

**Optimización del diagnóstico precoz del cáncer de próstata
clínicamente significativo. Validación del modelo predictivo de Barcelona**

Nahuel Eduardo Paesano

ADVERTIMENT. L'accés als continguts d'aquesta tesi queda condicionat a l'acceptació de les condicions d'ús establertes per la següent llicència Creative Commons:  <https://creativecommons.org/licenses/?lang=ca>

ADVERTENCIA. El acceso a los contenidos de esta tesis queda condicionado a la aceptación de las condiciones de uso establecidas por la siguiente licencia Creative Commons:  <https://creativecommons.org/licenses/?lang=es>

WARNING. The access to the contents of this doctoral thesis it is limited to the acceptance of the use conditions set by the following Creative Commons license:  <https://creativecommons.org/licenses/?lang=en>



**Optimización del diagnóstico precoz del cáncer de próstata
clínicamente significativo. Validación del modelo
predictivo de Barcelona.**

TESIS DOCTORAL

Autor:

Nahuel Eduardo Paesano

Directores:

Juan Morote Robles

Violeta Català Sventetzky

Enrique Trilla Herrera

Tutor:

Enrique Trilla Herrera

Programa de Doctorado en Cirugía y Ciencias Morfológicas

Departamento de Cirugía

Universitat Autònoma de Barcelona

Barcelona, 2026

“El placer más noble es el júbilo de comprender”

Leonardo da Vinci.

1452-1519.

AGRADECIMIENTOS

Al profesor Juan Morote, tutor y codirector de esta tesis, por su dedicación, paciencia y compromiso inquebrantable. Su impulso, constancia y sabiduría han sido fundamentales para que este proyecto fuera posible. Más allá de la medicina y la investigación, le agradezco profundamente todo lo que me ha enseñado con sus palabras, consejos y generosa humanidad. Eternamente agradecido.

A la Dra. Violeta Catalá, codirectora de esta tesis, por haberme permitido soñar con esta oportunidad y por confiar en mí para llevar adelante este proyecto. Gracias por hacernos sentir parte de su familia.

Al Prof. Enrique Trilla, codirector y tutor de esta tesis, por su compromiso, su apoyo y la confianza que siempre depositó en mí.

A los coautores de los artículos publicados, por su valiosa participación y colaboración en el desarrollo de este proyecto.

A mis amigos, parte estructural de mi vida, que han forjado en mí los cimientos sobre los que hoy camino. Bacha, Ignacio L, Ignacio F, Lucas, Checho, Fer, Andrés y toda la generación dorada por las charlas interminables, las risas compartidas, el apoyo incondicional y esa complicidad que sólo nace de los vínculos auténticos.

A mi hermano Fabián, guía de mi vida quien me inculcó el amor por esta profesión y especialidad.

A toda mi familia, a mis hermanos, cuñadas y sobrinos, fuente inagotable de amor y orgullo.

A mi Padre, a quien perdí en pleno proceso de esta tesis siendo un duro golpe en mi vida. En la distancia me mostró siempre su apoyo. Me siento feliz por el orgullo que sentía por mí al estar realizando esta tesis. Lo logramos Papá.

A mi Madre, por ser fuente de inspiración y por enseñarme todos los días lo fuerte que un ser humano puede llegar ser. Gracias Papá y Mamá por criarme con tanto amor.

Por último, a mi compañera de vida, Lara. Gracias por ser el motor de mi vida, de inspiración y fuente inagotable de amor. Gracias por tanto apoyo y por tanto amor. Es hermoso vivir la vida contigo. Gracias.

ACRÓNIMOS

5-ARI = inhibidores de la 5-alfa reductasa

AS = vigilancia activa

AUC = área bajo la curva

BCN-PM = modelo predictivo de Barcelona

BCN-RC = calculadora de riesgo de Barcelona

bpMRI = resonancia magnética biparamétrica

CI = intervalo de confianza

csPCa = cáncer de próstata clínicamente significativo

CUC = curva de utilidad clínica

DCA = *decisión curve analysis*

DCE = coeficiente de difusión

DNA = ácido desoxirribonucleico

DRE = tacto rectal

DOI = *Digital Object Identifier*

DWI = imágenes en difusión

ERSPC = *European Randomized Study of Screening for Prostate Cancer*

EAU = *European Association of Urology*

GG = grupo de grado

GS = suma de Gleason

iPCa = cáncer de próstata insignificante

ISUP = *International Society of Urological Pathology*

JCR= *Journal Citation Report*

mpMRI = resonancia magnética multiparamétrica

MRI = resonancia magnética

MRI-PM = modelo predictivo basado en resonancia magnética

PCa = cáncer de próstata

PCA3 = *Prostate Cancer Antigen 3*

PHI = *Prostate Health Index*

PI-RADS = *Prostate Imaging-Reporting and Data System*

PICO = *Participants, Intervention, Comparator, Outcomes*

PRISMA = *Preferred Reporting Items for Systematic Reviews and Meta-analyses*

PSA = antígeno prostático específico

PSAD = densidad de PSA

QUADAS = *Quality Assessment of Diagnostic Accuracy Studies*

RC = calculadora de riesgo

RNA = ácido ribonucleico

ROC = *receiver operating characteristic*

ROM = modelo organizado de riesgo

TRUS = ultrasonografía transrectal

WW = vigilancia expectante

ÍNDICE

RESUMEN	13
SUMMARY	23
1. INTRODUCCIÓN	33
1.1. EPIDEMIOLOGÍA Y ETIOLOGÍA DEL CÁNCER DE PRÓSTATA	35
1.2. SOSPECHA DE CÁNCER DE PRÓSTATA	39
1.2.1. ANTÍGENO PROSTÁTICO ESPECÍFICO	39
1.2.2. TACTO RECTAL	42
1.2.3. RESONANCIA MAGNÉTICA NUCLEAR PÉLVICA	43
1.3. DIAGNÓSTICO DEL CÁNCER DE PRÓSTATA	45
1.3.1. BIOPSIA PROSTÁTICA	45
1.3.2. SISTEMAS SOFTWARE PARA BIOPSIAS DE PRÓSTATA POR FUSIÓN DE IMÁGENES.....	47
1.3.3. DEFINICIÓN DE CÁNCER DE PRÓSTATA CLÍNICAMENTE SIGNIFICATIVO	48
1.4. MÉTODOS PARA MEJORAR LA SELECCIÓN DE CANDIDATOS A BIOPSIA PROSTÁTICA	51
1.4.1. DENSIDAD DE PSA	51
1.4.2. NUEVOS MARCADORES TUMORALES.....	52
1.4.3. MODELOS PREDICTIVOS.....	54
2. JUSTIFICACIÓN DEL PROYECTO	59
3. HIPÓTESIS.....	63
4. OBJETIVOS	67
5. COMPENDIO DE PUBLICACIONES.....	71
5.1. PUBLICACIÓN 1	73
5.2. PUBLICACIÓN 2	85
5.3. PUBLICACIÓN 3	99

5.4. PUBLICACIÓN 4	113
5.5. PUBLICACIÓN 5	129
5.6. PUBLICACIÓN 6	141
5.7. PUBLICACIÓN 7	163
5.8. PUBLICACIÓN 8	173
5.9. PUBLICACIÓN 9	185
6. RESUMEN GLOBAL DE RESULTADOS	199
7. RESUMEN GLOBAL DE LA DISCUSIÓN	211
8. CONCLUSIONES	225
9. LÍNEAS DE FUTURO.....	229
10. BIBLIOGRAFÍA	235
11. ANEXO	261

RESUMEN

INTRODUCCIÓN

El cáncer de próstata (PCa) es la neoplasia maligna más frecuentemente diagnosticada en varones y la tercera causa de mortalidad por cáncer. Su sospecha se establece a partir de la elevación sérica del antígeno prostático específico (PSA) y/o de un tacto rectal (DRE) sospechoso, mientras que el diagnóstico se confirma a través de la biopsia prostática. El paradigma del diagnóstico precoz del PCa ha cambiado gracias a la introducción de la resonancia magnética (MRI) y de las biopsias dirigidas a las lesiones sospechosas de cáncer clínicamente significativo (csPCa). Actualmente, el diagnóstico precoz de PCa se focaliza en la máxima detección de csPCa, reducción de biopsias innecesarias y sobredetección de PCa insignificantes (iPCa). La biopsia prostática dirigida se indica cuando existen lesiones sospechosas de csPCa identificadas en la MRI, mediante el Prostate Imaging-Reporting and Data System (PI-RADS) igual o superior a 3, obteniendo entre dos y cuatro muestras de cada una y siempre complementada por la clásica biopsia sistemática que obtiene entre 10 y 12 muestras. Recientemente se ha recomendado sustituir el abordaje transrectal por el transperineal para reducir las complicaciones infecciosas y el consumo de antibióticos. Sin embargo, la proporción de biopsias innecesarias sigue siendo elevada, especialmente en escenarios inciertos como el PI-RADS 3. La Asociación Europea de Urología (EAU) recomienda aplicar modelos predictivos de csPCa, basados en MRI y datos clínicos (MRI-PM) para mejorar la selección de candidatos a biopsia prostática, siendo el MRI-PM de Barcelona (BCN-MRI PM) el más eficaz en nuestro medio, aunque fue desarrollado y validado utilizando el PI-RADS v 2.0 y biopsias prostáticas realizadas por vía transrectal, excluyendo pacientes tratados con inhibidores de la 5-alfa reductasa (5-ARI).

Después de una amplia revisión de la literatura hemos identificado algunos aspectos que pueden optimizar el diagnóstico precoz del csPCa: i) Utilizar la lectura experta de la MRI, ii) Desarrollar modelos predictivos para limitar la realización de biopsias sistemáticas, iii) Utilizar una plataforma apropiada para realizar la biopsia prostática transperineal con fusión de imágenes (MRI-TRUS) y un protocolo de saturación de lesiones sospechosas y áreas perilesionales, y iv) Validar el BCN-MRI PM en pacientes tratados con 5-ARI, clasificados con el PI-RADS v 2.1, y utilizando un protocolo de biopsia por saturación de las lesiones sospechosas y áreas perilesionales por vía transperineal.

HIPÓTESIS

La presente tesis plantea la hipótesis de que una estrategia diagnóstica integrada basada en la interpretación experta de la resonancia magnética prostática, la utilización de modelos predictivos basados en MRI, el abordaje transperineal y la realización de biopsias dirigidas mediante un protocolo de saturación de las lesiones sospechosas y áreas perilesionales permite optimizar el diagnóstico precoz del cáncer de próstata clínicamente significativo, aumentando su detección y reduciendo las biopsias innecesarias y el sobrediagnóstico de tumores clínicamente insignificantes. Asimismo, se postula que el modelo predictivo BCN-MRI PM mantiene su capacidad discriminativa y su utilidad clínica cuando se aplica en pacientes tratados con inhibidores de la 5-alfa reductasa, evaluados mediante la clasificación PI-RADS v2.1 y sometidos a biopsia prostática por vía transperineal utilizando un protocolo de saturación de lesiones sospechosas y áreas perilesionales.

OBJETIVO PRINCIPAL

Optimizar el diagnóstico precoz del cáncer de próstata clínicamente significativo mediante la evaluación de una estrategia diagnóstica integrada basada en la interpretación experta de la resonancia magnética prostática, la utilización de modelos predictivos basados en MRI, el abordaje transperineal y la biopsia dirigida mediante protocolos de saturación de las lesiones sospechosas y áreas perilesionales, así como mediante la validación del modelo predictivo BCN-MRI PM en distintos escenarios clínicos.

