrates inside and between the non-neoplastic prostate glands, feeling smaller size glands than in previously.
4	Spreading stromal infiltration between normal glands. There is a gland fusion (characteristics differentiator with respect to the degree III).
5	The tumor infiltrates forms diffuse stages, no gland formation is seen. The cells are poorly differentiated and bear little ressemblance to normal prostate tissue.

The International Society of Urological Pathology (ISUP), in the 2005 and 2014 meetings, reach a consensus to eliminate the Gleason Scores 1 and 2, and a new strategy for grading was implemented. This new system takes into account the two most predominant types of cell populations (one and two) and are graded separately defining a primary (predominant) pattern and a secondary pattern (second most prevalent). If only a single pattern is present, the value needs to be doubled to yield the Gleason Score. Similarly to the original Gleason Score the higher scores cells appear less differentiated are the disease will be more aggressive.

The ISUP (**International Society of Urological Pathology**) **grading system**, also known as the Prostate Cancer Grading System (PCGG), and the Gleason score are related but distinct methods for grading and staging prostate cancer. The main goal for both systems, Gleason Score and ISUP, is to assess the grade of aggressiveness for the cancer and make decisions about the treatment.

The ISUP grading system, was introduced as a way to simplify and harmonize the Gleason grading system. In 2014 and 2019, the ISUP meetings endorsed a new grading system (Table 4).

Table 4. Internationally Society of Urological Pathology 2014 grade system and their equivalent Gleason Score [8].

Gleason Score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9 – 10 (4+5 or 5+4 or 5+5)	5

In conclusion, the most common type of prostate cancer is adenocarcinoma (95%). The malignancy originates from the cells secretory cells. It seems that there could be pre-malignant lesions such us PIN and PIA but their influence on becoming malignant is still under study. The Gleason score is a detailed grading system for prostate cancer and the ISUP is a newer and simpler system to grade this cancer. The ISUP was created to more accessible and easy to use for the physicians. Both grading systems are not only is used to evaluate aggressiveness of the tumour but also for choosing the more suitable treatment, prognosis, and life expectancy for each patient.

5.2.3 Risk factors

Risk factors for prostate cancer are characteristics, behaviours, or conditions that increase a man's likelihood of developing this cancer. It is important to note that presenting one or more risk factors does not guarantee the development of prostate cancer, and many individuals with prostate cancer may not have any identifiable risk factors. However, understanding these risk factors can help individuals and healthcare professionals to assess the need for screening and early detection.

The most common risk factors will be summarized below.

Age. Prostate cancer is more common in older men. The risk increases with age, and it is rare in men under 40. Most prostate cancer cases are diagnosed in men over 65 (6 out of 10 cases in patients over 65 years. However, prostate cancer diagnosed on younger people tend to be more aggressive, and occur on men with family history. In contrast, elder men often have slow-growth cancers, but their age and other pathologies (co-morbilities) might make treatment difficult [6 11].

Family History. A family history of prostate cancer, especially in first-degree relatives (father, brother), can significantly increase the risk, and appear at early ages. It is estimated that 20% of men diagnosed with prostate cancer have a family history. The risk of suffering from it also depends on the number of affected relatives. For example, if there is only a relative and was diagnosed before the age of 60, the individual’s risk would be 2.5. If the relative was diagnosed after the age of 60, the risk would be 1.6. If there were two family relatives diagnosed under the age of 60, the risk would rise to 5.7 and if they were over 60, the risk would lower to 3.5 [5].

Genetics. Some gene mutations might be inherited or might be newly acquired. The inherited line mutations usually are found on DNA repair genes, the most common mutations being on BRACA2, CHEK2, ATM and BRAC1. Mutations also can appear on genes specific to the prostate gland such as HOX13 responsible for the development of the gland. Men with these gene mutations may have a higher risk of aggressive prostate cancer [5 6 8 12].

Ethnicity. Prostate cancer is more common in African-American men than in men of other racial and ethnic backgrounds. It tends to be more aggressive and diagnosed at an advanced stage in men from African descent. The reasons behind this might be genetic (there are more likely to suffer from it or the more severe cases) or it might be explained by socio-economic causes. The access to health care, the systemic racism or residential segregation are reasons that could explain why the men from African descent are 2 to 3 times more prone to die from prostate cancer on the USA [5 6].

Geographical Area. The incidence of prostate cancer varies by geographic region, with higher rates in Australia/New Zealand, North America, and Western and Northern Europe. It is less common in Asian, particularly South and South-central. This topic was discussed on Epidemiology.

Diet. There are many studies that aimed to find an association between prostate cancer and a specific food. There have been studies on alcohol, coffee, dairy, fat (fried-foods), lycopenes (found in tomatoes), meat, soy, vitamin D and vitamin E. However, the evidences found on these studies were not strong enough to be able to support a cause-and-effect statement. Hence, there is no prevention strategy related to diet in prostate cancer [5 6 8].

Obesity. There have been many studies on the impact of obesity, metabolic syndrome, cholesterol/statins, diabetes and the use of metformin in prostate cancer, and the results were controversial or not significant enough to claim an association. Hence, there is no clear statement to prevent or protect from prostate cancer. However, these conditions might be related to a higher risk of mortality while suffering from this cancer [8].

Tobacco. Although the link between smoking and prostate cancer is controversial and not as strong as with other cancers, it has been proved that smoking is associated with adverse pathological features and worsens the oncological control [5].

Occupational Exposures. Certain occupational exposures, such as asbestos, pesticides, chromium may be associated with an increased risk of prostate cancer.

Hormonally active medication. 5-alpha-reductase inhibitors (5-ARIs), a drug commonly used in Benign Prostate Hyperplasia (BPH), blocks the pathway from testosterone to dihydrotestosterona preventing prostate's growth. It has been proposed that it could prevent or delay the growth of tumours on the prostate, as well. Studies show that this drug reduces the incidence for low grade PIN (non pathological) and the incidence of high grade PIN (possibly pathological) remains the same. Although there might be a slight beneficial effect in non pathological cases, it must be taken into account their side effects (gynecomastia and erectile dysfunction). Therefore, the European Medicine Agency did not approve the use of this treatment for this pathology [6 8].

In summary, the exact causes of prostate cancer are not fully understood at present, but there are environmental and individual risk factors that might contribute to this pathology. There are many researches going on these topics. Additionally, while these risk factors may increase the likelihood of developing prostate cancer, they do not guarantee that someone will develop the disease. The health professional needs to consider these factors when assessing each case and choosing the more convenient diagnostic strategy.

5.2.4 Signs and Symptoms

Signs and symptoms usually associated with prostate cancer are unspecific and can be related to a variety of pathologies. However, it might create an alert for the patient to visit the doctor and seek assistance [3 6]. Those unspecific signs and symptoms are the following.

Problems or **difficulties with urination**. Patients refer to a slow or weak urinary system. The urinary flow is decreased or less potent. Sometimes patients refer a delay or difficulty to initiate the urine flow with or without pain or burning feeling. It is also common to experience interruptions of the urinary flow with inability to resume urination.

This might be caused by the overgrowth of the tumour, increasing the prostate volume and creating an obstruction of the urinary flow.

Pollakiuria and **nocturia**. The need for urination is increased. This is more noticeable during the night when the patient must wake up for the need of urination (nocturia). As mentioned before, prostate cancer may obstruct the urinary flow generating difficulties in urination and emptying the bladder. The bladder is not emptied completely and the residual urinary volume is increased. The filling time of the bladder is reduced since it has not been completely emptied. Due to this, the patient needs to urinate more frequently.

Haematuria and **hematospermia**. It is the presence of blood in the urine and semen, respectively. Prostate cancer can manifest these signs because its growth is uncontrolled and relies on angiogenic factors to generate new blood vessels. The new blood vessels will be more friable, and if they invade prostate ducts (connected to the urethra), blood might appear into urine or semen.

Erectile dysfunction. It is the inability to get or maintain an erection for sexual intercourse. Prostate cancer might not cause an erectile dysfunction directly but if a growing prostate tumour causes lower urinary tract symptoms, such as prostate hypertrophy, it could decrease sexual function [13].

5.2.5 Diagnosis

Prostate cancer has a high predominance: in 2020 it was estimated that 1,41 millions of new cases were diagnosed around the world. Despite being so predominant, there is no unanimous strategy to diagnose it. Population screening was discarded, since it also detected non-clinically significant cancers that resulted in over-diagnosis and over-treatment and consequently, there was no significant reduction in mortality [6] [8].

In general, the diagnosis involves a combination of medical history, physical examination, the prostate-specific antigen (PSA) test, digital rectal examination (DRE), and prostate biopsy guided by imaging usually ultrasounds (TRUS). These procedures might be missing 50 to 80% of prostate cancers [14]. For this reason, new diagnostic techniques have been introduced: medical examinations and imaging.

The medical examinations are blood test to measure PSA (total, free), PSA density and the risk calculator. They take into account some parameters and estimated a risk. Depending on the risk, the physician and patient will decide on the following steps (further diagnosis or monitoring).

Imaging techniques are based on ultrasounds or MRI. These are also used as guidance during biopsies and to visualise/locate suspicious areas that will be biopsied later on.

At present, the European Association of Urology designed an algorithm to diagnose clinically significant cancer [8]. Nature published an adaptation of this algorithm (Figure 4) [15].

This algorithm aims to reduce prostate cancer-specific mortality and metastatic disease using new risk stratification tools to improve the success of the PSA test and, at the same time, reduce unnecessary testing, overdiagnosis and subsequent overtreatment.

The PSA test in itself is a powerful stratification tool to establish a baseline PSA level among healthy men. In order to avoid false-positive PSA tests other tools such us family history, PSA density and risk calculator tools are recommended. Those with low-risk disease are then recommended to undergo a form of watchful waiting using interval PSA testing, because one-time screening does not reduce prostate cancer-specific mortality.

Men at an intermediate risk or high risk are recommended to undergo a MRI to grade the suspicious areas with a Prostate Imaging–Reporting and Data System (PI-RADS). Score of 1 or 2 do not rise a suspicion of cancer (advised to follow up with monitoring of PSA levels watchful waiting). A PIRADS score of 3 is termed equivocal (PSA density and risk calculators might be used to further test and asses the need of biopsy), and PI-RADS values of 4 and 5 are indicators of be malignant lesion (strongly recommendation to be biopsied).

If the biopsy shows prostate cancer, the patient will be refereed to a specialist to discuss treatment options: active treatment for high-risk prostate cancer that includes surgery and radiotherapy or active surveillance for low-risk prostate cancer avoiding side effects of overtreatment.