OBJETIVOS SECUNDARIOS

1. Analizar el impacto clínico de la lectura experta de la MRI y limitar las biopsias sistemáticas a partir de un modelo predictivo.
2. Comparar la efectividad de la biopsia prostática, realizada por vía transrectal y transperineal, para detectar csPCa
3. Comparar la eficacia de un protocolo de biopsia dirigida por saturación (mapping cada 0.5 mm) a las lesiones sospechosas y áreas perilesionales frente al protocolo actualmente

recomendado, analizando además la utilidad clínica de las plataformas de fusión MRI-TRUS empleadas en el abordaje transperineal para la detección de csPCa.

4. Validar el BCN-MRI PM en pacientes tratados con 5-ARI, clasificados con el PI-RADS v 2.1, utilizando la vía transperineal y un protocolo de biopsia dirigida por saturación (*mapping* cada 0.5 mm) a las lesiones sospechosas y áreas perilesionales en una plataforma apropiada.

METODOLOGÍA

Esta tesis doctoral se presenta como un compendio de nueve publicaciones. Los estudios se basaron en análisis retrospectivos y prospectivos de una cohorte multicéntrica reportada por 10 centros participantes del programa de cribado oportunístico de csPCa de Cataluña, además de una revisión sistemática. En las seis primeras publicaciones se analizaron los siguientes aspectos para optimizar el diagnóstico precoz del csPCa:

1. El impacto clínico de la lectura experta de la MRI (PI-RADS v 2.1) en una serie prospectiva de 222 biopsias prostáticas realizadas en el centro de diagnóstico Cruz Blanca de Barcelona.
2. El desarrollo de un modelo predictivo, para limitar la utilización de las biopsias sistemáticas, a partir de las variables predictoras independientes obtenidas en 2.122 varones sometidos a biopsia prostática dirigida y sistemática seleccionados entre 3.557 varones con sospecha de PCa reportados prospectivamente en 10 centros participantes del programa de cribado oportunístico de csPCa de Cataluña.
3. La comparación de la biopsia prostática transrectal y transperineal para detectar el csPCa. Este estudio se realizó en un grupo pareado de 650 casos seleccionados a partir de una cohorte de 4.029 casos reclutados en el programa de cribado oportunístico de csPCa de Cataluña en los que se utilizó el mismo protocolo de biopsia prostática.
4. El impacto clínico de la aplicación de un protocolo de biopsia transperineal dirigida por saturación (*mapping* cada 0.5 mm) de la lesión índice y su área perilesional. Se trató de un estudio prospectivo que incluyó 309 varones con sospecha de PCa biopsiados en el centro diagnóstico Cruz Blanca de Barcelona.

5. La comparación entre un protocolo de biopsia prostática transperineal, dirigida por saturación (*mapping* cada 0.5 mm) a las lesiones sospechosas y áreas perilesionales y habitualmente recomendado, que obtiene entre dos y cuatro muestras de cada lesión. Este estudio se realizó en un grupo pareado de 261 casos seleccionados a partir de 1.161 varones con sospecha de PCa biopsiados prospectivamente en cuatro centros participantes en el programa de cribado oportunístico de csPCa de Cataluña en los que se utilizó siempre la vía transperineal.

6. Una revisión sistemática de la literatura sobre la eficacia de las plataformas existentes para realizar biopsias prostáticas por fusión de imágenes MRI-TRUS mediante abordaje transperineal.

En las publicaciones siete a nueve se realizaron las siguientes validaciones del BCN-MRI PM:

7. En 120 varones con sospecha de PCa sometidos a tratamiento con 5-ARI. Este grupo fue seleccionado retrospectivamente a partir de 2.212 varones sometidos a biopsia prostática, recogidos prospectivamente en 10 centros participantes del programa de cribado oportunístico de csPCa de Cataluña.

8. En 969 varones sometidos a biopsia transperineal obteniendo entre dos y cuatro muestras de las lesiones sospechosas y/o biopsia sistemática con obtención de 12 muestras. Estos casos fueron reportados prospectivamente por cuatro hospitales participantes en el programa de cribado oportunístico de csPCa de Cataluña, en los que se realizaba la biopsia prostática por vía transperineal.

9. En 457 varones sometidos a biopsia prostática dirigida por saturación (*mapping* cada 0.5 mm) de lesiones sospechosas y áreas perilesionales, recogidos prospectivamente en el centro diagnóstico Cruz Blanca de Barcelona en el que se utilizó la plataforma ArtemisTM.

Este proyecto fue aprobado por el comité de ética del Hospital Universitario Vall d'Hebron (PRAG 02/2021) y financiado por el Instituto de Salud Carlos III (PI20/01666), co-financiado por el Fondo Europeo para el Desarrollo Regional “Un camino para hacer Europa”.

RESULTADOS

La concordancia entre la lectura de la MRI reportada por radiólogos no expertos y una radióloga experta fue sólo del 49,1%. La lectura experta permitió reclasificar el PI-RADS 2.1 de las lesiones detectadas y reducir un 28,8% la indicación de biopsia prostáticas sin comprometer la detección de csPCa, además del 29,4% de sobrediagnóstico de iPCa. La concordancia fue superior en casos con PI-RADS 4-5 y en glándulas próstatas de menor volumen.

La concordancia entre la detección de csPCa en la biopsia sistemática y dirigida fue del 76%. El 13,9% de csPCa se detectó sólo en las biopsias sistemáticas y el 35,7% sólo en las biopsias dirigidas. Se identificaron como factores predictivos de csPCa en las biopsias dirigidas la edad, volumen prostático, tipo de resonancia (1.5T vs. 3T), PI-RADS, técnica de fusión y vía de abordaje. A partir de estas variables se desarrolló un modelo predictivo que permitió reducir el 18,3% de biopsias sistemáticas con una pérdida en la detección de csPCa inferior al 5%.

La biopsia prostática dirigida por vía transperineal detectó un 44,6% de csPCa frente a un 30,8% en las biopsias transrectales, siendo superior la detección en lesiones localizadas en las zonas anterior y apical de la glándula prostática. En cambio, las biopsias sistemáticas detectaron más csPCa cuando el abordaje fue transrectal (35,1% vs. 24,3%).

La aplicación de un protocolo *mapping* cada 0.5 mm, con abordaje transperineal, dirigido a la lesión índice y su área perilesional detectó el 96,3% csPCa. Sólo el 1,6% de csPCa se identificó exclusivamente en biopsias sistemáticas y el 2,1% en las lesiones sospechosas secundarias. Este protocolo de biopsia presentó un AUC de 0,918 y permitió evitar el 23,3% de las biopsias sin perder csPCa. Esta estrategia permitió limitar la agresividad de la biopsia prostática reduciendo el 72,8% de punciones.

La comparación entre dos esquemas de biopsia prostática dirigida mostró que el protocolo *mapping* cada 0.5 mm de las lesiones sospechosas y áreas perilesionales detectó el 71,9% de csPCa frente al 47,9% cuando se obtuvieron entre dos y cuatro muestras de cada lesión sospechosas. La detección de iPCa se redujo del 18,8 al 11,1%. Estas diferencias fueron más marcadas en lesiones PI-RADS 4 y 5. La proporción de csPCa detectados únicamente en biopsias sistemáticas fue inferior cuando se aplicó el protocolo *mapping* cada 0.5 mm (1,5 vs. 5,0%).

Una revisión sistemática de la literatura evaluó la eficacia clínica de las plataformas de fusión de imágenes (MRI-TRUS) en biopsias prostáticas. Se incluyeron 30 artículos que incorporaron más de 11.000 casos. Las plataformas con registro rígido obtuvieron mayores tasas de detección de csPCa que aquellas con registro elástico. También se evidenció que la vía transperineal ofrece mejores resultados que la vía transrectal en la detección de csPCa. Esta revisión también constató la complementariedad actual de las biopsias sistemáticas.

El BCN-MRI fue validado satisfactoriamente en pacientes sometidos a tratamiento con inhibidores de la 5-alfa reductasa (5-ARI). Se observó un AUC de 0,824 en pacientes tratados con 5-ARI y de 0,849 en varones no sometidos a este tratamiento ($p > 0.05$). El BCN-MRI PM permitió evitar el 23,8 y 25% de biopsias prostáticas, respectivamente, manteniendo una sensibilidad para detectar el csPCa del 95%.

El BCN-MRI se validó satisfactoriamente en biopsias prostáticas realizadas por vía transperineal. Mostró un AUC de 0,847 para detectar csPCa en biopsias prostáticas realizadas por vía transrectal y de 0,830 en biopsias transperineales ($p > 0.05$). La aplicación del BCN-MRI PM permitió evitar el 24,3% de biopsias protáticas utilizando ambas vías manteniendo una sensibilidad del 95%. La efectividad diagnóstica de csPCa fue de 45,9% para vía transperineal y 41% para la vía transrectal.

El BCN-MRI PM se validó satisfactoriamente en varones con sospecha de PCa, clasificados con el PI-RADS v 2.1, y sometidos a un protocolo de biopsia transperineal dirigido a las lesiones sospechosas y áreas perilesionales, *mapping* cada 0.5 mm, en la plataforma Artemis™. El AUC para detectar csPCa fue 0,862, y su aplicación permitió evitar el 24,9% de las biopsias manteniendo una sensibilidad del 95%. Este beneficio fue especialmente útil cuando el PI-RADS fue 2 y 3.

CONCLUSIONES

1. La lectura experta de la MRI mejora la clasificación de las lesiones evaluadas con el PI-RADS v 2.1, permitiendo reducir el número de biopsias prostáticas sin comprometer la detección de csPCa.
2. La biopsia prostática sistemática tiene un valor residual cuando se utiliza un modelo predictivo específico, desarrollado a partir de las variables predictoras edad, volumen

prostático, potencia de la MRI, categoría PI-RADS, técnica de fusión de imágenes y vía de abordaje de la biopsia.

3. El abordaje transperineal para realizar la biopsia prostática mejora la detección del csPCa respecto de la vía transrectal, especialmente en localizaciones anterior y apical de la glándula prostática.

4. El protocolo de biopsia por saturación mediante *mapping* cada 0.5 mm, dirigido a las lesiones sospechosas, incluida la lesión índice y sus áreas perilesionales, mejora la detección de cáncer de próstata clínicamente significativo (csPCa) en comparación con el protocolo estándar basado en la obtención de dos a cuatro cilindros por lesión. Además, permite omitir la biopsia del resto de las lesiones sospechosas y la biopsia sistemática, con una pérdida diagnóstica de csPCa inferior al 5%, y demuestra una mayor eficiencia diagnóstica que el protocolo convencional recomendado.

5. Las plataformas para realizar biopsias por fusión de imágenes MRI-TRUS por vía transperineal que utilizan registro de imagen rígido parecen tener mayor eficacia que las que utilizan registro elástico. La complementariedad de las biopsias sistemáticas se sugiere en todas las plataformas analizadas.

6. El BCN-MRI PM ha sido validado satisfactoriamente en pacientes con sospecha de PCa sometidos a tratamiento con 5-ARI, cuando se utiliza el PI-RADS v 2.1, vía de abordaje transperineal y un protocolo de biopsias dirigidas *mapping* cada 0.5 mm de lesiones sospechosas y áreas perilesionales.

SUMMARY

INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed malignant neoplasm in men and the third leading cause of cancer-related mortality. Its suspicion is established through elevated serum prostate-specific antigen (PSA) levels and/or an abnormal digital rectal examination (DRE), while the diagnosis is confirmed by prostate biopsy. The paradigm of early PCa diagnosis has shifted due to the introduction of magnetic resonance imaging (MRI) and targeted biopsies of lesions suspicious for clinically significant prostate cancer (csPCa). Currently, early PCa diagnosis focuses on maximizing csPCa detection, reducing unnecessary biopsies, and limiting overdiagnosis of insignificant PCa (iPCa). Targeted prostate biopsy is indicated when lesions suspicious for csPCa are identified on MRI, using the Prostate Imaging-Reporting and Data System (PI-RADS) version 2.1 with a score equal to or greater than 3, obtaining between two and four samples per lesion. This is always complemented by classical systematic biopsy, which obtains between 10 and 12 samples. Recently, it has been recommended to replace the transrectal approach with the transperineal route to reduce infectious complications and antibiotic use associated with prostate biopsy. However, the proportion of unnecessary biopsies remains high, particularly in uncertain scenarios such as PI-RADS 3. The European Association of Urology (EAU) recommends applying predictive models for csPCa, based on MRI and clinical data (MRI-PM), to improve the selection of candidates for prostate biopsy. The Barcelona MRI-PM (BCN-MRI PM) has proven the most effective in our setting, although it was developed and validated using PI-RADS v2.0 and prostate biopsies performed via the transrectal approach, excluding patients treated with 5-alpha reductase inhibitors (5-ARI).

Following a comprehensive literature review, we identified several aspects that may optimize early csPCa diagnosis:

- i) Use of expert MRI reading,
- ii) Development of predictive models to limit systematic biopsies,
- iii) Use of an appropriate platform to perform transperineal prostate biopsy with MRI-TRUS image fusion and a saturation protocol targeting suspicious lesions and perilesional areas, and

iv) Validation of the BCN-MRI PM in patients treated with 5-ARI, classified with PI-RADS v2.1, and undergoing a saturation biopsy protocol targeting suspicious lesions and perilesional areas via the transperineal approach.

HYPOTHESIS

This thesis hypothesizes that an integrated diagnostic strategy based on expert interpretation of prostate magnetic resonance imaging, the use of MRI-based predictive models, the transperineal approach, and the performance of targeted biopsies using a saturation protocol of suspicious lesions and perilesional areas may optimize the early diagnosis of clinically significant prostate cancer, increasing its detection while reducing unnecessary biopsies and the overdiagnosis of clinically insignificant tumors. Furthermore, it is postulated that the BCN-MRI PM predictive model maintains its discriminative performance and clinical utility when applied to patients receiving 5-alpha reductase inhibitors, evaluated using PI-RADS v2.1 and undergoing transperineal prostate biopsy with a saturation protocol targeting suspicious lesions and perilesional areas.

MAIN OBJECTIVE

To optimize the early diagnosis of clinically significant prostate cancer through the evaluation of an integrated diagnostic strategy based on expert interpretation of prostate magnetic resonance imaging, the use of MRI-based predictive models, the transperineal approach, and targeted biopsy using saturation protocols of suspicious lesions and perilesional areas, as well as through the validation of the BCN-MRI PM predictive model in different clinical scenarios.

SECONDARY OBJECTIVES

1. To analyze the clinical impact of expert MRI reading and limit systematic biopsies based on a predictive model.
2. To compare the effectiveness of prostate biopsy performed via the transrectal and transperineal approaches for csPCa detection.

3. To compare the efficacy of a saturation-targeted biopsy protocol (mapping every 0.5 mm) for suspicious lesions and perilesional areas with the currently recommended protocol, also analyzing the clinical utility of MRI-TRUS fusion platforms used in the transperineal approach for csPCa detection.
4. To validate the BCN-MRI PM in patients treated with 5-ARI, classified with PI-RADS v2.1, using the transperineal approach and a saturation-targeted biopsy protocol (*mapping* every 0.5 mm) for suspicious lesions and perilesional areas, on an appropriate platform.

METHODOLOGY

This doctoral thesis is presented as a compendium of nine publications and has been developed from retrospective and prospective studies designed with a multicenter approach, allowing for a rigorous, representative, and clinically applicable evaluation. In the first six, the following aspects were analyzed to optimize early diagnosis of csPCa:

1. The clinical impact of expert MRI reading (PI-RADS v2.1) in a prospective series of 222 prostate biopsies referred to the Cruz Blanca diagnostic center in Barcelona.
2. The development of a predictive model to limit the use of systematic biopsies, based on independent predictive variables obtained from 2122 men who underwent targeted and systematic prostate biopsy, selected from among 3557 men with suspected PCa prospectively reported in a multicenter study conducted in 10 hospitals participating in the opportunistic csPCa screening program in Catalonia.
3. The comparison between transrectal and transperineal prostate biopsy in the detection of csPCa. This study was conducted in a matched group of 650 cases selected from a cohort of 4029 cases prospectively recruited in 10 hospitals participating in the opportunistic csPCa screening program in Catalonia, all of which used the same biopsy protocol.
4. The clinical impact of applying a transperineal saturation-targeted biopsy protocol (mapping every 0.5 mm) of the index lesion and its perilesional area. This was a prospective study that included 309 men with suspected PCa biopsied at the Cruz Blanca diagnostic center in Barcelona.

5. The comparison between a transperineal saturation-targeted prostate biopsy protocol (mapping every 0.5 mm) targeting suspicious lesions and perilesional areas, and the protocol obtaining between 2 and 4 cores per lesion. This study was conducted in a matched group of 261 cases selected from 1161 men with suspected PCa biopsied prospectively in four centers participating in the opportunistic csPCa screening program in Catalonia, all of which consistently used the transperineal route.

6. A systematic literature review of existing platforms for performing MRI-TRUS fusion-guided prostate biopsies via the transperineal approach.

Publications 7 to 9 focused on validating the BCN-MRI PM:

7. In 120 men with suspected PCa who had undergone treatment with 5-ARI. This group was retrospectively selected from 2212 men who underwent prostate biopsy, prospectively collected in 10 hospitals participating in the Catalonia opportunistic csPCa screening program.

8. In 969 men who underwent transperineal biopsy, obtaining between two and four samples of suspicious lesions and/or 12-core systematic biopsies. These cases were prospectively reported by four hospitals participating in the Catalonia csPCa screening program where prostate biopsy was performed transperineally.

9. In 457 men who underwent saturation-targeted prostate biopsy (mapping every 0.5 mm) of suspicious lesions and perilesional areas, prospectively collected at the Cruz Blanca diagnostic center in Barcelona, where the Artemis™ platform was used.

This project was approved by the ethics committee of Vall d'Hebron University Hospital (PRAG 02/2021), funded by the Carlos III Health Institute (PI20/01666), and co-financed by the European Regional Development Fund “A way to build Europe.”

RESULTS

The concordance between MRI readings reported by non-expert radiologists and those reported by an expert radiologist was only 49.1%. Expert interpretation enabled reclassification of PI-RADS 2.1 lesions and reduced prostate biopsies by 28.8% without compromising csPCa detection and decreased iPCa overdiagnosis by 29.4%.

Concordance was higher in cases with PI-RADS 4 and 5 and in prostates with smaller volumes.

The concordance between csPCa detection in systematic and targeted biopsies was 76%. csPCa was detected exclusively by systematic biopsies in 13.9% of cases and exclusively by targeted biopsies in 35.7%. Predictive factors for csPCa detection in targeted biopsies included age, prostate volume, MRI type (1.5T vs. 3T), PI-RADS category, fusion technique, and biopsy approach. Based on these variables, a predictive model was developed that allowed for the omission of 18.3% of systematic biopsies, with a csPCa detection loss of less than 5%.

Transperineal targeted prostate biopsy detected 44.6% csPCa compared to 30.8% for transrectal biopsies, with superior detection in anterior and apical zones. In contrast, systematic biopsies detected more csPCa when performed via the transrectal approach (35.1% vs. 24.3%).

Applying a mapping protocol every 0.5 mm via the transperineal route, targeting the index lesion and its perilesional area, detected 96.3% of csPCa. Only 1.6% of csPCa was identified exclusively by systematic biopsies and 2.1% by secondary suspicious lesions. This biopsy protocol demonstrated an AUC of 0.918 and allowed for the omission of 23.3% of biopsies without losing csPCa. This strategy reduced biopsy aggressiveness by lowering the number of samples taken by 72.8%.

Comparison between targeted biopsy protocols showed that the 0.5 mm mapping protocol targeting suspicious lesions and perilesional areas detected 71.9% of csPCa versus 47.9% when applying the protocol of obtaining two to four samples per suspicious lesion. Detection of iPCa was reduced from 18.8% to 11.1%. These differences were more marked in PI-RADS 4 and 5 lesions. The proportion of csPCa detected only by systematic biopsies was lower when using the 0.5 mm mapping protocol (1.5% vs. 5.0%). These results suggest the superior efficacy of saturation protocols targeting suspicious lesions and perilesional areas in the diagnosis of csPCa.

A systematic review of the literature assessed the clinical efficacy of MRI-TRUS fusion-guided biopsy platforms for prostate biopsies. Thirty articles were included, identifying available technologies used in more than 11,000 patients. Platforms with rigid registration showed higher csPCa detection rates than those with elastic registration. The review also showed that the transperineal route yielded better results than the transrectal route in

csPCa detection. The continued relevance of systematic biopsies was also confirmed across all platforms analyzed.

The BCN-MRI was successfully validated in patients treated with 5-alpha reductase inhibitors (5-ARI), showing an AUC of 0.824 in patients treated with 5-ARI and 0.849 in untreated patients ($p > 0.05$). The BCN-MRI PM avoided 23.8% and 25% of prostate biopsies, respectively, while maintaining 95% sensitivity for csPCa.

The BCN-MRI was also successfully validated in transperineally performed biopsies. It showed an AUC of 0.847 for detecting csPCa in transrectal biopsies and 0.830 in transperineal biopsies ($p > 0.05$). The BCN-MRI PM avoided 24.3% of biopsies using both approaches, with a sensitivity of 95%. Diagnostic effectiveness for csPCa was 45.9% for the transperineal route and 41% for the transrectal route.

The BCN-MRI PM was successfully validated in men with suspected PCa, classified with PI-RADS v2.1, who underwent a transperineal biopsy protocol targeting suspicious lesions and perilesional areas using 0.5 mm mapping on the Artemis™ platform. The AUC for csPCa detection was 0.862, and its use avoided 24.9% of biopsies while maintaining a 95% sensitivity. This benefit was particularly useful in PI-RADS 2 and 3 cases.

CONCLUSIONS

1. Expert MRI interpretation improves the classification of lesions evaluated with PI-RADS v2.1, allowing for a reduction in unnecessary prostate biopsies without compromising csPCa detection.
2. Systematic prostate biopsy has a residual value when a specific predictive model is applied, developed from variables such as age, prostate volume, MRI strength, PI-RADS category, image fusion technique, and biopsy route.
3. The transperineal approach for performing prostate biopsy improves csPCa detection compared to the transrectal route, especially in anterior and apical locations.
4. The saturation biopsy protocol using 0.5 mm mapping, targeted to suspicious lesions, including the index lesion and its perilesional areas, improves the detection of clinically significant prostate cancer (csPCa) compared with the standard protocol based on

obtaining two to four cores per lesion. Furthermore, it allows omission of biopsy of the remaining suspicious lesions and systematic biopsy, with a diagnostic loss for csPCa below 5%, and demonstrates greater diagnostic efficiency than the conventionally recommended protocol.