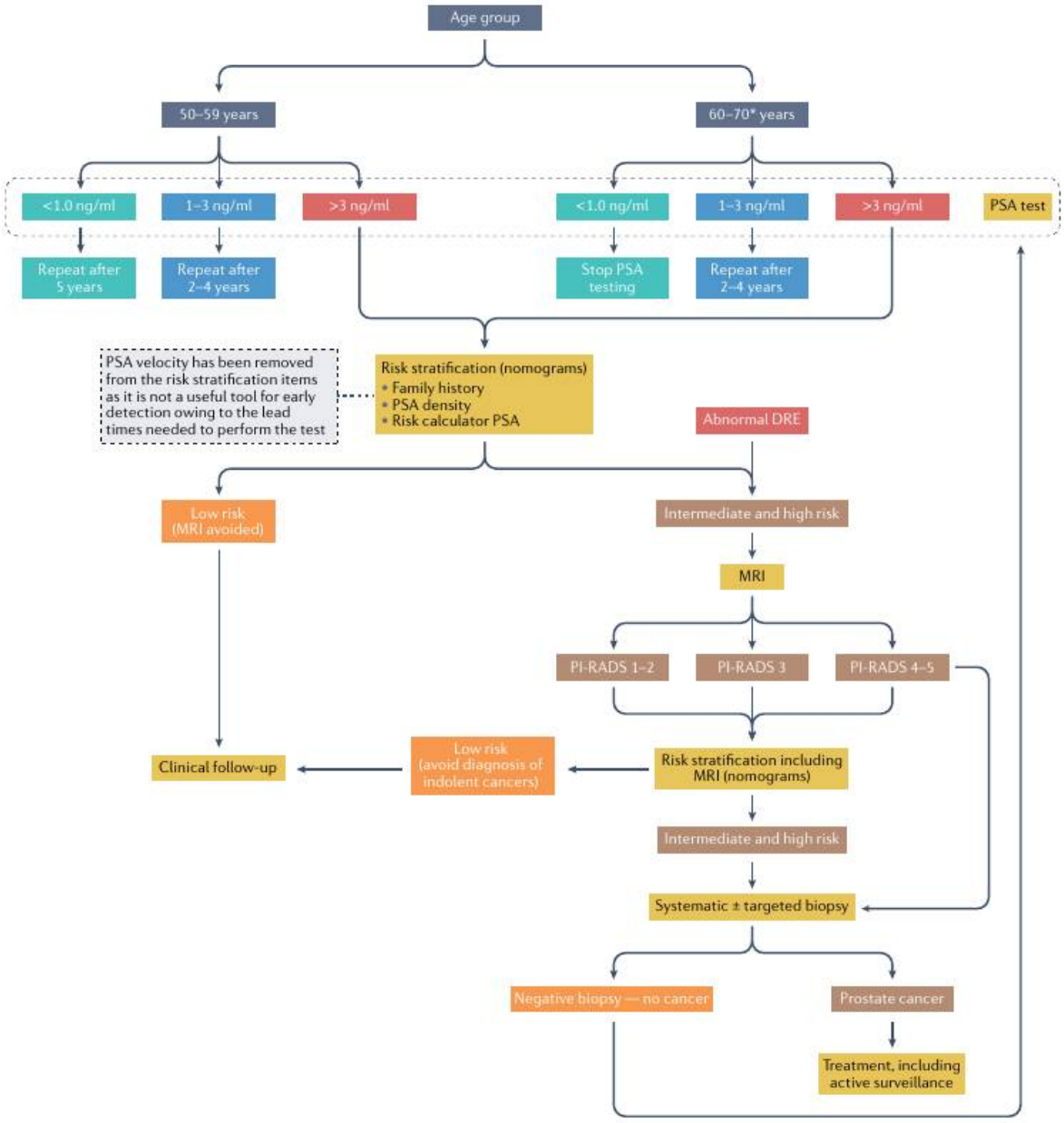


Figure 4. Algorithm of the risk-adapted strategy for the early detection of prostate cancer from [15].

5.2.5.1 Medical examinations

Prostate-Specific Antigen PSA. This is a protein produced by cells in the prostate gland. It is organ-specific but not cancer-specific [16]. There are many reasons that increase blood levels of PSA, some are benign and some are malignant: recent ejaculation, vigorous exercise, prostatitis or urinary tract infections (UTI), Benign Prostatic Hyperplasia (BPH) and prostate cancer [6]. Despite this uncertainty, PSA is commonly used as part of the diagnosis of prostate cancer. Depending on the age, the threshold value for PSA changes (see figure 4). PSA can be found in blood, bound to proteins or unbound. Free PSA and total PSA (sum of unbound and bound PSA) might provide additional information to the physician and assist with the diagnostic strategy.

PSA density. Is the result of dividing total PSA by prostatic volume (measured in image Ultrasound or MRI).

Sometime, this is not enough to determine the risk of prostate cancer and therefore, risk calculators are created.

Risk calculators are a useful tool that improves the accuracy of diagnosis and categorizes the patient into low, intermediate and hight risk of having clinically significant prostate cancer. Low risk patients are followed by monitoring PSA and risk calculators periodically (Figure 4). Intermediate and high risk are asked to take an mpMRI, and images are assessed with PIRADS in order to estimate the likelihood of having clinically significant cancer [6 15 16].

These are the most commonly used risk calculators:

4KScore. It calculates the risk taking into account multiple factors: total PSA, free PSA, intact PSA, human Kallikrein2 (hK2), age, DRE.

Prostate Health Index. It calculates the risk taking into account multiple factors: total PSA, free PSA, proPSA and age.

Digital Rectal Examination (DRE). It is important to include this examination into the diagnosis of prostate cancer because relevant information can be obtained. For example, the size, shape, and texture of the prostate gland and if there are any bumps or hardened areas that could suggest prostate cancer [6 17]

5.2.5.2 Imaging techniques

Imaging techniques play a crucial role in the diagnosis, staging, and monitoring of prostate cancer.

Several imaging methods are commonly used for prostate cancer assessment.

Trans Rectal Ultrasound. Trans rectal ultrasound (TRUS) is an intervention where the ultrasound probe is introduced into the rectum to visualise the gland (Figure 5). It is used to measure the size of the gland, to guide the needle during the TRUS biopsy and to look for suspicious areas that appear as hypoechoic [6] [17].

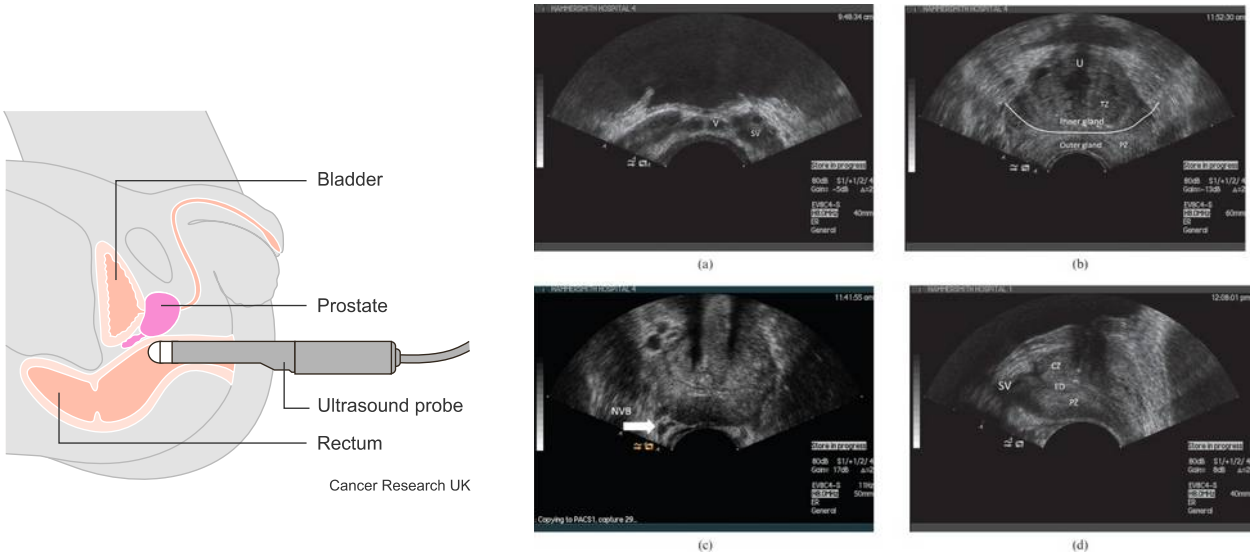


Figure 5 Left. Sagittal plane of a man's pelvis. The probe is introduced into the rectum and the prostate is situated over it (ventrally) (pink) [4] . Right. Four images of the prostate gland in Axial trans rectal ultrasound (a–c) and longitudinal images of the normal prostate (d). CZ, central zone; ED, ejaculatory duct; NVB, neurovascular bundle; PZ, peripheral zone; SV, seminal vesicle; TZ transition zone; U, urethra; V, vas deferens [18]

Magnetic Resonance Imaging (MRI) This technique is used in men with abnormal screening test (PSA, DRE or Risk calculators). Its main application is to locate suspicious areas, and to determine the extent of the prostate cancer (staging). It uses gadolinium. (ACS).

Multi Parametric MRI (mpMRI) is a type of MRI that combines different MRI sequences: T1, T2, diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCEI) and Magnetic Resonance Spectroscopy Imaging (MRSI)(Table 4). The comparison between these sequences allows the physician to assess the prostate structure, blood flow and tissue characteristics (Figure 6 and 7) [6] [8] [10].

Table 4. Description of each sequence. Data obtained from Stabile 2020

Mp MRI sequence	Description
T1	This sequence is used to evaluate regional lymph nodes and bone structures.
T2	This sequence is used to visualise the architecture of the prostate with excellent soft tissue contrast. It reflects the water content of the tissue (**Annex 1**) Healthy: -peripheral zone appears homogeneous and hyper-intense due to high glandular ductal tissue -transitional zone tends to exhibit high cellular density and appear heterogeneous and hypo-dense Prostate Cancer -peripheral zone there is high cellularity and the content of water is reduced appearing as hypo-intense -transitional zone detection cancer is challenging since prostatitis, scars irradiation might appear similarly
DWI	This sequence quantifies the degree of random movement from the water molecules within tissue Healthy: water molecules move relatively «free» Cancer: water molecules movement is restricted due to high cellularity and volume of epithelium This areas appear as bright spots surrounded by low signalling tissue Apparent Diffusion Coefficient (ADC) reflects the capability of water to move. An ADC map can be obtained from DWI sequence. Pathological area will appear as low signal
DCEI	This sequences asses the tumour angiogenesis by administrating intra venously a contrast. The sequences evaluates the velocity and intensity of uptake and wash of of the organ.
MRSI	This sequence provides information about the composition of the tissue, specially, metabolites of citrate and choline (important component of the cellular membrane) **(Annex 1)** Citrate is produced by healthy tissue. A reduction in concentration might indicate prostate cancer Choline concentrations in healthy tissue are low vs. in pathological tissue are high