5. The systematic literature review conducted to evaluate platforms enabling MRI-TRUS image fusion biopsies via the transperineal approach suggests greater clinical efficacy of those using rigid registration over elastic registration. The complementarity of systematic biopsies is supported across all platforms analyzed.

6. The BCN-MRI PM has been successfully validated in patients with suspected PCa who are being treated with 5-ARI, when using PI-RADS v2.1, the transperineal route, and a saturation biopsy protocol with 0.5 mm mapping of suspicious lesions and perilesional areas.

1. INTRODUCCIÓN

1.1. EPIDEMIOLOGÍA Y ETIOLOGÍA DEL CÁNCER DE PRÓSTATA

El cáncer de próstata (PCa) constituye el segundo tumor maligno más frecuentemente diagnosticado a nivel mundial y representó la quinta causa de muerte entre los varones en el año 2020. En ese período se registraron 1,4 millones de nuevos casos y aproximadamente 375.000 fallecimientos atribuibles a esta enfermedad (1).

Estudios basados en autopsias han demostrado que la prevalencia del PCa es similar entre distintas poblaciones del mundo. No obstante, se observa una notable variabilidad entre países, influida principalmente por la existencia —o ausencia— de programas de cribado, ya sean estructurados o de carácter oportunista (2).

En países como Canadá, Estados Unidos y Australia, la incidencia del PCa aumentó bruscamente a finales de los años ochenta y principios de los noventa, como consecuencia del uso generalizado del antígeno prostático específico (PSA) en programas de cribado oportunista, lo que permitió la detección temprana de la enfermedad antes de la aparición de síntomas (3). De forma más tardía y progresiva, este aumento también se evidenció en Europa, así como en algunos países de Centroamérica y Asia, hasta alcanzar una estabilización en los últimos cinco años (4).

En los países más desarrollados, la mortalidad por PCa ha disminuido en los últimos años, gracias a la implementación de estrategias de detección precoz y la eficacia de los tratamientos disponibles (5). La incidencia y mortalidad por PCa en los 136 países analizados por Globocan en 2022 se ilustran en los mapas de las **Figuras 1 y 2**, respectivamente (1).

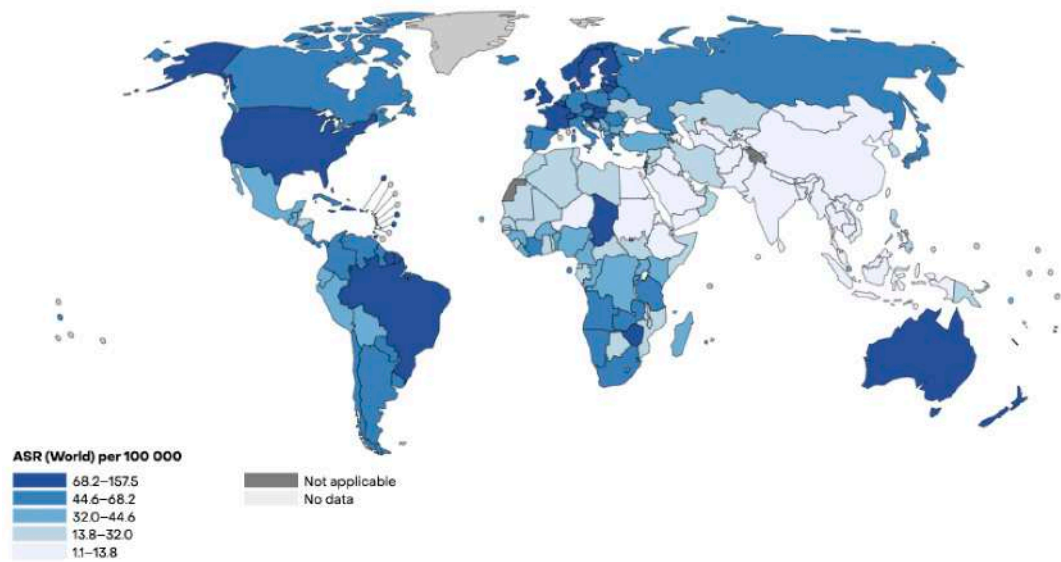


Figura 1 Incidencia de *PCa* estandarizada por edad en cada país, según Globocan en 2022 (1)

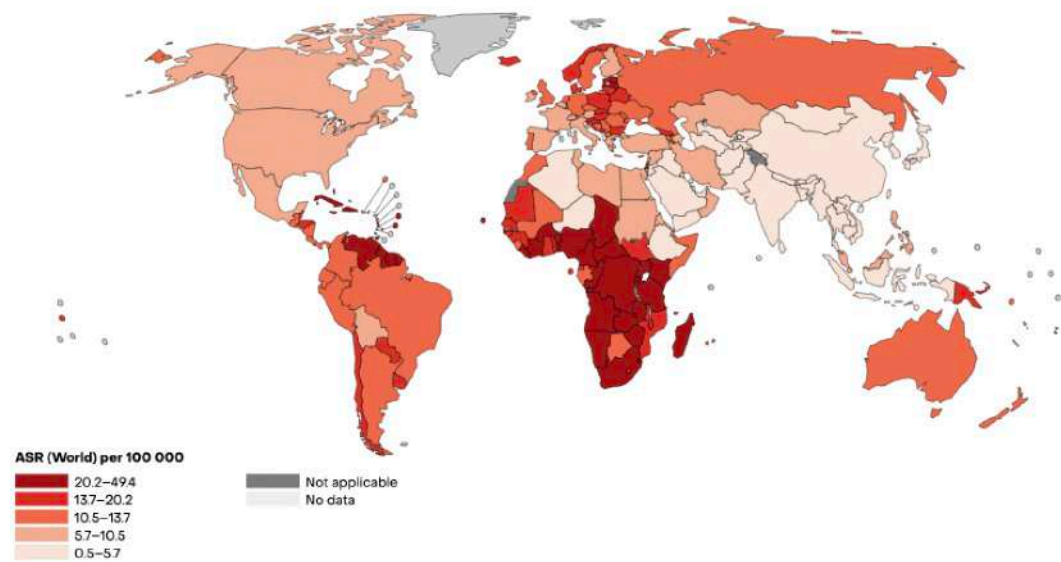


Figura 2 Tasa de mortalidad por *PCa* estandarizada por edad en cada país, según Globocan en 2022 (1)

La incidencia del PCa y su mortalidad varían sustancialmente. En Europa, la incidencia de PCa en los países escandinavos es la mayor del mundo, reduciéndose sustancialmente en los países mediterráneos, **Figura 3 (1)**.

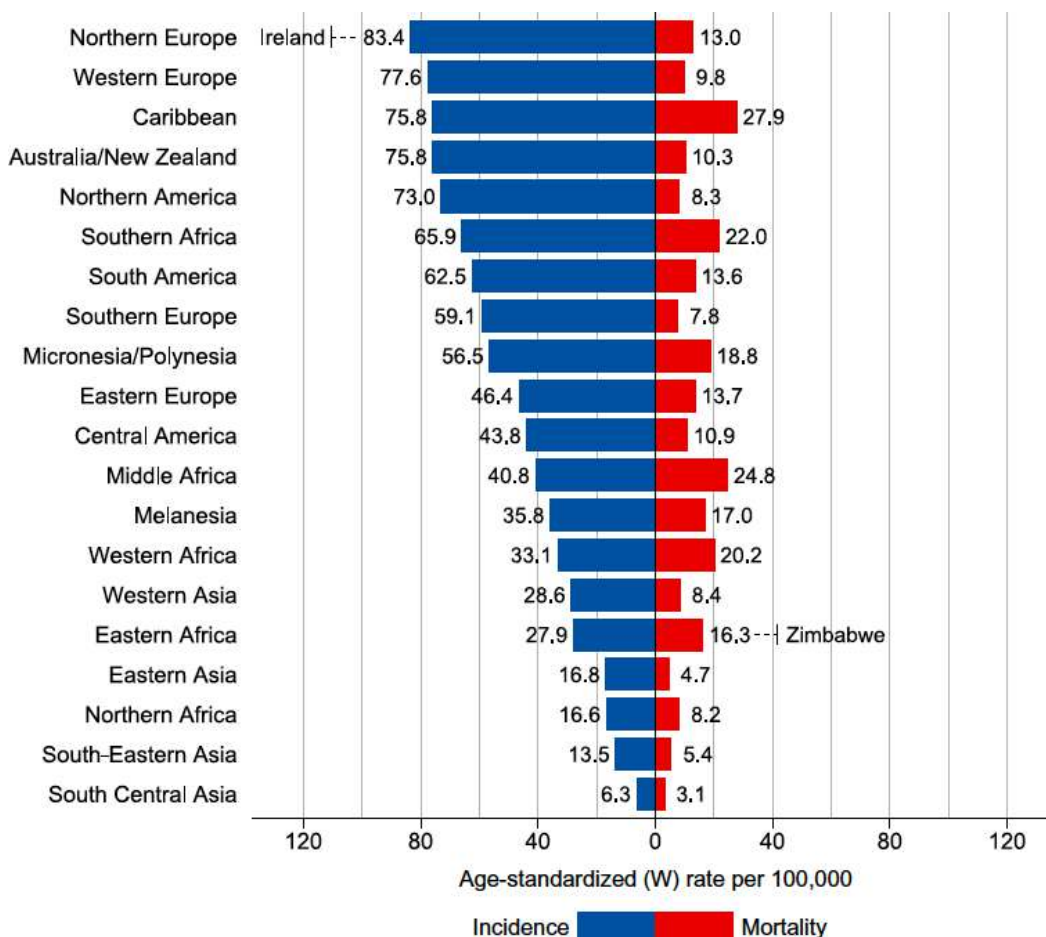


Figura 3 Incidencia y mortalidad por PCa estandarizada por edad según *Globocan* en 2022 (1)

En España, según el informe de la Sociedad Española de Oncología Médica, el cáncer de próstata (PCa) fue el tumor con mayor incidencia entre los varones en 2022 diagnosticándose 29.900 nuevos casos. En cuanto a la mortalidad específica, el PCa ocupó el tercer lugar con 5.900 defunciones (6). En Cataluña, esa misma tendencia se mantuvo, siendo el cáncer de próstata el de mayor incidencia con 4.470 nuevos diagnósticos en 2022 (6).

La edad es el principal factor de riesgo para el desarrollo del PCa. Una revisión sistemática de estudios realizados en autopsias reveló una prevalencia global del 5 % en

hombres menores de 30 años, en contraste con el 59 % en aquellos mayores de 79 años (7). Otro factor de riesgo importante es la historia familiar, aunque sólo en una pequeña proporción de los pacientes diagnosticados se identifica esta asociación (8). Se ha documentado que los hombres con antecedentes familiares de PCa presentan un riesgo relativo 2,3 veces mayor de desarrollar la enfermedad, un riesgo 3,4 veces superior de diagnóstico precoz, un riesgo 2,2 veces mayor de mortalidad específica y un riesgo 2,3 veces superior de padecer un cáncer clínicamente significativo (csPCa) (9).