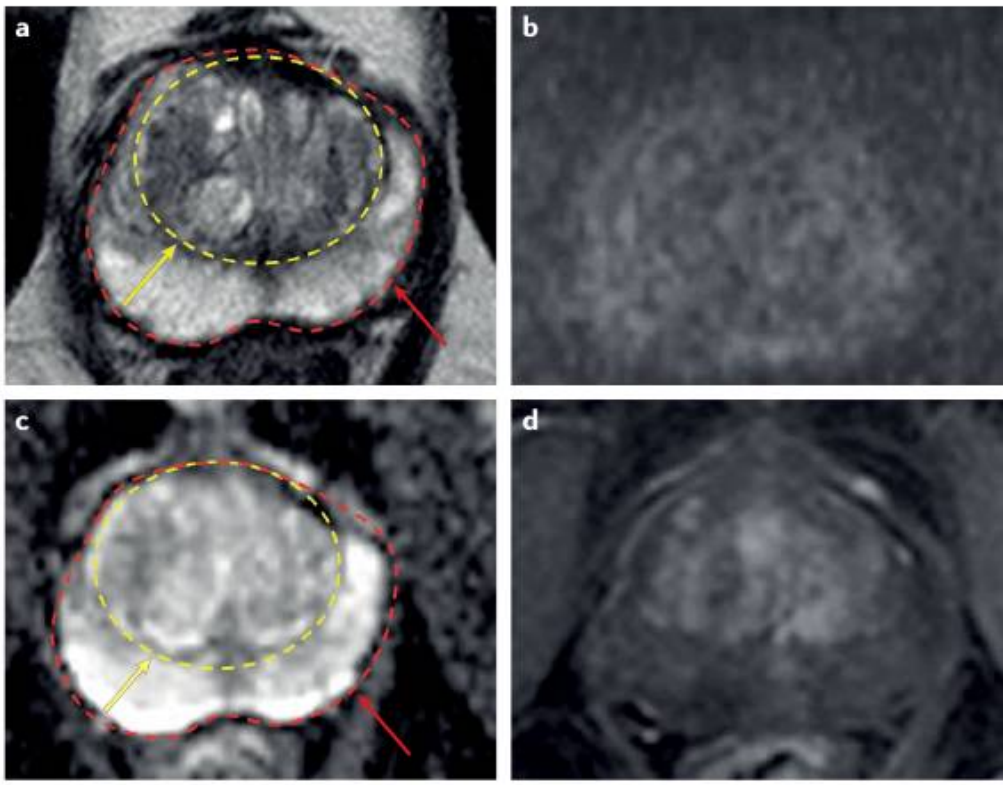


Figure 6. MpMRI of a healthy prostate gland. **a)** T2 Peripheral zone appears hypeintense (bright) and the transitional zone appears heterogeneously hypointense (dark) **b)** DWI There is no restricted diffusion (dark) **c)** ADC map with no restrictive diffusion (healthy areas appear as bright spots) **d)** DCEI with no early enhancement. Red arrows and red dashed lines indicate the peripheral zone; yellow arrows and yellow dashed lines indicate the transitional zone [10].

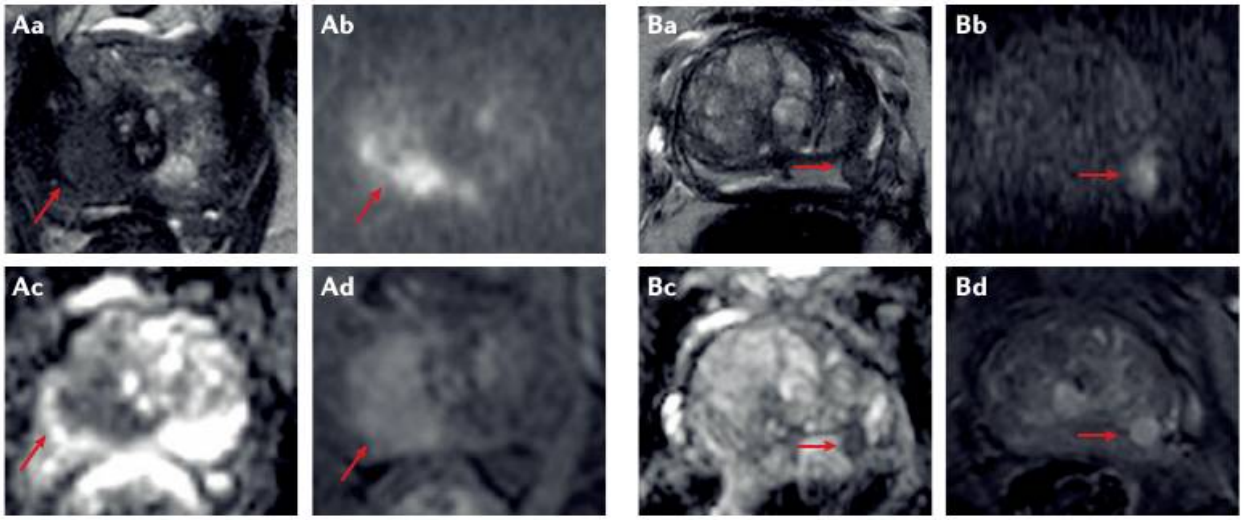


Figure 7. mpMRI cancerous prostate **a)** There is a tumour in the right peripheral zone. Arrows mark the lesion **Aa.** T2 lesion is hypointense (dark) **Ab.** DWI lesion shows restricted movement (bright) **Ac.** ADC map the lesion is hypointense (dark) **Ad.** DCEI lesion shows earlier enhancement than the rest of the gland. Lesion A is graded PIRADS 5 targeted biopsy showed a Gleason 4+3.
b) There is a tumour on the left peripheral zone. Arrows mark the lesion **Ba** T2 lesion is hypointense (dark) **Bb** DWI lesion shows restricted movement (bright) **Bc** ADC map the lesion is hypointense (dark) **Bd** DCEI lesion shows earlier enhancement than the rest of the gland. Lesion is graded PIRADS 4 and the biopsy is graded as Gleason 3+4. Image extracted from [10].

5.2.5.3 Evaluation

This images must be evaluated with a system that reflects the probability to present clinically significant prostate cancer. Hence, a system was created.

PIRADS stands for Prostate Imaging Reporting and Data System. It is a standardized system used to evaluate images obtained from MRI and report the results for the detection and assessment of prostate cancer. PIRADS system was designed to provide a standardised way for radiologists to communicate the likelihood of clinically significant prostate cancer based on MRI imaging. Moreover, this grading system helps guide to clinical decision-making and treatment planning.

The PIRADS system uses a scale of 1 to 5:

PIRADS 1: Very low (clinically significant cancer is highly unlikely)
PIRADS 2: Low (clinically significant cancer is unlikely)
PIRADS 3: Intermediate (the presence of clinically significant cancer is equivocal)
PIRADS 4: High (clinically significant cancer is likely)
PIRADS 5: Very high (clinically significant cancer is highly likely)

The meaning of PIRADS score and the clinical intervention for each grade are as follows [15].

PIRADS 1: This score indicates that it is highly unlikely that clinically significant prostate cancer is present in the MRI images. No further tests are requested.
PIRADS 2: This score suggests that clinically significant cancer is unlikely, but it cannot be ruled out completely. No further investigation is recommended.
PIRADS 3: This score means that the presence of clinically significant cancer is uncertain and needs further investigation (physicians use value of PSA to determine need for biopsy).
PIRADS 4: This score indicates a higher likelihood of clinically significant cancer being present in the MRI images, and a prostate biopsy is be recommended.
PIRADS 5: This score suggests a high likelihood of clinically significant prostate cancer, and a biopsy is strongly recommended.

Radiologists need to study the images and then assign PIRADS scores based on various features such us the appearance of the lesions, their size, and enhancement patterns. The value of PIRADS will determine if the patient needs further investigation (PIRADS ≥ 3) or if it is save to avoid further investigation since the images show low risk of clinically significant prostate cancer.

5.2.5.4 Biopsy

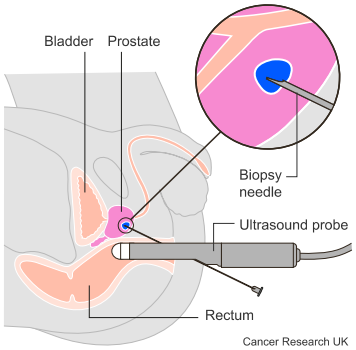
The most definitive method for diagnosing prostate cancer is a prostate biopsy. Biopsies occur after other tests indicated a high likelihood of cancer. Then, a biopsy is performed to obtain tissue samples for analysis. The biopsy is guided by imaging ultrasound (TRUS) or MRI. Originally, there were two ways: transrectally or transperineally. Nowadays, the transrectal approach is rarely used since there is a higher risk for infections (sepsis) due to the natural flora of the rectum.

There are different sampling approaches: systematic, targetted or mapping. **Systematic** biopsies take samples (cores) from multiple areas (normally 6 cores from each lobe) to identify cancerous regions across the organ. **Targeted** biopsies are performed after an imaging technique (usually MRI) has located and delimited a suspicious area, and cores are obtained from this abnormal zone. The diagnostic performance of a targeted biopsy is higher than that of a systemic biopsy. Lastly, **mapping** biopsies takes samples from the entire gland at fixed distances from each other.

The cores obtained from the procedure are sent to a pathology for examination. A pathologist evaluates the tissue samples to determine the presence of cancer and assess its aggressiveness (Gleason score) already explained in 5.2.2 Anatomical pathology evaluation section.

Biopsy guided by Ultrasounds

This technique is the most commonly used due to its availability, low cost and lack of special equipment. The prostate tumour appears as hypoechoic, but only 30-40 % of hypoechoic areas on the prostate are really cancer. The imaging is used to visualise the organ and guide the needle to suspicious areas (Figure 8) [17]. This test has 30-40% chance to detect a cancer [19]. Consequently, 50-80% of clinically significant prostate cancer cases are missed [14].This technique has a sensitivity of 48% and negative predictive value of 74%. The specificity is 96% and the positive predictive value is 90% [20]. For these reasons, new techniques with better diagnostic performance are being sought.



Figures 8. Biopsy guided by TRUS. Probe is introduced inside the rectum and the gland is seen. The imaging is also used to guide the needle to hypoechoic areas [4] .

The use of MRI images was proposed to increase the sensibility and specificity of the diagnostic, increasing the diagnostic performance. There are two main techniques that involve MRI imaging: cognitive targeted biopsy and MRI-TRUS fusion biopsy.

Cognitive targeted biopsy This biopsy does nor required extra equipment. The experienced radiologist will evaluate the MRI images and locate the suspicious area. Then, the ultrasound probe will be introduced into the rectum and remember the location of the suspicious area on the MRI images and targeted on the ultrasound and obtain the cores. This technique is cheaper because it does not require extra equipment but is professional dependant and it has been shown that on the performers there is a learning curve. The beginners target less suspicious areas than the more experienced ones [19].

In order to prevent this performer dependency, the MRI-TRUS Fusion biopsy was used.

MRI-TRUS fusion biopsy Biopsy guided by MRI

This technique fuses pre-biopsy MRI images of the prostate with real-time ultrasound images during a prostate biopsy procedure. Four phases are required. Firstly, a mpMRI provides detailed images form the gland and the presence or absence of suspicious areas. The gland is graded using the PIRADS system and if the result are PIRADS ≥ 3, then a biopsy of the suspicious area is requested to determine presence / absence of prostate cancer. Secondly, the ultrasound probe is introduced in real time and the gland is visualised and delimited. Then, the previous images from mpMRI are fused with the real images the TRUS. Finally, the physician has targetted the suspicious area and is able to extract cores from this suspicious region with high precision (Figure 9).

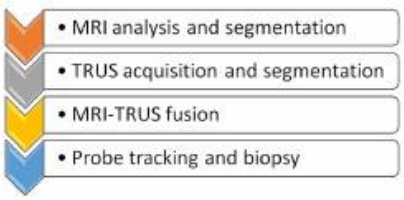


Fig. 1 Diagram representing the four key steps in the MRI–TRUS fusion biopsy of the prostate

Figure 9. Representation of steps for the MRI-TRUS fusion biopsy to diagnose prostate cancer [21]

This technique reduces the number of biopsies in those cases where the mpMRI showed areas with low probability of significant cancer (PIRADS 1 and PIRADS 2). Moreover, with MRI-TRUS fusion biopsy the detection of non-clinically significant cancers are reduced and the detection of clinically significant cancers is increased. Due to this, the over-diagnosis and over-treatment are reduced [20].

6 Justification

Prostate cancer is the 4th most common cancer worldwide: in 2020 1.41 millions of new cases were diagnosed [8] [14]. This disease is the most deadly for men between 45 and 60 years old in the Western countries [12]. One in nine men will suffer from it [7] [10]. Hence, it is essential to have an efficient diagnosis to detect and discern between the clinically significant cases and non-pathological cases.

There are many tests but none of them is precise and accurate enough. PSA blood levels are organ specific but not cancer-specific [6] [16]. Imaging may assist with the location of the lesion, and the biopsy can confirm its diagnosis. The most common image technique is Trans Rectal Ultra Sound (TRUS) which allows to measure the organ, visualize suspicious areas and guide the needle during biopsy [6]. This has 30-40% chance to detect a cancer [21.] Consequently, 50-80% of the clinically significant prostate cancer cases are missed [14]. In order to improve that, a combination with MRI was introduced. MRI has a higher sensibility (75-89%) and specificity (77-91%) and can be used to visualize the organ, evaluate and rate the lesion (PI-RADS Prostate Imaging Reporting & Data System) and guide the biopsy [10]. In spite of those advantages, MRI is more expensive and less common (reduced availability) than Ultrasounds.

At present, the European Association of Urology (EAU) only recommends MRI – Ultrasound fusion-guided prostate biopsy on those patients with a previous negative biopsy guided by Ultrasound (TRUS) and steady (or rising) high PSA blood levels. In the procedure considered here, these patients undergo an MRI and their PI-RADS must be equal or higher than 3 (likely to be malignant) [15] .

The main goal of the study is to evaluate the incidence of prostate cancer in men with a second targeted biopsy using MRI-TRUS fusion technique. In those patients, the first biopsy was guided by ultrasounds (TRUS) and had a negative result. The second biopsy will be guided by a previous MRI that showed a PIRADS ≥ 3. Then, those MRI images will be overlapped with the ultrasound images in real time.

Due to the high incidence of the disease, 94.9 in Western and 85 in Northern Europe in 2020 [8] it is important to diagnose those patients suffering from clinically significant prostate cancer and treat them. Likewise, those cases with low risk of malignancy might benefit from active surveillance and avoiding the side effects from unnecessary treatment [6].

As mentioned before, there are two types of guided biopsy by MRI: cognitive targeted and MRI-TRUS fusion biopsy. There are previous studies related to the cognitive targeted prostate biopsy, but

only a few on MRI-TRUS fusion biopsy: one in Madrid [22] and none in Catalonia. Since, the cognitive depends on the experience of the performer, it seems the MRI-TRUS fusion biopsy might be better approach [19] . Our results would be compared to previous studies with cognitive targeted MRI and the recent study on MRI-TRUS fusion biopsy in Madrid.

The study will assess the efficiency of the MRI-TRUS fusion biopsy.

Ultrasounds are widely used, and its access is easy. On the other hand, the MRI is more expensive, less accessible and requires more resources (highly specialized hospital personnel, hospital equipments /operating rooms and time). Using this technique only on dubious cases might be time and money saving. It might also help to prioritize individuals in regions were the access to MRI is scarce.

The estimated cost for this study is 8,900 euros and it could be used as a pilot study to asses the benefits of using this innovative technique, MRI-TRUS fusion biopsy, in the Catalan population.

7 Hypothesis

7.1 Main Hypothesis

The MRI – ultrasound fusion guided biopsy will diagnose prostate cancer in those patients with a previous negative biopsy guided by ultrasound (TRUS) and having a maintained / increasing PSA blood levels.

7.2 Secondary hypotheses

The MRI – ultrasound fusion guided biopsy will diagnose clinically significant prostate cancer, if present, in those patients with a previous negative biopsy guided by ultrasound (TRUS) and having a maintained / increasing PSA blood levels.

8 Objectives

8.1 Main objective

To evaluate the incidence of prostate cancer in men with a previous negative biopsy guided by ultrasounds (TRUS) which were exposed to a second targeted biopsy using the MRI-Ultrasound fusion software imaging.

8.2 Secondary objectives

To evaluate the incidence of clinically significant prostate cancer in men with a previous negative biopsy guided by ultrasounds (TRUS) which were exposed to a second targeted biopsy using the MRI-Ultrasound fusion software imaging.

9 Methodology

9.1 Study design

The cross-sectional study will be a retrospective, descriptive and observational performed in *Hospital Universitari Dorcor Josep Trueta* in Girona for 4 years staring in June 2021 first time this diagnostic procedure was performed at the hospital.

9.2 Study population

The population are men between 45-80 years old currently under study for prostate cancer at *Hospital Universitari Doctor Jospe Trueta*. The first prostate biopsy, which was systemic and targeted, and guided by Ultrasounds (TRUS), was negative. The PSA blood levels remain high or are increasing. An MRI was performed and showed a PIRADS ≥ 3. A second biopsy is performed with the imaging technique MRI - ultrasound fusion- guided.

9.2.1 Inclusion criteria

The inclusion criteria to enter this study are:

Man currently under study for prostate cancer diagnosis
The prostate biopsy guided by ultrasounds (TRUS) was negative for prostate cancer
The PSA remains ≥ 4 ng/dL
The multi-parametric MRI showed an area of the prostate with an index PIRADS ≥ 3
Consent to the procedure signed by the patients
They are able to undergo anaesthesia

9.2.2 Exclusion criteria

Patient will not be included in the study if they meet any of the requirements:

Life expectancy less than 10 years.
Unable to undergo an MRI (pacemaker) or anaesthesia.
Have an impediment for the introduction of the ultrasound device through the rectum.
Previous diagnosis of prostate cancer.
MRI images are not compatible with the KOELIS Trinity®

9.3 Sampling and sample

9.3.1 Sample selection

This study will use a non-probabilistic consecutive method. All patients from *Hospital Universitari Dorctor Josep Trueta* who meet the inclusion criteria and none of the exclusion criteria will be selected to participate in the study for a period of 4 years starting in June 2021.

9.3.2 Sample size determination

The sample size was calculated using the formula «estimation of proportion» given by Dr. Rafael Ramos and the recommended bibliography [23].

$$n = \frac{Z_\alpha^2 \cdot p_0 \cdot q_0}{d^2}$$

n is the number of patients for the sample

$\mathbf{Z_\alpha}$ confidence level determined by the value of **α**

$\mathbf{p_0}$ proportion of subjects that present the characteristic.

$\mathbf{q_0}$ proportion of subjects that do NOT present the characteristic $\mathbf{q_0 = 1 - p_0}$

d precision is the amplitude or width of said interval

For this study, the confidence level was 95% (**α = 0,05**). Hence, $\mathbf{Z_\alpha}$ was **1,960**. The value p_0 was obtained from bibliography [23]. His study showed that 59,5% of patients in Madrid that underwent a second biopsy guided by MRI using imaging software fusion had prostate cancer. Consequently, $\mathbf{p_0}$ the value of **59,5%**. The value of q_0 is obtained by the following formula $q_0 = 1\text{-}p_0$ so $\mathbf{q_0}$= 1 – 0,595 = **0,405**. The **d**, maximum error admitted, is **10%**. D is half of the confidence interval. Thus, the confidence interval is 20%. The value of **n** is 92,57. The sample size for this study is **93** patients.

9.3.3 Estimated time of recruitment

This diagnostic technique was introduced into *Hospital Universitari Doctor Josep Trueta* in June 2021. Since then, according to the urology department there has been 54 cases (in October 2023) in 28 months. There is a ration of 1,93 patients per month. In order to obtain 93 patients, it is estimated it might take 48,2 months which is about 4 years since June 2021. The collection of data will last until **June 2024**.

9.4 Variables

9.4.1 Independent variable

Performance of the diagnostic procedure MRI-Ultrasound fusion biopsy by Koelis Trinity®.

9.4.2 Dependant variable

Presence or absence of prostate cancer in the cores obtained in the second biopsy guided by MRI-Ultrasound fusion by software. It is a qualitative nominal dichotomous categorical variable : presence or absence of prostate cancer.

Presence of prostate cancer is defined by the pathologist who finds at least 1 core from the biopsy with a Gleason ≥ 6 or a ISUP group ≥ 1.

The clinically significant prostate cancer is defined in this study by the pathologist when finding a core with a Gleason ≥7 or an ISUP grade ≥ 2.

9.4.3 Covariates

The following variables must be taken into account because they might influence the results of this study (Table 6).

Age. A quantitative continuous but expressed as discrete. Expressed in years old (without taking into account months) at the time of the diagnostic procedure.

Digital Rectal Examination (DRE). A qualitative nominal expressed as Yes or No for the presence of bumps or hardened areas from the DRE.

Signs and symptoms. A qualitative nominal expressed in Yes or No. Patient reports signs and symptoms such as pollakiuria (need to urinate more of then than usual), slow or weak urine stream, hematuria (presence of blood in the urine), hematospermia (presence of blood in semen) or erectile dysfunction.

PSA (total and free). A quantitative continuous expressed in ng/dL accepting one decimal.
PSA Density. A quantitative continuous variable expressed in ng/ml/cc. The result is obtained from dividing the total PSA value by the prostatic volume obtained from the MRI.
Prostatic volume. A quantitative continuous variable expressed in cc accepting one decimal. Obtained from the MRI.

Number of suspicious areas. A quantitative, discrete value expressed in natural numbers.

PIRADS classification. A qualitative ordinal. Expressed as PIRADS 3, PIRADS 4 or PIRADS 5 for each suspicious area.

Size of the lesion. A quantitative discrete variable expressed in mm of the lesion at its major axis.

Location of the lesion there are 36 anatomical areas within the prostate according to Sector MAP for PIRADS V2.0

BASE:
Anterior right: TZa (1), PZa (2), AS (3).
Anterior left: TZa (4), PZa (5), AS (6).
Posterior right: TZp (7), CZ (8), PZpl (9).
Posterior left: TZp (10), CZ (11), PZpl (12).
MID:
Anterior right: TZa (13), PZa (14), AS (15).
Anterior left: TZa (16), PZa (17), AS (18).
Posterior right: TZp (19), PZpm (20), PZpl (21).
Posterior left: TZp (22), PZpm (23), PZpl (24).
APEX:
Anterior right: TZa (25), PZa (26), AS (27).
Anterior left: TZa (28), PZa (29), AS (30).
Posterior right: TZp (31), PZpm (32), PZpl (33)
Posterior left: TZp (34), PZpm (35), PZpl (36).