Numerosas mutaciones germinales en genes reparadores del ácido desoxirribonucleico (DNA) se han asociado con el PCa hereditario (10). Estas mutaciones, que se transmiten de padres a hijos, han sido identificadas en diversos estudios. En una cohorte de 1.328 pacientes con PCa, se hallaron mutaciones germinales en el gen BRCA2 en el 4,5 %, en CHEK2 en el 2,2 %, en ATM en el 1,8 % y en BRCA1 en el 1,1 % de los casos. La presencia de una suma de Gleason superior a 8 y la existencia de enfermedad metastásica se asociaron de manera significativa con una mayor incidencia de mutaciones en genes reparadores del DNA (11,12).

La relación entre el uso de inhibidores de la 5-alfa reductasa (5-ARI) y el riesgo de cáncer de próstata (PCa) sigue siendo controvertida. Algunos estudios han sugerido que los 5-ARI podrían reducir el riesgo de desarrollar PCa, mientras que otros han reportado un aumento en el riesgo de tumores de alto grado (13–16). En cuanto a la terapia con testosterona en pacientes con hipogonadismo, los datos disponibles no han demostrado un incremento del riesgo de PCa (17). Por el contrario, un estudio publicado en 2018 indicó que los hombres con niveles séricos bajos de testosterona libre presentaban un menor riesgo de desarrollar la enfermedad (18).

La etnicidad también se ha identificado como un factor de riesgo relevante. En Estados Unidos, la incidencia de PCa es más elevada en hombres afroamericanos en comparación con los de origen caucásico (19). Los hombres de origen chino y japonés presentan un riesgo significativamente menor que los varones de países occidentales. Sin embargo, se ha observado que aquellos que emigran a Estados Unidos adquieren un riesgo similar al de la población estadounidense a partir de la segunda generación (19).

Asimismo, se han propuesto diversos factores ambientales, como el grado de exposición solar, pero hasta el momento ningún factor ambiental o dietético ha sido claramente

definido como factor de riesgo para el desarrollo del PCa. Por esta razón, actualmente no se han establecido recomendaciones específicas para su prevención (20).

1.2. SOSPECHA DE CÁNCER DE PRÓSTATA

En la actualidad, la mayoría de los casos de PCa se diagnostican en varones asintomáticos. Por ello, establecer una sospecha clínica precoz es fundamental ya que permite detectar la enfermedad en estadios iniciales y reducir la proporción de casos diagnosticados en fases avanzadas y la mortalidad específica (21).

La sospecha de PCa se basa principalmente en la elevación de los niveles séricos del PSA y/o en la detección de hallazgos anómalos en el tacto rectal (DRE). Sin embargo, el diagnóstico definitivo se confirma mediante la realización de una biopsia prostática (22).

1.2.1. ANTÍGENO PROSTÁTICO ESPECÍFICO

El PSA es una serina proteasa, también conocida como calicreína humana 3, que fue descrita por primera vez en 1975 (23,24). Esta proteína es codificada por el gen hKLK3, ubicado en el cromosoma 19 (25), y su expresión está regulada principalmente por los andrógenos (26). El PSA se sintetiza en los conductos y acinos prostáticos, y su función fisiológica principal es la licuefacción del coágulo seminal mediante la ruptura de los enlaces entre semenogelina I y II y fibronectina (27).

La introducción del PSA como marcador tumoral del cáncer del PCa supuso un hito en el diagnóstico precoz de esta enfermedad, y su uso combinado con el DRE ha sido ampliamente incorporado en estrategias de cribado. No obstante, a pesar de su alta sensibilidad, el PSA presenta una especificidad limitada, ya que niveles elevados pueden observarse también en patologías benignas como la hiperplasia prostática benigna y la prostatitis (28).

Aunque no existe una estandarización universal para la determinación del PSA, la mayoría de los ensayos disponibles consideran valores inferiores a 4 ng/ml como normales (29). Sin embargo, algunos hombres con niveles de PSA dentro de ese rango pueden presentar PCa, aunque en un porcentaje reducido como se indica en la Tabla 1

(30). En aquellos casos en los que el PSA se sitúa en la denominada “zona gris” (entre 4 y 10 ng/ml), se recomienda repetir la medición para confirmar su elevación.

Tabla 1 Riesgo de presentar PCa en función del nivel sérico de PSA (30)

Nivel de PSA (ng/ml)	Riesgo de PCa (%)	Riesgo de PCa ISUP-GG ≥ 2 (%)
0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

PCa = cáncer de próstata, PSA = antígeno prostático específico, ISUP-GG = grupo de grado de la *International Society of Urological Pathology*

La periodicidad óptima para la cuantificación de PSA aún no ha sido claramente establecida, aunque se han propuesto estrategias basadas en los niveles iniciales del marcador (31). Una de estas estrategias plantea que, en hombres sin antecedentes familiares de cáncer de próstata, puede diferirse la siguiente determinación hasta ocho años si el PSA es inferior a 1 ng/ml a los 40 años, o menor a 2 ng/ml a los 60 años, dado que su riesgo de progresión y mortalidad por PCa es muy bajo (32). Para el resto de los hombres considerados de mayor riesgo, se ha sugerido repetir el PSA sérico con una frecuencia bianual (33).

Con el objetivo de mejorar la especificidad del PSA y distinguir entre PCa e hiperplasia benigna, se ha propuesto la utilización del cociente entre el PSA total y su fracción libre (34). En pacientes con niveles de PSA total entre 4 y 10 ng/ml, el porcentaje de PSA libre ofrece una sensibilidad y especificidad del 70 % y 50 %, respectivamente, para el diagnóstico del PCa. No obstante, su utilidad clínica se reduce significativamente cuando el PSA total supera los 10 ng/ml (35). Recientemente, este valor ha vuelto a adquirir

importancia al ser incorporado en modelos predictivos junto con otros nuevos marcadores tumorales (36).

En 2012, la U.S. Preventive Services Task Force (USPSTF) desaconsejó el cribado del PCa mediante PSA, argumentando que no existía un beneficio significativo en la reducción de la mortalidad específica por PCa. Además, destacó los perjuicios asociados a un exceso de biopsias innecesarias y al sobrediagnóstico de cánceres de próstata clínicamente insignificantes (iPCa). Todo ello motivó su posicionamiento en contra del testeo sistemático con PSA (37). Esta postura fue adoptada un año más tarde por las guías estadounidenses para el manejo del PCa (31). Como consecuencia, se observó un incremento en el diagnóstico de tumores en estadios avanzados, así como un repunte en la mortalidad específica, que previamente había mostrado una tendencia descendente sostenida durante las dos décadas posteriores a la implementación del cribado con PSA (38,39). En respuesta a esta evolución, en 2017 la USPSTF revisó su recomendación y propuso considerar el cribado del PCa con PSA en hombres de entre 55 y 69 años como una decisión individualizada, enmarcada en una información que contemple los posibles beneficios y riesgos del procedimiento (40).

El Consejo de la Unión Europea ha reconocido una evidencia robusta que respalda el beneficio del cribado con PSA en la reducción de la mortalidad específica por PCa (41). Si bien el sobrediagnóstico y el sobretratamiento del iPCa continúan representando desafíos relevantes, la implementación de estrategias complementarias —como la fijación de un límite de edad superior para el cribado y la incorporación sistemática de la resonancia magnética multiparamétrica (mpMRI)— podría mitigar estos inconvenientes y optimizar la relación beneficio-riesgo del cribado (41).

El ensayo aleatorizado de cribado de cáncer de próstata de Göteborg constituye una de las evidencias más robustas en la evaluación del impacto del cribado con PSA sobre la mortalidad por esta enfermedad. Iniciado en 1995, este estudio incluyó 20.000 hombres nacidos entre 1930 y 1944, asignados aleatoriamente a un grupo de intervención (cribado bienal con PSA desde los 50 hasta los 69 años) o a un grupo control sin intervenciones programadas (42). Tras 22 años de seguimiento, se observó una reducción del 29% en la mortalidad por PCa en el grupo invitado al cribado, y una reducción del 41% entre aquellos que participaron al menos en una ronda. No obstante, la incidencia de PCa fue un 42% mayor en el grupo cribado reflejando un incremento significativo de diagnósticos de tumores de bajo riesgo. El análisis por subgrupos reveló que los hombres que nunca

participaron en el programa o comenzaron el cribado después de los 60 años presentaron un riesgo significativamente mayor de muerte por PCa. Asimismo, se detectó un aumento importante en la mortalidad durante los diez años posteriores a la finalización del programa de cribado, lo que sugiere que suspender el cribado de forma generalizada a los 70 años puede ser prematuro. Este estudio, con su diseño poblacional, prolongado seguimiento y acceso a registros de alta calidad, ofrece la evidencia más sólida a favor del cribado poblacional organizado mediante PSA. No obstante, sus limitaciones incluyen la creciente tasa de cribado oportunista en el grupo control y la no participación de una proporción relevante de hombres en el grupo de intervención, factores que podrían haber diluido el efecto real del cribado.

En conclusión, el cribado sistemático con PSA desde los 50 años y con una periodicidad bianual permite reducir de forma significativa la mortalidad por cáncer de próstata. Sin embargo, debe considerarse cuidadosamente el riesgo de sobrediagnóstico y sobretratamiento, así como individualizar la edad de inicio y suspensión del cribado para optimizar su eficacia y minimizar efectos adversos.

1.2.2. TACTO RECTAL

El control mediante el tacto rectal y determinación de PSA ha sido, tradicionalmente, una estrategia básica para el diagnóstico del cáncer de próstata (PCa) (43). No obstante, el uso del DRE como única herramienta en el ámbito de la atención primaria presenta limitaciones importantes, con una sensibilidad y especificidad inferiores al 60 % (44). En comparación, el PSA demuestra un mejor rendimiento como marcador diagnóstico. En una cohorte de 6.630 pacientes, el 18 % de los casos de PCa fueron detectados únicamente mediante el DRE, mientras que el 45 % fueron identificados exclusivamente a través del PSA. Sin embargo, la combinación de ambas pruebas resultó ser más eficaz que su uso individual para la detección del PCa (43). Además, la coexistencia de un PSA elevado y un DRE sospechoso se ha asociado con mayor probabilidad de identificar cánceres de alto grado (puntuación de Gleason > 7) (45).

En la actualidad, el DRE se emplea principalmente como herramienta de estadiaje clínico del PCa, constituyendo un predictor sólido de enfermedad localmente avanzada (46). Se

considera un DRE patológico a partir del estadio cT2a, y se sospecha afectación extracapsular a partir del estadio cT3a (47).

1.2.3. RESONANCIA MAGNÉTICA NUCLEAR PÉLVICA

La estrategia tradicional de realizar biopsias prostáticas sistemáticas en varones con niveles elevados de PSA y/o un DRE anormal ha demostrado limitaciones significativas, como la omisión de un número considerable de csPCa, así como la sobredetección de iPCa (48). A lo largo del tiempo, se han explorado diversas técnicas para optimizar el rendimiento diagnóstico de las biopsias sistemáticas, entre ellas la ecografía transrectal (TRUS), aunque esta no ha mostrado una utilidad suficiente para identificar con precisión las lesiones sospechosas de PCa (49).

La mpMRI de pelvis ha representado un avance sustancial de la imagen, al combinar imágenes morfológicas obtenidas mediante secuencias potenciadas en T1 y T2 con imágenes funcionales derivadas de la difusión (DWI) y del coeficiente de difusión aparente (DCE). Esta combinación permite localizar con mayor precisión las áreas sospechosas de csPCa, permitiendo además la toma de biopsias de forma dirigida (50).