Systemic biopsy **Number of cores obtained.** A quantitative discrete the number of cores will be obtained.

Guided biopsy **Number of cores obtained from the suspicious area.** A quantitative discrete for the numbers of cores obtained from the suspicious area.

Pathological results (ISUP score / Gleason score) A qualitative ordinal categoric. The results are shown on the table 5.

Table 5. Internationally Society of Urological Pathology 2014 grade system and their equivalent Gleason Score (EAU,2023)

Gleason Score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9 – 10 (4+5 or 5+4 or 5+5)	5

Proportion of systemic cores affected. A quantitative continuous expressed in %. It is the result of the number of affected cores obtained from the systemic biopsy divided by the total number of extracted cores (obtained by systematic biopsy). It accepts one decimal.

Proportion of guided cores affected. A quantitative continuous expressed in %. It is the result of

the number of affected cores obtained from the guided biopsy divided by the total number of cores (obtained by guided biopsy). It accepts one decimal.

Table 6. The variables that might influence the incidence of prostate cancer (main goal for the study) will be recorded and taken into account.

Covariates	Definition	Level of measurement	Operating level
Demographic variable			
Age	Years old as expressed on the clinical history	Quantitative, continuous but expressed as discrete values	Numeric
Clinical variables			
DRE	Presence or absence of bumps or hard areas	Qualitative nominal	Yes or No
Signs and symptoms	Presence or absence of signs and symptoms	Qualitative nominal	Yes or No
From blood analysis			
PSA	Concentration expressed as ng/ml	Quantitative continuous	Numeric with one decimal
PSA density	Expressed in ng/ml/cc. Result of dividing PSA by prostatic volume from mpMRI	Quantitative continuous	Numeric
From mpMRI			
Prostate Volume	Volume expressed as cc	Quantitative continuous	Numeric
Number of suspicious areas	Number of suspicious area that appear on MRI by radiologist	Quantitative discrete	Numeric (natural number)
Pi-RADS		Quantitative ordinal categoric	PIRADS 3 PIRADS 4 PIRADS 5
Size	Expressed in mm from the major axis of the lesion	Quantitative discrete	Numeric
Location	36 anatomical areas	Quantitative ordinal categoric	36 anatomical areas
Biopsy variables			
Systemic biopsy			
Number of cores systemic	Number of cores from the systemic biopsy	Quantitative discrete	Numeric
Number of positive cores	Number of cores that have cancer from systemic biopsy	Quantitative discrete	Numeric
Proportion of systemic cores affected	Result of nº affected cores divided by total nº of cores obtained. Expressed in %	Quantitative continuous	Numeric accepting one decimal
Guided biopsy from the suspicious area			
Number cores from lesion	Number of cores from the guided biopsy	Quantitative discrete	Numeric
Number of positive cores from lesion	Number of cores from guided biopsy that show cancer	Quantitative discrete	Numeric
Proportion of guided cores afected	Result of nº affected cores divided by total nº of cores obtained. Expressed in %	Quantitative continuous	Numeric accepting one decimal
Gleason Score	Pathologist evaluation	Quantitative ordinal categoric	1 Gleason 6 2 Gleason 3+4 3 Gleason 4+3 4 Gleason 8 5 Gleason 9 - 10

9.5 Procedure

Patients are under study for suspicion of prostate cancer at the hospital. The first biopsy guided by ultrasounds was negative. However, there is still a suspicion of the disease (remaining or increasing levels of PSA in blood). The urologist requests a multi parametric MRI to see the gland and be able to identify suspicious areas, if there are any. The patient is informed about this imaging technique and sings the form.

After the multi parametric MRI, the radiologist and the urologist meet and discuss the results. If the images show areas with PIRARDs ≥3, it is likely that these areas include a clinically significant cancer. It is necessary to confirm or discard the diagnosis with a pathologist, therefore a second biopsy is mandatory.

Hence, they are candidates for the MRI software fusion-guided prostate biopsy (systemic and targeted) via the perineum. In contrast to the systemic biopsy which involves 6 cores for each lobule of the prostate gland, in this fusion-guided biopsy more cores are obtained from the suspicious areas (previously seen on the mpMRI).

The patient is informed about the diagnostic procedure and its complications or side effects. They have some days to make a decision. If agreed, patients sign the informed consent (**Annex 2**).

Once the patient has accepted, the anaesthesiologist evaluates the patient. If the patient is using anti-platelet or anti-coagulant drugs, it is possible that the treatment will be interrupted for a few days or the dose might change to prevent complications on the biopsy. The patient will receive and explanation and a written document about the preparation for the procedure.

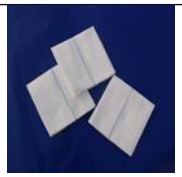
The procedure is an ambulatory major surgery which means the patient does not required to stay overnight at the hospital. The preparation for it consists in the cleansing and prophylaxis. Three to two hours prior, a 250mL enema is introduced into the rectum for cleansing. At the same time, a prophylactic dose of Levofloxacin 500 mg is administrated orally in order to prevent infections.

The anaesthesiologist will sedate the patient deeply to prevent his movements as well as to avoid discomfort or pain during the test. The patient is in supine position. Once the patient is sedated, the patient will be in a lithotomy position with the assistance of padded foot rests which are attached to the surgical table.

The equipment used to perform the biopsy is listed on the table below [24]

9.5.1 Equipment

This equipment descriptions are obtained from the manufacturer website [24]

		
Disposable needle guide	**Perine Mini Grid**	**Perine Full Grid**
The disposable guide is designed to adapt on the 3D End-Fire endocavity probe. This guide, made in polycarbonate and delivered sterile, is meant to be a single-use guide. The guide is straight and makes the needle insertion easy. It shows smooth angles for patient comfort.	It allows freedom of movement during freehand transperineal biopsy. With its ease of use and 3mm. interval this guide makes it possible to reach every area of the prostate with any angle.	At KOELIS® we decided to see beyond biopsy by offering an all-in one solution providing accuracy at every step of the prostate cancer journey from biopsy and active surveillance to treatment and follow-up.
		
Steady Pro® Transperineal support	**Steady Pro®**	**3D side-fire ultrasound probe**
It lets the clinician manipulate the probe and reach a specific position with no limits Rotation: X= +/- 6° Y = +/- 80° Z= +/- 30°	Steady Pro secured the probe to ensure the biopsy or intervention is successfully performed while minimizing movement	K3DEL00 is a high-resolution 3D endocavity ultrasound probe ideal for transperineal prostate biopsies, transperineal focal prostate treatments, and prostate examinations. Wide side-fire field of view to see the entire prostate on the live ultrasound image Integrated 3D motorization for a complete scan of the prostate in less than 6 seconds Available with single-use or reusable needle guides Clinical Applications: Urology, Gynecology Frequency: 4 – 9 MHz Field of view: 72 mm 3D sweep: 170° Imaging modes: B-mode 2D, B-mode 3D, Colour Doppler, Power Doppler
		
Gauze	**Condom**	**Lubricant**

9.5.2 Transperineal prostate biopsy

A 3D side-fire ultrasound probe (with 170º of vision and 75 mm length) is used. Condom and lubricant are applied to the probe avoiding air bubbles.

Then a Perine Mini Grid (3 mm distance) is applied with adjustable position and easy lock system (to fixate the position).

Steady Pro® Transperineal support and an articulated probe holder are used to hold the probe allowing freedom of movement. The system has an easy lock to fix the convenient position.

Panorama acquisition. The 3D side-fire ultrasound probe is introduced inside the rectum and allows to visualize the whole prostate without moving the prove (Figure10).

Prostate contouring. The prostate contouring from the ultrasound images is done (Figure 11).

Multi-modal images import. The images from previous MRI, where the prostate contour was drawn and the lesion was located, are imported (figure 12).

Elastic Fusion technology is used to adjust images from MRI and Ultrasound and to place the exact location of the lesion.

Virtual biopsy. The ultrasound probe shows the image of the prostate and lesion and the position of the Grid. The doctor is able to choose the core position that is best suited to target the lesion (Figure 13).

Real biopsy. A needle is introduced with the help of needle guide. The needle is seen on the ultrasound. The core location is registered and levelled as guided or systemic. They are sent to the pathologist to analyse (Figure 14).

In order to obtain another core the process must be repeated. (virtual and real biopsy)

Prostate cartography. All cores are registered in a patient specific 3D map. The histopathological results (biopsy length, tumour length and Gleason score for each core) will complete the map and help with diagnostic and treatment decisions (Figure 15).

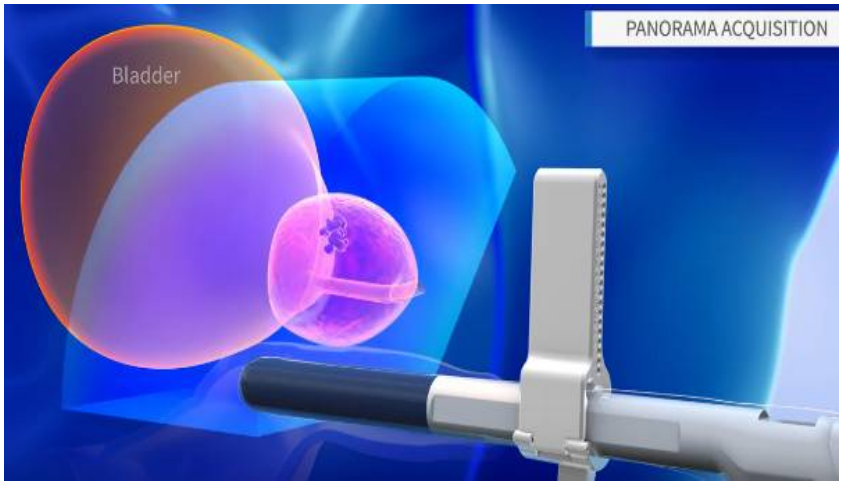


Figure 10. Panorama acquisition [24] .

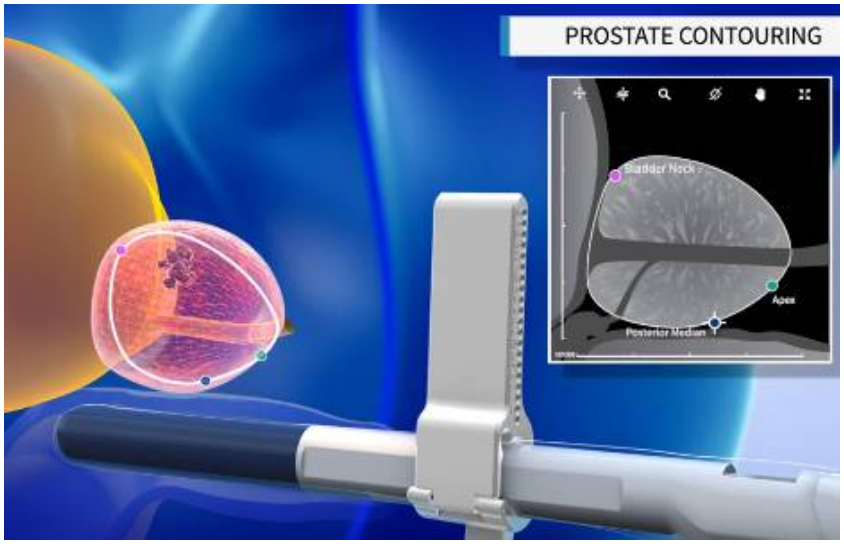


Figure 11. Prostate contouring [24] .