Un metaanálisis ha reportado que la sensibilidad y especificidad globales de la mpMRI para la detección del PCa con un grado ISUP-GG ≥ 2 son del 91 % y 37 %, respectivamente (51). En el caso de tumores con grado ISUP-GG ≥ 3 , la sensibilidad aumenta al 95 %, mientras que la especificidad permanece en torno al 35 %. No obstante, la capacidad de detección disminuye ante lesiones pequeñas o de bajo grado (ISUP-GG 1), lo que evidencia que la mpMRI no detecta con igual eficacia todos los tipos de cáncer (50). La probabilidad de detectar csPCa en función de las características observadas en la mpMRI fue estandarizada por primera vez en 2011 mediante la escala de Likert, y posteriormente, en 2012, con la introducción del sistema PI-RADS (Prostate Imaging–Reporting and Data System), el cual ha sido actualizado en sus versiones 2.0 y más recientemente 2.1 (52–54).

Actualmente, el PI-RADS constituye la herramienta de clasificación más utilizada en el reporte de la MRI prostática. Se basa en una escala de cinco puntos que estima la probabilidad de que una lesión corresponda a un csPCa, tomando en cuenta tanto sus características anatómicas como funcionales en las imágenes obtenidas (55). La **Tabla 2** resume las probabilidades estimadas de csPCa de acuerdo con las categorías de PI-RADS v2.1.

Tabla 2 Probabilidad de csPCa según la categoría PI-RADS (54)

Categoría de <i>PI-RADS</i>	Probabilidad de <i>csPCa</i>
PI-RADS 1	Muy baja
PI-RADS 2	Baja
PI-RADS 3	Intermedia
PI-RADS 4	Alta
PI-RADS 5	Muy alta

csPCa = cáncer de próstata clínicamente significativo, *PI-RADS* = *Prostate Imaging- Reporting and Data System*

La interpretación experta de la resonancia magnética prostática es fundamental para un diagnóstico preciso del csPCa. La experiencia del radiólogo permite una mejor caracterización de las lesiones sospechosas, una adecuada asignación de la puntuación PI-RADS y una reducción de errores diagnósticos. Esto puede traducirse en menos biopsias innecesarias, menor sobrediagnóstico de tumores indolentes y una mayor eficiencia en la toma de decisiones clínicas. La lectura experta, respaldada por formación específica y alto volumen de casos, mejora sustancialmente la calidad del proceso diagnóstico (56).

El papel de las biopsias dirigidas en ausencia de biopsias sistemáticas ha sido ampliamente estudiado en los últimos años. Diversos metaanálisis han demostrado que la tasa de detección de cánceres clínicamente significativos ($\text{ISUP-GG} \geq 2$) es superior cuando se realizan biopsias dirigidas, en comparación con las sistemáticas, especialmente en varones sometidos a una primera biopsia o con antecedentes de biopsias previas negativas (51,57,58). Por otro lado, varios estudios han reportado una menor tasa de detección de csPCa ($\text{ISUP-GG} 1$) con el uso exclusivo de biopsias dirigidas (58–60). Estos hallazgos sugieren que las biopsias dirigidas no solo podrían reemplazar a las sistemáticas, sino también contribuir a reducir el sobrediagnóstico de iPCa. En cuanto al valor añadido de combinar biopsias dirigidas con sistemáticas, se ha observado un

incremento en la tasa de detección de csPCa de aproximadamente un 20 % en biopsias iniciales, y hasta un 40 % en biopsias de repetición. Sin embargo, omitir la biopsia sistemática podría conllevar una pérdida diagnóstica de cerca del 16 % de csPCa en hombres sometidos a una primera biopsia y del 10 % en biopsias repetidas (58).

Las guías clínicas actuales recomiendan que, en varones sin biopsia previa y con lesiones PI-RADS ≥ 3 , se realicen tanto biopsias dirigidas como sistemáticas. En varones con puntuaciones PI-RADS < 2 , la biopsia podría evitarse, salvo que exista un riesgo clínico elevado (61). Asimismo, en hombres con biopsias previas negativas y lesiones PI-RADS ≥ 3 , se sugiere realizar exclusivamente biopsias dirigidas (62). En el caso de una MRI negativa (PI-RADS < 2), dada su alta capacidad predictiva negativa, podría considerarse la omisión de la biopsia (61).

Debido al aumento en la demanda de mpMRI, algunos centros altamente especializados han empezado a utilizar la resonancia magnética biparamétrica (bpMRI), la cual omite la secuencia dinámica con contraste (DCE), reduciendo así tanto el costo como la duración del estudio (63). Aunque ciertos metaanálisis han concluido que la incorporación de la secuencia DCE no aporta mejoras significativas en la detección de csPCa frente a las secuencias T2 y DWI por sí solas (64,65), otros estudios han mostrado resultados contradictorios (66). Por tanto, no es posible generalizar la eficacia de la bpMRI en todos los contextos clínicos. Actualmente, existe la necesidad de estandarizar su uso y validar la reproducibilidad de los informes sobre lesiones sospechosas obtenidas mediante esta técnica (67).

1.3. DIAGNÓSTICO DEL CÁNCER DE PRÓSTATA

1.3.1. BIOPSIA PROSTÁTICA

El diagnóstico definitivo del PCa se establece a través del análisis histopatológico de las muestras obtenidas mediante biopsia. El sistema de gradación de Gleason, desarrollado por Donald Gleason en 1974, clasifica las neoplasias prostáticas en cinco patrones, en función del grado de desorganización arquitectónica de las glándulas (68). En 2005, se consensuó que la puntuación de Gleason (GS) debe calcularse como la suma del patrón más prevalente (primario) y el segundo más frecuente (secundario). En los casos en que se identifica un único patrón, este debe duplicarse para estimar la puntuación

final (69). Este sistema ha demostrado ser un excelente predictor pronóstico, independientemente del tratamiento aplicado. Una puntuación de Gleason ≤ 6 suele asociarse con tumores clínicamente insignificantes (iPCa), mientras que una puntuación ≥ 8 indica una forma más agresiva de la enfermedad, con mayor riesgo de diseminación metastásica (70). Es fundamental que el informe histopatológico incluya también la presencia de ciertos subtipos tumorales como el carcinoma intraductal, el patrón cribiforme o el componente neuroendocrino, ya que todos ellos se asocian a un peor pronóstico (71,72).

Con el fin de simplificar y estandarizar la clasificación del PCa, la International Society of Urological Pathology (ISUP) propuso en 2014, y posteriormente ratificó en 2019, un sistema que agrupa los distintos grados de Gleason en cinco Grupos de Gradación ISUP (ISUP-GG), los cuales se describen en la **Tabla 3** (73,74).

Tabla 3 Puntuación de Gleason y correspondencia con los grados de la ISUP 2019 (72)

Puntuación de Gleason	ISUP-GG
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 o 3+5 o 5+3)	4
9-10 (4+5 o 5+4 o 5+5)	5

ISUP = International Society of Urological Pathology, GG = grupo de grado

La biopsia prostática se realiza mediante una aguja gruesa que permite obtener cilindros de tejido prostático. Como se ha mencionado previamente, existen dos tipos principales: las biopsias sistemáticas o aleatorias, guiadas por TRUS, y las biopsias dirigidas a lesiones sospechosas identificadas mediante MRI (62). Las biopsias sistemáticas deben focalizarse en la zona periférica lateral de ambos lóbulos prostáticos. Se recomienda obtener un total entre 10 y 12 cilindros, distribuidos equitativamente entre los dos lóbulos (5-6 por lóbulo) (75). En el caso de biopsias dirigidas, el número ideal de cilindros por lesión oscila entre 3 y 5, aunque esta recomendación se basa en un nivel de evidencia moderado (76).

El abordaje de la biopsia prostática puede realizarse por vía transrectal o transperineal. La vía transperineal ha demostrado una mayor sensibilidad para la detección de csPCa en comparación con la vía transrectal. Un metaanálisis publicado en 2019 informó una sensibilidad del 86 % para la vía transperineal frente al 73 % para la transrectal, siendo especialmente superior en la detección de lesiones localizadas en la zona fibromuscular anterior de la próstata (80). En la actualidad, se recomienda preferentemente la vía transperineal, no solo por su mayor sensibilidad, sino también por su perfil de seguridad ya que permite reducir significativamente la tasa de complicaciones sépticas asociadas a la vía transrectal y el uso indiscriminado de antibióticos (81–83).

1.3.2. SISTEMAS SOFTWARE PARA BIOPSIAS DE PRÓSTATA POR FUSIÓN DE IMÁGENES

Los softwares de fusión de imágenes MRI–TRUS constituyen una innovación tecnológica clave en el diagnóstico del csPCa, al permitir la superposición precisa de imágenes obtenidas por MRI con imágenes ecográficas en tiempo real. Esta técnica, conocida como biopsia por fusión, posibilita dirigir las muestras hacia las lesiones sospechosas previamente identificadas en la MRI, mejorando la tasa de detección de csPCa y reduciendo el sobrediagnóstico de tumores insignificantes (84). El proceso de fusión se basa en algoritmos de registro que alinean espacialmente ambas modalidades de imagen. Existen dos tipos principales de registro: rígido y elástico. En la fusión rígida, el operador rota manualmente las imágenes para alinearlas, sin modificar su forma; en cambio, la fusión elástica emplea algoritmos que deforman la imagen de resonancia para adaptarse a la anatomía cambiante observada en la ecografía intraoperatoria (85). Diversos estudios han abordado las diferencias entre ambas modalidades. Görtz et al. encontraron que los sistemas de registro rígido lograban una mayor tasa de detección de csPCa en biopsias transperineales dirigidas, posiblemente por ofrecer una mejor concordancia espacial entre las imágenes (86). Sin embargo, otros autores, como Venderink et al., no observaron diferencias significativas en la tasa de detección entre ambos métodos, lo que sugiere que la eficacia global también depende de factores como la calidad de la segmentación, la curva de aprendizaje del operador y la estrategia de navegación empleada (87).

1.3.3. DEFINICIÓN DE CÁNCER DE PRÓSTATA CLÍNICAMENTE SIGNIFICATIVO

El interés por identificar el csPCa se remonta a varias décadas, cuando se observó una elevada prevalencia de PCa en autopsias de individuos que nunca habían presentado síntomas de la enfermedad. Este hallazgo puso de manifiesto la existencia del iPCa (88).

Estudios anatomopatológicos en especímenes de prostatectomía radical han demostrado que los tumores clasificados como ISUP-GG 1 se asocian con una tasa extremadamente baja de extensión extraprostática (0,3 %), una tasa de recidiva bioquímica del 3,5 %, y ausencia de invasión de vesículas seminales o ganglios linfáticos. Por este motivo, la mayoría de los estudios definen al csPCa en función de la presencia de un ISUP-GG ≥ 2 y un volumen tumoral superior a 0,5 cc en los especímenes quirúrgicos (89–91).

En el ámbito de la biopsia prostática, Ahmed et al. propusieron dos definiciones de csPCa basadas en parámetros de carga tumoral obtenidos mediante biopsia perineal por mapeo. El primer criterio se basó en la longitud total de tejido afectado, considerando umbrales de ≥ 10 mm y ≥ 6 mm, en función de variables como edad, comorbilidades y expectativa de vida. El segundo criterio se centró en la longitud máxima de afectación en un solo cilindro, con umbrales de ≥ 6 mm y ≥ 4 mm. Estos parámetros se combinaron con la presencia de patrón 4 de Gleason, dominante o no dominante, para establecer dos definiciones de csPCa:

1. GS $\geq 3+4$ con una longitud máxima afectada ≥ 4 mm y una longitud total ≥ 6 mm.
2. GS $\geq 4+3$ con longitud máxima ≥ 6 mm y longitud total ≥ 10 mm.