Figure 12. Multi-modal import [24] .

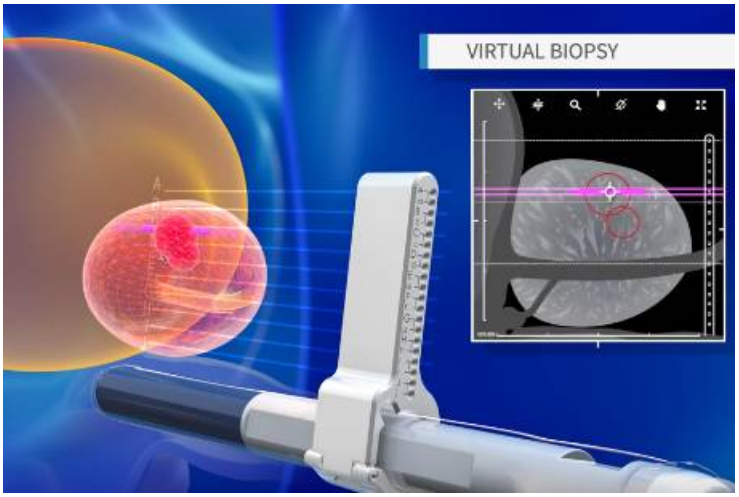


Figure 13. Virtual biopsy. Suspicious area located on the image and the position of the grid to identify which level of the grid is more suited to target the area [24] .

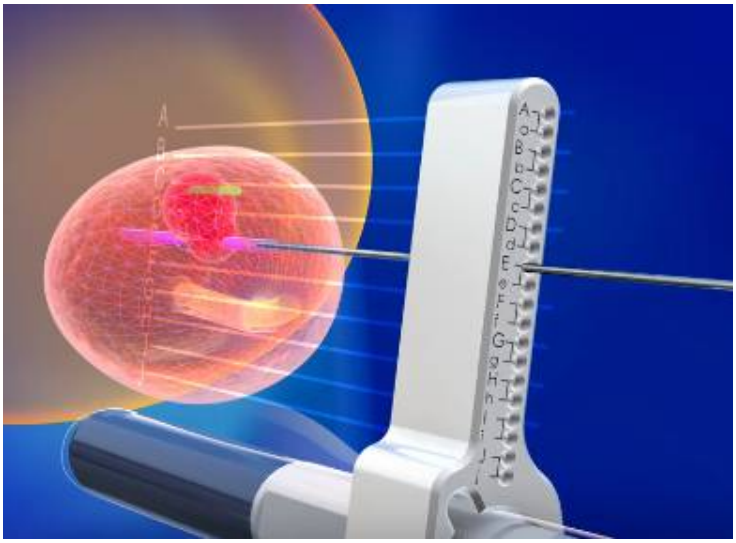


Figure 14. Real biopsy. The needle is introduced at the specific location of the grid to target the area [24] .

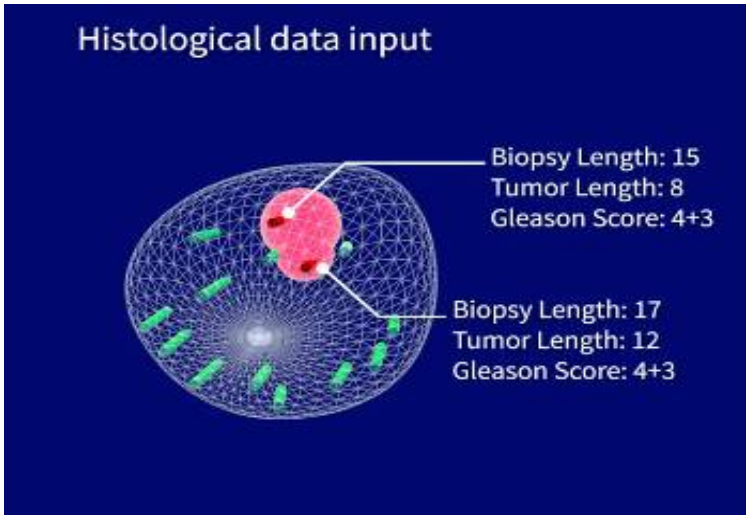


Figure 15. Prostate cartography [24] . All cores obtained from the biopsy and their location are registered on a 3D map.

9.6 Data collection

This protocol is done with pseudo anonymization after period of data collection (estimated to finish in June 2024). The encryption team will access the clinical history and obtained the study variables described on the section *9.4.3. Covariates*. The co-variates from this study are: age, results from DRE, presence or absence of symptoms, PSA (total and free), PSA density, prostatic volume, number of suspicious areas, PIRADS classification, size of the lesion, location, number of cores obtained, number of cores obtained from the suspicious area, ISUP score / Gleason Score, proportion of systemic cores affected and proportion of guided cores affected.

The encryption team will transfer the encrypted information the the research team. The main investigator will meet the statistical specialist to discuss the objectives and the best way to analyses the data taking into account all the co-variables. The statistical will analyses the data and send the results to the main investigator. The researchers will meet and discuss the results to reach conclusions from the study.

9.7 Statistical analysis

9.7.1 Descriptive analysis

The main variable of the study is the results of the biopsy (positive or negative) for any type of prostate cancer (main goal) and for clinically significant prostate cancer (positive or negative) (secondary goal).

Categorical variables were expressed in percentages and continuous variables through indices of central tendency (mean, median), and dispersion (deviation standard and interquartile range).

9.7.2 Bivariate inference

The comparison of the proportion of Prostate cancer and clinically significant prostate cancer between mpMRI – TRUS fusion biopsy and TRUS biopsy will be studied using the Chi square test.

Comparison of the proportion of positive cylinders for the biopsy will be performed with the Student test.

The relationship between PIRADS (3, 4 and 5) and prostate cancer will be studied with the Chi square test and the relationship between PIRADS (3, 4 and 5) and the ISUP grade group, will be studied with the Chi test square.

9.7.3 Multivariate analysis

The statistic analysis to be used will be a binary logistic regression model. Variables proposals for the predictive model will be: age, DRE, total PSA, PSA free, PSA density, prostatic volume, PIRADS grading, localization (36 areas). This is done to asses multiple simultaneously and asses the combined influence on presence/absence of prostate cancer.

10 Strengths and limitations

A cross-sectional study only views a moment of the process that is under study. Thus it is not possible to draw conclusions of causality nor associations. For this study, the main goal is to ensure the performance of the MRI software fusion biopsy for prostate cancer in doubtful cases. Therefore, causality and associations are not relevant.

This study uses a consecutive, non-probabilistic sampling method. Patients that go to the doctor to check a health issue are selected if they meet the criteria for the study. Hence, all the population that does not come to the doctor due to fear, distrust, mobility issues, language barrier, working schedules, poverty, or unawareness of prostate cancer will not come to the doctor. This is a selection bias. Only those men which i) are aware of the risk of prostate cancer and ii) are capable of attending doctor's appointments will be more likely to be diagnosed for this illness and participate into this study.

In order to prevent confusion bias, covariates such as age, PSA levels, prostate volume, location of the suspicious area, PIRADS value, and number of biopsy cores are taken into account. These factors might influence the incidence of prostate cancer. However, it is possible that other unknown factors for prostate cancer are not taken into account in the study and might influence on the result.

In those patients, the first biopsy was guided by ultrasounds only and its results can be explorer-dependant. In order to prevent the inter-variation between doctors, those biopsies are done systemically. Despite the attempts to systematize the diagnostic procedure, those remain explorer-dependant.

There is no masking throughout the process. All the professionals know, before the procedure, where the lesion is located and have studied the results from the multi parametric MRI (size, PIRADS, location) so they are able to elaborate the best extraction strategy for the biopsy.

The population for this study has several inclusion and exclusion criteria. Thus, the results only represent a specific population. The results and conclusions of the study cannot be extrapolated to a more general population.

This study was performed with KOELIS Trinity® equipment. Results might vary if another equipment is used to diagnose and guide the MRI/US fusion prostate biopsy.

The equipment required for this research is limited to a few models and manufacturers (mp MRI or KOELIS Trinity®), needs trained personnel to perform the procedures, and it is expensive. If this

procedure were to be implemented widely, some health centres might find it difficult if they are lacking the equipment or trained personnel.

To avoid information bias and inter variability, the same team of doctors, radiologists, urologist and pathologists will be doing the evaluation of the images, performing the procedure and analysing the cores, respectively. Hence, avoiding inter- variability.

The sample size of 93 patients might seem small. However, it would be enough for the purpose of the study which is to prove that the diagnostic performance of the MRI/US fusion prostate biopsy in Girona is similar to other regions of Spain.

11 Legal and ethical considerations

This study will be performed following "The ethical principles for medical research involving humans subjects" included in the World Medical Association Declaration of Helsinki and revised in 2013 [25] . Before the start of the research, this protocol will be presented to the *Comité d'Ètica de l'Hospital Universitari Doctor Josep Trueta* (CEIC). The research will start once the committee has approved the protocol.

Similarly, the four bioethics principles defined by Beauchamp and Childress[26] will be implemented.

Autonomy. Patients will be informed of the diagnostic procedure the complications that may arise and its risks. This will be done verbally and in writing in an understandable language. The patient will have some days to think whether he wants to undergo this diagnostic procedure or not, complying with his freedom to participate. If agreed, the informed consent will be signed.

Confidentiality. In order to preserve patients' anonymity, the stuff will be divided into two groups within the study: the encryption and the researchers. The encryption has access to medical records and will encrypt personal information, making it impossible to identify the patients. The research team will only use the valuable data related to the study without knowing who they belong to providing confidentiality to the study.

Beneficence. The goal for the study is to find a better tool to detect prostate cancer and clinically significant prostate cancer. This will benefit patients as they will know with more certainty if they have prostate cancer and what type (clinically significant or non-clinically significant). They might benefit from active surveillance avoiding the risk of overtreatment.

Non-maleficicence. There is no ill intention to the patients undergoing this study.

Justice. All patients that meet the inclusion criteria will received access to the latest trend in diagnosis available in Europe for prostate cancer, hence this study enables the same opportunity for diagnosis (avoiding any type of discrimination).

This study will comply with the European and Spanish law on data protection, namely:

Reglamento (UE) 2016-679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativa a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de datos

Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales

Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.

12 Work plan and chronogram

12.1 Research Team members

Main investigator: this person leads the research team, writes the scientific article and coordinates all members and aspects of the study

Urologists: their functions are to identify the candidates for the diagnostic procedure, inform the patient, do the procedure and assist the main investigator with the analysis and writing.

Radiologists: their function is to evaluate the multi-parametric MRI and identify the possible candidates for the study. On the day of the procedure,they will be on the operating room assisting the urologist.

Anaesthesiologists: their function is to evaluate if the patient is a candidate to undergo sedation, and sedate the patient during the diagnostic procedure

Pathologists: their function is to analyse the cores from the systemic and targeted biopsy and do the histological diagnosis of prostate cancer.

Statistical specialists: their function is to analyse the data obtained and assist the researchers with their conclusion of the study

Encryption team: their function is to access the medical records of the patients and encrypt their personal information. They will send only the data related to the study to the research team.

12.2 Study Stages

Stage 0 Preparation and protocol elaboration

Estimated duration of 3 months from September to November 2023.

The main investigator will do a bibliographical review of the topic of study.

The main and secondary objectives and their hypothesis will be defined.

The methodology best suited for the study will be chosen.

The population for the study will be defined and selected.

Stage 1 Ethical approval

Submission protocol and approval. Estimated duration 3 months from December to February 2024.

The protocol will be presented to the research ethics committee (CEIC) at the hospital. If required, protocols might suffer some adjustments to fulfil the CEIC requirements.

Stage 2 Data collection

The data collection is estimated to finish in June 2024 with a sample of 93 patients.

The encryption team will access the clinical history of those patients that meet all the requirements and encrypt the personal information preserving their privacy.

Stage 3 Data analysis

The estimated duration is 4 months from July to October 2024.

The encrypted data will be passed to the research team.

The statistician will analyse the data and calculate the results from the study according to the objectives and co-variables .

The research team will meet and discus the results and reach a conclusion for the study. The main investigator will write the scientific article in collaboration with the other researchers.

They will have the support of the statistician

Stage 4 Publication and dissemination

This stage estimated duration is 2 months from November to December 2024.

The article will be published and presented in a national congress.

Table 7. Chronogram where the stages and tasks of the protocol are listed. Duration and time line is shown with colouring.

Year	**2023**				**2024**											
Months	**S**	**O**	**N**	**D**	**J**	**F**	**Mr**	**A**	**M**	**Jn**	**J**	**A**	**S**	**O**	**N**	**D**
STAGE 0 Protocol elaboration Bibliographical research Definition of objectives, hypothesis and population																
STAGE 1 Ethical approval Submission of protocol to CEIC Approval of protocol																
STAGE 2 Data collection																
STAGE 3 Data analysis Statistician will analyse the data Researcher will discuss the results and reach conclusion Write the scientific paper																
STAGE 4 Publication and dissemination Participation on a national congress																

J January, **F** February, **Mr** March, **A** April, **M** May, **Jn** June, **J** July, **Ag** August, **S** September, **O** October, **N** November, **D** December

13 Budget

The budget for this research is be divided into: personnel, insurance/taxes, meetings, publication and dissemination.

Personnel. Some personnel required for this study will be provided by the Catalan national health service (ICSs) such as urologists, radiologists, anaesthesiologists, pathologists and nurses. Staff related to the study such as the statistician and encryption team must be hired.

Insurance. There is no need for insurance since the biopsy guided by MRI- Ultrasound fusion images is listed as a recommended tool for the diagnosis for prostate cancer by the European Urology Association (EAU). It is a study of low level of intervention.

Taxes. This study is non-commercial: none of the researches shall benefit economically from it. Hence, taxes for carrying out the study could be saved.

Meetings. The meetings to organize and discuss results will be held at the *Hospital Universitari Doctor Josep Trueta* where all the care professionals work. The statistician and encryption team, if necessary, might join the meeting by video-call avoiding travel expenses.

Publication and dissemination. The publication fees are related to paper revision and publication. Paper revision might include checking the academic English, edition, and creation of graphs and images to support the article.

The study will be presented at a national congress by the main investigator and an assistant. The accommodation, dietary and travel expenses are included.

In total, it is estimated the budget required to perform this study is 8,900 euros. The budget breakdown can be found on the following table (Table 8).

Table 8. The expenses for the protocol are related to personnel, publication and dissemination

Expenses	Unit cost	Units	Cost
PERSONNEL			
Statistician	35 € per hour	60 hours	2,100 €
Encryption team	35 € per hour	60 hours	2,100 €
Anaesthesiologists, radiologists, urologists, pathologists and nurses	National health employees during their working hours		
			4,200 €
PUBLICATION			
Paper revision			500 €
Paper publication			2,000 €
			2,500 €
DISSEMINATION			
National congress	500 € per person	2	1,000 €
Accommodation, travel and food expenses	600 € per person	2	1,200 €
			2,200 €
TOTAL BUDGET			**8,900 €**

14 Clinical and healthcare impact

Prostate cancer has a high predominance: in 2020 it is estimated that 1,41 millions of new cases were diagnosed around the world. Despite being so predominant, there is no unanimous strategy to diagnose it. Population screening was discarded, since it also detected non-clinically significant cancers that resulted in over-diagnosis and over-treatment and there was no significant reduction in mortality [6] [8]. In general, the diagnosis involves a combination of medical history, physical examination, the prostate-specific antigen (PSA) test, digital rectal examination (DRE), and prostate biopsy guided by imaging usually ultrasounds (TRUS). These procedures might be missing 50 to 80% of prostate cancers [14] .

New imaging techniques use multi parametric MRI (mpMRI) to analyse the presence/absence of suspicious areas with the grading system PIRADS and, if present, imaging also helps to delineate the affected areas. This delineation will be useful for the guided biopsy. The technique used in this study is MRI-TRUS fusion biopsy and might have a significant impact on the diagnosis of the disease and on the health system.

The MRI-TRUS fusion biopsy is more accurate than TRUS biopsy (the current diagnostic tool) or then mpMRI alone. The sensitivity of MRI-TRUS fusion biopsy is 93% compared to a 48% of TRUS biopsies and the negative predictive values are 89% vs 74 %, respectively. MpMRI by itself has a low specificity (41%) and a moderate positive predictive value (51%). Because of this, an TRUS biopsy guided by the images from mpMRI is necessary to asses the suspicions areas, and then the pathologist will confirm/dismiss the presence of prostate cancer [20] .

This fusion technique also reduces the over-diagnosis and consequently, over-treatment. Results show that, with a previous mpMRI a 25% of men will have lesions with PIRADS below 3 (highly unlikely to have a clinically significant cancer) and will avoid the biopsy and the side effects of that procedure. Moreover, this fusion technique reduces the number of positive diagnoses in non-clinically significant cancers compared to TRUS (reducing over-diagnosis) [20] .

The use of mpMRI imaging allows the physician to localise the lesion beforehand and target that suspicious area (for targeted biopsy) reducing the number of core biopsies required. The side-effects and discomfort from the procedure are reduced compare with TRUS biopsy [27] .

This procedure might result in cost saving. According to *Clinica Creu Blanca* [28] in Barcelona this procedure costs 2.290 euros. As mentioned before, only those patients with an abnormal mpMRI

(PIRADS ≥3) will undergo the procedure, avoiding unnecessary diagnosis and costs. In addition, having previews images optimizes the localization for the suspicious are and its target, improving the rate of diagnosis.

To conclude, the use of MRI-TRUS fusion biopsy to diagnose prostate cancer have a positive impact on our health system. The number of unnecessary biopsies will decrease and the cost of this procedures will be saved. Likewise, this technique tends to reduce the number of diagnoses for non-clinically significant cancer (avoiding over-diagnosis). The number of cores and the side effects are reduces thanks to the previous imaging of the suspicious are and delineation with less discomfort to the patient.

15 Feasibility

Medical team. The care staff is employed by the Catalan Health Service (ICS) and is familiar with the procedure since the team was assembled in 2021 with the first MRI/US fusion prostate biopsy was performed at the *Hospital Universitari Doctor Josep Trueta*. Their salaries are provided by the state. Two additional employees should be hired for this project: an statistician and an encryption expert.

Resources. The equipment required to perform the diagnostic procedure is already available at the Catalan Health Service: MRI, ultrasounds, KOELIS Trinity®, operating rooms, surgical material and blood analysis. Hence, there is no extra-cost for the study.

The procedure is ambulatory which means patients will not stay for the night at the hospital (avoiding the need for available beds within the hospital).

Patients. There had been 54 cases at the *Hospital Universitari Doctor Josep Trueta* since the beginning of the procedure over two tears ago (June 2021). Thus, it is estimated that after two more years the sample of 93 patients will be reached out, which is our sample size.

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17 Annexes

Annex 1. Sequences of mpMRI. First figure is MRSI and the second figure is T2 sequenced [10] .

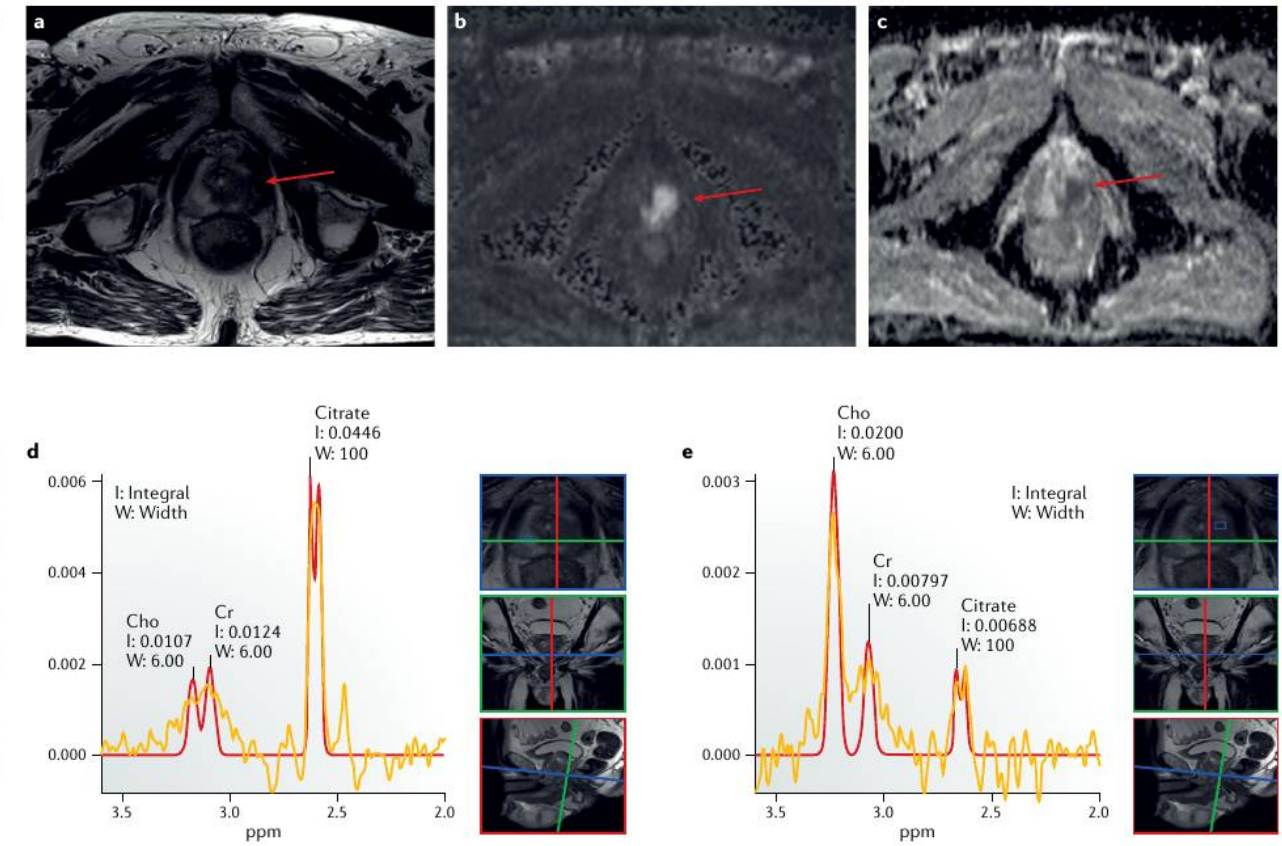

Fig. 3 | **mpMRI of a cancerous prostate using magnetic resonance spectroscopy imaging.** Multiparametric MRI of a left apical lesion. This lesion scored Prostate Imaging Reporting and Data System (PI-RADS) 4 using a T2-weighted imaging sequence (part **a**), a diffusion-weighted sequence (part **b**) and an apparent diffusion coefficient map (part **c**); red arrows indicate the lesion. Using a magnetic resonance spectroscopy imaging sequence, normal prostatic tissue shows low levels of choline and high levels of citrate (part **d**). Conversely, in a suspicious area, choline levels are high and citrate levels are low (part **e**). Prostate biopsy showed adenocarcinoma with Gleason score 4 + 4 in the left apex. Cho, choline; Cr, creatine; ppm, parts per million.