No obstante, una limitación importante de estas definiciones es que no fueron validadas frente a especímenes de prostatectomía (92).

En 2016, Epstein et al. propusieron una definición de iPCa basada en la presencia de GS 3+3 que afecta a dos cilindros o menos, con una proporción de afectación inferior al 50 % en cada uno, y una densidad de PSA menor a 0,15 ng/ml/cc. Este perfil se asocia con un riesgo mínimo de csPCa en la prostatectomía radical (93). Dichos criterios fueron clasificados como de “muy bajo riesgo” por las guías de la National Comprehensive Cancer Network (NCCN) (94).

Actualmente, la investigación se orienta a ampliar dichos criterios. Algunos grupos proponen definiciones más laxas de iPCa, que incluyen tumores con un componente de patrón 4 de Gleason inferior al 10 % (95–97). A través del conocimiento de la alta prevalencia del iPCa, surgió la necesidad de evitar los efectos adversos del tratamiento activo, fundamentalmente, cirugía y radioterapia, introduciéndose el término vigilancia activa (AS) (98). Los criterios para implementar la AS se suelen superponer en muchas ocasiones a la definición de iPCa (99). En la Tabla 4 se recogen diferentes criterios clínicos y anatomopatológicos de entrada en AS publicados por diferentes grupos de trabajo.

La vigilancia activa (VA) se define como una estrategia de manejo conservador del cáncer de próstata (PCa), con la posibilidad de iniciar un tratamiento curativo en el momento en que se detecte progresión tumoral. Está indicada en pacientes con PCa localizado de bajo riesgo y una esperanza de vida superior a 10 años (108). En contraste, la denominada vigilancia expectante o watchful waiting (WW) se reserva para pacientes con PCa localizado que no son candidatos a tratamiento curativo. En estos casos, se opta por una observación clínica sin intervenciones hasta la aparición de síntomas, momento en el cual se instauran medidas paliativas (109). Mientras que el seguimiento en WW se adapta a la situación clínica general del paciente y sus comorbilidades, la VA implica un control más riguroso, sistemático y protocolizado (98).

El estudio ProtecT incluyó a 1.643 pacientes con PCa localizado, quienes fueron aleatorizados a recibir prostatectomía radical, radioterapia o VA. El 60 % de los participantes presentaban enfermedad de bajo riesgo, con niveles de PSA < 10 ng/ml en el 90 %, ISUP-GG 1 en el 77 % y tacto rectal (DRE) normal en el 76 %. El resto presentaba, mayoritariamente, enfermedad de riesgo intermedio (110). El hallazgo principal del estudio fue que la supervivencia cáncer-específica a 10 años en el grupo de VA fue del 98,8 %, frente al 99 % observado en los grupos de tratamiento activo. No obstante, la tasa de diseminación metastásica fue mayor en el grupo de VA (6 % frente a 2,6 %) (110).

Tabla 4 Criterios clínicos y anatomopatológicos de para implementar vigilancia activa según diferentes estudios (99)

Institución	Estadio clínico	PSA (ng/dl)	Gleason	PSAD (ng/dl/cc)	Num. Cil. Pos.	% afectación
RM (100)	T1/T2	< 15	< 65y ; ≤ 6 ≥ 65 ; ≤ 3+4 = 7	-	≤ 50 %	-
UoTSB (101)	T1/T2b ≥ 70 años ; ≤ T2c	≤ 10 ≥ 70 años ; ≤ 15	6 ≥ 70años ; ≤ 3+4	-	-	-
UCSF (102)	T1/T2a	<10	≤ 6	-	≤ 33%	-
UoTPM (103)	≤ T2a	≤ 10	≤ 6	-	≤ 3	≤ 50
PRIAS (104)	T1/T2	≤ 10	≤ 6	< 0.2	≤ 2	-
UM (105)	T1/T2	≤ 15	≤ 6	-	≤ 2	≤ 50
JH (106)	T1c	≤ 15	≤ 6	< 0.15	≤ 2	≤ 50
MSKCC (107)	T1/T2a	< 10	≤ 6		≤ 3	≤ 50

PSA = antígeno prostático específico, PSAD = densidad de PSA, Num. Cil. Pos. = Número de cilindros positivos, RM = Royal Marsden, UoTSB = University of Toronto- Sunnybrook, UCSF = University of California San Francisco, UoTPM = Princess Margaret Cancer Centre, PRIAS = Prostate Cancer Research International Active Surveillance, UM = University of Miami, JH = Johns Hopkins, MSKCC = Memorial Sloan Kettering Cancer Center

Para profundizar en estos hallazgos, se han analizado las características clínico-patológicas que distinguieron a los pacientes con progresión de aquellos con enfermedad estable tras 10 años de seguimiento. La edad, los niveles de PSA, el ISUP-GG, el estadio clínico, el número de cilindros positivos, la longitud máxima de afectación tumoral y la

invasión perineural se identificaron como predictores de progresión. Es relevante señalar que el protocolo de seguimiento en VA dentro del estudio ProtecT no estaba estandarizado, y se basaba principalmente en controles periódicos de PSA (111).

El estudio DETECTIVE buscó estandarizar los criterios de seguimiento durante la VA. Sin embargo, aún no es posible definir un protocolo de vigilancia basado en evidencia de alto nivel que establezca claramente los criterios de seguimiento y de salida hacia tratamiento curativo. De manera consensuada, se recomienda medir el PSA cada 6 meses, realizar un tacto rectal anual y considerar una resonancia magnética multiparamétrica (mpMRI) durante el seguimiento, sin una frecuencia determinada ni un umbral claro para su repetición. Se acuerda que debe repetirse la biopsia si se observa progresión en la mpMRI (aumento del PI-RADS, tamaño de la lesión o estadio radiológico), si aparece un tacto rectal patológico o si se detecta progresión del PSA (108).

1.4. MÉTODOS PARA MEJORAR LA SELECCIÓN DE CANDIDATOS A BIOPSIA PROSTÁTICA

Actualmente la selección de candidatos para realizar una biopsia prostática en los hombres con sospecha de PCa se basa en la información de la MRI. No obstante, siguen existiendo escenarios inciertos como el PI-RADS 3 en el que la probabilidad de csPCa no supera el 20% y además existe una sobredetección de iPCa que puede llegar al 50% (112). Con el objetivo de mejorar la selección de candidatos para la biopsia prostática se ha recomendado utilizar la densidad de PSA, nuevos marcadores del PCa, y modelos predictivos.

1.4.1. DENSIDAD DE PSA

La densidad de *PSA* (*PSAD*) es la cantidad de PSA en suero por cada centímetro cúbico de próstata. La *PSAD* fue introducida por Benson et al. en 1992 como una herramienta para incrementar la especificidad del PSA y poder diferenciar hombres portadores de *PCa* de aquellos con una hiperplasia benigna de próstata, especialmente en la llamada zona gris del *PSA* definida por un incremento moderado entre 4 y 10 ng/ml (113,114). Cuanto más elevada es la *PSAD* mayor es la probabilidad de que exista *csPCa* (115). Algunos estudios han sugerido un punto de corte de 0.15 ng/ml/cc como mejor

predictor de *csPCa*, existiendo por el contrario una baja probabilidad cuando la PSAD está por debajo de 0.09 ng/ml/cc (116,117).

Se ha observado que el valor predictivo negativo de la MRI para la detección de *csPCa* mejora del 84,4 % al 90,4 % cuando la *PSAD* es inferior a 0,15 ng/ml/cc (118,119). Un metaanálisis reciente sugiere que, incluso ante una MRI negativa, el riesgo de *csPCa* en hombres con una *PSAD* superior a 0,15–0,2 ng/ml/cc oscila entre el 27 % y el 40 % (120).

Nuestro grupo ha demostrado que la relación entre PSAD y PI-RADS es dinámica en la detección precoz del *csPCa*, de modo que el umbral óptimo de PSAD se incrementa conforme aumenta la puntuación PI-RADS. Por lo tanto, la PSAD representa una variable clínica prometedora para su integración en modelos predictivos (121).

El cálculo de la PSAD requiere una estimación precisa del volumen prostático. Tradicionalmente, se ha utilizado la ecografía transrectal (TRUS) aplicando la fórmula del elipsoide para calcular dicho volumen. Sin embargo, actualmente la práctica de realizar una TRUS exclusivamente con este objetivo está en desuso. Aun así, la mayoría de los estudios sobre PSAD han empleado valores de volumen obtenidos mediante TRUS en el contexto de la biopsia prostática (122). Como alternativa, se ha propuesto la estimación del volumen prostático mediante tacto rectal para su uso en modelos predictivos antes de realizar una MRI (123). No obstante, la PSAD calculada con volumen estimado por tacto rectal ha demostrado ser menos precisa que la estimada a partir del volumen medido por MRI (124).

Actualmente, se ha renovado el interés en la utilización de la PSAD, dado que el volumen prostático suele incluirse en los informes estándar de la MRI de próstata. A pesar de ello, tanto el PSA como el volumen prostático son variables predictivas independientes del *csPCa*, por lo que la PSAD o ambas variables por separado se integran frecuentemente en los modelos predictivos más eficaces (125).

1.4.2. NUEVOS MARCADORES TUMORALES

El *Prostate Health Index* (PHI) es una prueba sérica que combina el PSA libre, el PSA total y la isoforma p2PSA. Su determinación ha demostrado ser más específica que el porcentaje de PSA libre para detectar cáncer de próstata clínicamente significativo (*csPCa*) en hombres sometidos a su primera biopsia (126).

El *4Kscore test* es otra prueba sérica que cuantifica PSA total, libre e intacto, además de la calicreína tipo 2 (hK2), combinando estos datos con variables clínicas como la edad, el tacto rectal digital (DRE) y el tipo de biopsia (inicial o repetida). Una revisión sistemática que incluyó a más de 10.000 pacientes mostró un área bajo la curva (AUC) superior a 0,80 para el 4Kscore en la discriminación de csPCa (127).

Varios estudios prospectivos han demostrado que tanto el PHI como el 4Kscore superan al porcentaje de PSA libre en la detección del csPCa (128). Sin embargo, un estudio ha reportado que ambos presentan una capacidad de predicción comparable en el contexto de biopsias iniciales (129).

Proclarix es una prueba sérica más reciente que combina la medición de trombospondina-2, catepsina D, PSA total y libre, junto con la edad. Estima el riesgo de csPCa, siendo especialmente útil en hombres con lesiones PI-RADS 3 (132). Además, se ha asociado con una mayor agresividad tumoral, mostrando un mejor rendimiento en casos de cáncer avanzado y alto ISUP-GG (130).

El *Prostate Cancer Antigen 3* (PCA3) es un gen que transcribe un ARN mensajero largo no codificante, sobre-expresado en tejido prostático tumoral. Este puede detectarse en la orina tras un masaje prostático, y se calcula como la relación entre los niveles de ARN de PCA3 y los del PSA (131). Diversos estudios han indicado que el PCA3 score es más preciso que el PSA total y el porcentaje de PSA libre para detectar PCa en hombres con biopsias previas negativas (132,133). No obstante, dado que el objetivo clínico actual es detectar preferentemente el csPCa, su utilidad práctica es incierta (131).