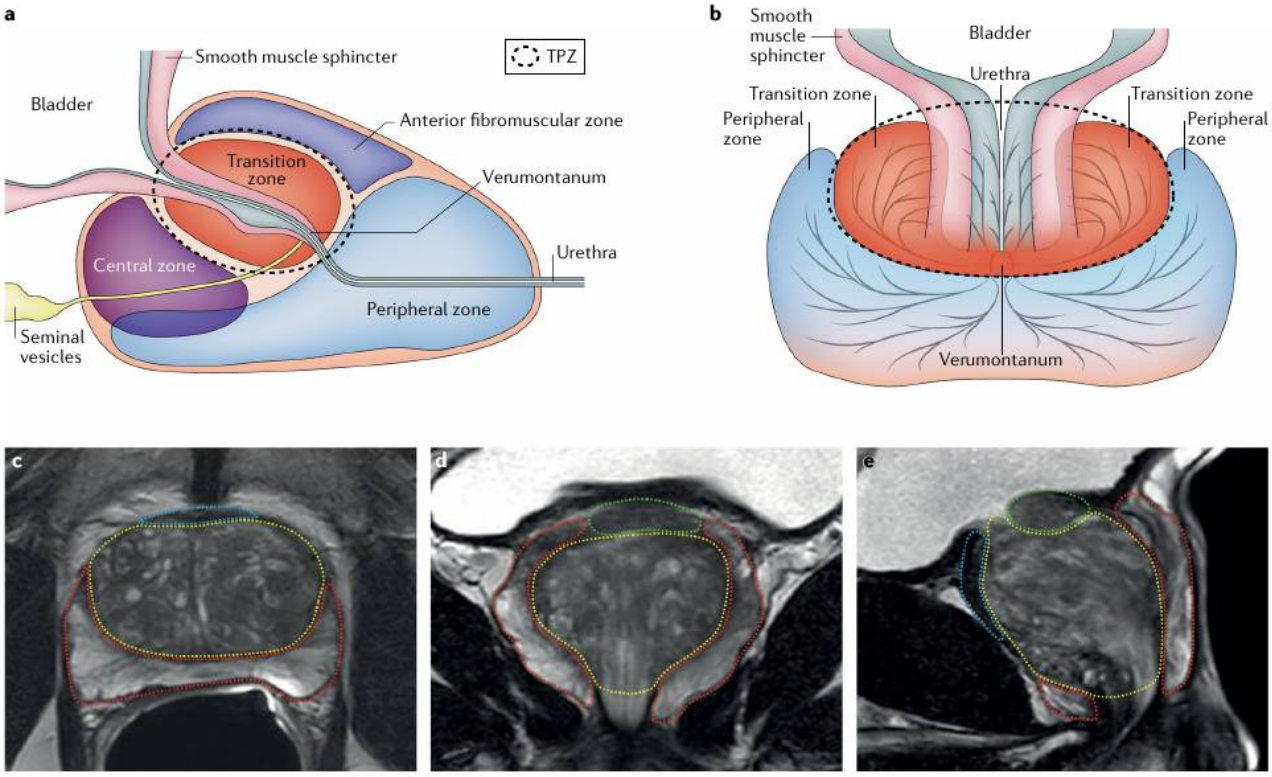

Fig. 4 | **The anatomy of the prostate and T2-weighted mpMRI imaging.** The anatomy of the prostate in the prone position (part **a**) and the upright position (part **b**). The appearance of the prostate using T2-weighted imaging on the axial (part **c**), frontal (part **d**) and sagittal (part **e**) view. On the images obtained, the red dotted line indicates the peripheral zone; the yellow dotted line indicates the transition zone; the green dotted line indicates the central zone; and the blue dotted line indicates the anterior fibromuscular zone. TPZ, transition–periurethral zone. Parts **a** and **b** reproduced from REF.[182], Springer Nature Limited.

Annex 2. Informed consent for MRI- TRUS fuison guided biopsy from *Hospital Dr. Josep Trueta*

Trueta
Hospital de Girona

Institut Català de la Salut

Primer cognom
Segon cognom
Nom
Data de naixement **Sexe** HOME
NHC **DNI**
CIP
Episodi origen

Consentiment informat

Nom del representant legal en cas d'incapacitat del pacient per consentir, ja sigui per minoria d'edat, incapacitat legal o incompetència, amb la indicació del caràcter en el qual intervé (pare, mare, tutor legal, etc).
Sra./Sr.
amb D.N.I. **, en qualitat de** .

Nom del procediment

Aspiració percutània de pròstata

En què consisteix

Mitjançant aquest procediment es pretén poder diferenciar entre malalties benignes de la pròstata i les que no ho són, és a dir, determinar si existeix o no un càncer de pròstata. El metge m'ha explicat que el procediment pot requerir l'administració d'anestèsia local. L'anestèsia local consisteix en la injecció de medicaments anomenats anestèsics locals en la proximitat dels nervis de la pròstata que provoquen l'absència de dolor a la zona corresponent. D'aquesta manera el procediment serà més confortable. L'administració dels fàrmacs imprescindibles en l'anestèsia local poden produir, excepcionalment, reaccions al·lèrgiques que poden arribar a ser greus i fins i tot mortals. Està desaconsellada la pràctica sistemàtica de proves d'al·lèrgia als fàrmacs anestèsics en pacients sense història prèvia de reacció adversa a aquests, igual que passa amb la resta dels fàrmacs. A més, aquestes proves no estan lliures de riscos i, tot i ser el seu resultat negatiu, els fàrmacs anestèsics provats poden produir reaccions adverses durant l'acte anestèsic. Mitjançant aquesta tècnica, amb una agulla fina de biòpsia, es fa una punció la pròstata a través del recte o del perineu, que és la zona situada entre els testicles i l'anus, obtenint múltiples mostres de teixit prostàtic. Per controlar el lloc exacte del qual s'obté, s'introdueix una sonda d'ultrasons per via rectal per a visualitzar la pròstata. De vegades és aconsellable biopsiar teixits del voltant de la pròstata com les vesícules seminals.
El metge m'ha explicat que per a la realització d'aquesta tècnica pot ser necessària una preparació prèvia de la qual seré informat, tot i que és possible la seva realització sense una preparació completa. Així mateix, les dades del seu procediment i resultats poden ser registrats en una base de dades per a ser posteriorment tractats, conjuntament amb els procedents d'altres pacients, amb fins científics, preservant sempre la seva naturalesa confidencial.

Possibles Efectes Adversos

Comprenc que, tot i l'adequada elecció de la tècnica i de la correcta realització, es poden presentar efectes indesitjables, tant els comuns derivats de tota intervenció i que poden afectar tots els òrgans i sistemes, com altres locals específics del procediment. Entre els primers, a part les reaccions a l'anestèsic local, es pot presentar una sèpsia o infecció generalitzada. Entre les complicacions locals, poden produir hematomes a la zona de la punció, hematúria o sang en l'orina, infecció, dificultat miccional, retenció aguda d'orina, uretrorràgia o aparició de sang en l'orifici uretral i rectorràgies o aparició de sang per l'anus. El metge m'ha explicat que aquestes complicacions habitualment es resolen amb tractament mèdic (medicaments, sèrums ...) però poden arribar a requerir una reintervenció, generalment d'urgència, incloent-hi un risc excepcional de mortalitat.
També m'ha explicat la necessitat d'advertir dels meus problemes de salut coneguts com a al·lèrgies medicamentoses, alteracions de la coagulació, malalties cardiopulmonars, existència de pròtesis, marcapassos, medicacions actuals o qualsevol altra circumstància. En cas de patir problemes de salut rellevants o estar sota els efectes d'una certa medicació de risc concomitant (antiagregants, anticoagulants, etc.) la probabilitat d'experimentar

Trueta
Hospital de Girona

Institut Català de la Salut

Primer cognom
Segon cognom
Nom
Data de naixement **Sexe** HOME
NHC **DNI**
CIP
Episodi origen

Consentiment informat

complicacions pot augmentar.

Riscos Personalitzats

Altres riscos o complicacions que poden aparèixer, tenint en compte les meves circumstàncies personals, són _____.

Alternatives

El metge m'ha explicat que no hi ha una altra alternativa més eficaç, ja que els marcadors prostàtics i les exploracions radiològiques i ecogràfiques són complementaris.

Autorització

He comprès les explicacions que se m'han facilitat en un llenguatge clar i senzill, i el facultatiu que m'ha atès m'ha permès realitzar totes les observacions i m'ha aclarit tots els dubtes que li he plantejat. També comprenc que, en qualsevol moment i sense necessitat de donar cap explicació, puc revocar el consentiment que ara presto. Per això, manifesto que estic satisfet amb la informació rebuda i que comprenc l'abast i els riscos del procediment. I en aquestes condicions CONSENTEIXO en què em faci la CIRURGIA PER BIÒPSIA PROSTÀTICA.
Aquest consentiment es formula d'acord amb el que estableix la Llei 16/2010, de 3 de juny, de modificació de la Llei 21/2000, de 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient i la documentació clínica, publicada al DOGC núm. 5647 del 10 de juny de 2010.

Servei sol·licitant	**Professional que informa**	**Número d'identificació**
UROLOGIA		

Signatura i DNI del/la pacient o responsable **Data** **Signatura del professional**

☐ Accepta

☐ No accepta

Revocació consentiment informat.

Jo, En/Na amb DNI/NIF revoco el consentiment prestat en data
declaro per tant que, després de la informació rebuda, no autoritzo a sotmetre'm al procediment de Aspiració percutània