Otro marcador urinario es *SelectMDx*, basado en la expresión del ARN mensajero de los genes HOXC6 y DLX1, ambos sobreexpresados en PCa. Sin embargo, su especificidad para detectar csPCa es limitada (134). Comparado con la resonancia multiparamétrica (MRI), esta última ha demostrado ser superior tanto en número de csPCa detectados como en reducción de biopsias innecesarias (135). Además, se ha observado que la combinación de SelectMDx con MRI puede aumentar el sobrediagnóstico de iPCa (135).

El marcador urinario *TMPRSS2-ERG* ha mostrado una mayor eficacia que el PSA total, con una especificidad del 93 % y un valor predictivo del 94 % para la detección de PCa (136). Se ha sugerido que su combinación con el PCA3 podría mejorar la detección de csPCa (137). No obstante, aunque estos biomarcadores muestran potencial, su valor añadido en la era de la MRI sigue siendo objeto de debate (138).

La realidad actual de los biomarcadores modernos para el diagnóstico del csPCa incluye barreras como su elevado coste, la necesidad de recolección adicional de muestras, y la competencia directa de los modelos predictivos basados en MRI y datos clínicos. La mayoría de los marcadores modernos incorporan variables clínicas, por lo que en esencia constituyen modelos predictivos combinados, y en varios casos no se ha demostrado que ofrezcan un rendimiento superior al de las variables clínicas por sí solas (138).

1.4.3. MODELOS PREDICTIVOS

Los modelos predictivos son herramientas diseñadas para estimar la probabilidad de ocurrencia de un evento futuro a partir de variables independientes históricas (139). Su desarrollo comienza con la recopilación de datos retrospectivos relacionados con el evento de interés. Estas bases de datos deben incluir tanto las posibles variables predictoras como la variable objetivo. Es fundamental realizar una depuración adecuada de los datos para eliminar errores, gestionar los valores perdidos y recodificar variables cuando sea necesario. En una segunda etapa, se identifican las variables predictoras independientes mediante análisis de regresión logística. Posteriormente, se construye el modelo predictivo, donde se generan las probabilidades asociadas a cada variable. A través de la estimación de odds ratios (razón de probabilidades) e intervalos de confianza (IC), se determina el peso específico de cada variable dentro del modelo (140).

La calibración del modelo evalúa la concordancia entre los valores predichos y los observados, mientras que su eficacia se mide mediante la capacidad de discriminación, habitualmente expresada como el área bajo la curva ROC (receiver operating characteristic), que relaciona sensibilidad y especificidad (139). También pueden utilizarse técnicas como la validación cruzada u otras formas de validación interna para estimar con mayor precisión el rendimiento del modelo en datos no utilizados para su construcción (141).

Una vez desarrollado y validado internamente, el modelo puede utilizarse para realizar predicciones en nuevos datos, generalmente mediante la elaboración de nomogramas (ver Figura 4). No obstante, su cálculo puede resultar laborioso y poco práctico en entornos clínicos con alta demanda. En este sentido, el desarrollo de aplicaciones web y para dispositivos móviles ha sido clave para transformar estos modelos en calculadoras de

riesgo accesibles y fáciles de usar, facilitando así su implementación en la práctica clínica diaria (142)

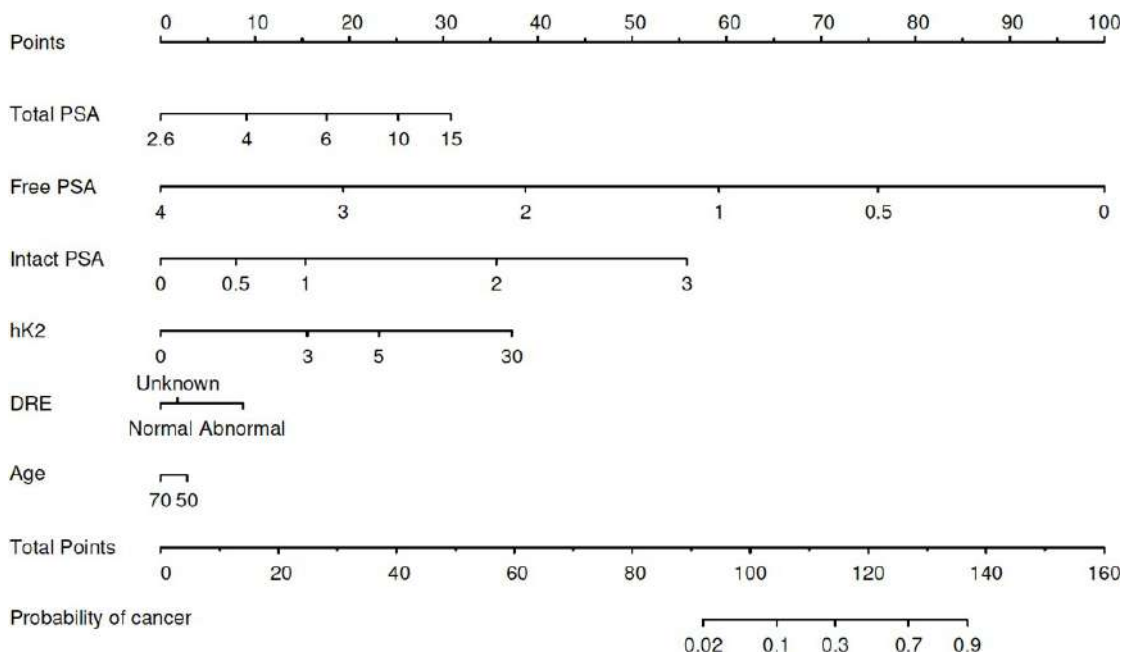


Figura 4 Nomograma para calcular el riesgo de *PCa* en la biopsia. Todos los marcadores se expresan en ng/ml excepto la kallikreina humana 2 que se expresa en 10 pg/ml. *tPSA*= *PSA* total; *fPSA* = *PSA* libre; *iPSA* = *PSA* intacto (143)

Es importante conocer que los modelos predictivos desarrollados no van a predecir con exactitud lo que ocurra en poblaciones distintas a la población de desarrollo, y de manera especial con una prevalencia de evento distinta (144). La elección y rendimiento de un modelo predictivo dependen en gran medida de la representatividad de sus variables predictoras en la población diana y de manera especial de la prevalencia del evento a predecir. Por ello, son necesarias las validaciones externas en las poblaciones donde se van a implementar los modelos desarrollados, y efectuar las oportunas recalibraciones y ajustes de los valores de corte del propio modelo para asegurar la exactitud de las predicciones (141).

Existen múltiples modelos predictivos para la detección de csPCa, pero sólo unos pocos han sido implementados con calculadoras de riesgo accesibles. La más reconocida es la calculadora de Rotterdam (www.prostatecancer-riskcalculator.com), desarrollada inicialmente a partir de la cohorte de Rotterdam del *European Randomized Study of Screening for Prostate Cancer* (ERSPC). El ERSPC fue publicado en 2009 y reportó una

reducción relativa del 30 % en la mortalidad específica por cáncer de próstata en el grupo de hombres sometidos a cribado con PSA (145). Posteriormente, la sección de Rotterdam se convirtió en un referente al cuestionar el equilibrio riesgo-beneficio del cribado basado exclusivamente en el PSA, proponiendo en su lugar el uso de factores predictores adicionales para seleccionar con mayor precisión a los candidatos a biopsia prostática (146).

Roobol et al. desarrollaron un modelo predictivo para estimar el riesgo de PCa y PCa de alto grado, utilizando regresión logística sobre variables independientes como el volumen prostático medido por TRUS, la presencia de áreas hipoeoicas en la ecografía y los hallazgos del DRE (147). Años más tarde, este modelo fue actualizado para incorporar los hallazgos de la mpMRI, incluyendo el sistema PI-RADS v1, lo que consolidó su uso a nivel mundial. El modelo ha sido validado externamente en múltiples poblaciones (148).

Otro modelo predictivo ampliamente utilizado en la práctica clínica es el desarrollado a partir del *Prostate Cancer Prevention Trial*. Este modelo incorpora variables como la edad, el PSA, el volumen prostático y el antecedente de biopsias negativas para estimar el riesgo de PCa (149). Distintos grupos han generado modelos predictivos basados en variables clínicas tradicionales (150–153), mientras que otros han incorporado biomarcadores séricos y urinarios como los incluidos en *Stockholm-3*, *SelectMDx*, *4Kscore* o *PHI* (154–157).

La introducción de la mpMRI ha cambiado el paradigma de la detección precoz del csPCa y actualmente la mayoría de los modelos incorporan el PI-RADS como la variable predictora de mayor peso (158). Ya que la estrategia actual de detección precoz del PCa es evitar la sobredetección de iPCa, los modelos más recientes tienden a predecir solamente el riesgo de csPCa y no del CaP en general (125). La recomendación vigente de la *European Association of Urology* (EAU) para implementar el cribado del PCa en los países de la Unión Europea consiste en estratificar a los varones con sospecha de PCa mediante una primera evaluación basada en la determinación sérica del PSA con un umbral superior a 3,0 ng/ml, con el objetivo de reducir la demanda de resonancias innecesarias. Una vez realizada la MRI, una segunda estratificación permite seleccionar de manera más precisa a los candidatos para biopsia prostática (159,160). La EAU considera que los modelos predictivos contruidos a partir de variables clínicas

constituyen el método más eficiente para esta estratificación, ya sea con el fin de reducir el número de MRI o de biopsias prostáticas (160).

En este sentido, se hace necesario desarrollar modelos predictivos aplicables en dos momentos distintos: uno para utilizar tras la sospecha clínica inicial de PCa, y otro posterior a la realización de la MRI. En el primero, pueden incluirse variables como la edad, los antecedentes familiares de primer grado, el tipo de biopsia (inicial o repetida) y el tacto rectal (normal o sospechoso). Dado que el volumen prostático es una de las variables más relevantes para predecir csPCa (161), pero suele no conocerse en esta fase, Roobol et al. propusieron estimarlo de forma categórica a través del tacto rectal. Esta metodología fue incorporada en el modelo ERSPC-Rotterdam (123), utilizando valores medianos de volumen en tres categorías: próstatas pequeñas (<30 cc), medianas (31–60 cc) y grandes (>60 cc) (162). En cuanto al segundo modelo, aplicable tras la realización de la MRI, pueden mantenerse las variables clínicas mencionadas, incorporando ahora el volumen prostático estimado por la resonancia y la categoría PI-RADS, como predictor clave.

Los modelos predictivos de Barcelona han sido desarrollos recientemente con el objetivo de seleccionar candidatos a MRI (BCN-PM 1) y a biopsia prostática (BCN-PM 2). Este último integra variables clínicas esenciales junto con los hallazgos de la mpMRI, y ofrece además una calculadora de riesgo gratuita y adaptable a través de la web (<https://mripcaprediction.shinyapps.io/MRIPCAPrediction/>) y recientemente en formato app para dispositivos móviles accesible en BCNRC.com.

El BCN-PM 2 utiliza la edad, antecedentes familiares de PCa, biopsias previas negativas, PSA, DRE, PI-RADS v 2.0 y volumen prostático derivado de la MRI para predecir el riesgo de csPCa en la biopsia prostática. Fué desarrollado a partir de una cohorte de 1.486 varones con sospecha de PCa, sin recibir tratamientos con 5-ARIs, sometidos mpMRI y biopsia prostática dirigida a las lesiones sospechosas obteniendo entre 2 y 4 muestras de cada una y/o una biopsia sistemática con 12 muestras en el Hospital Vall d'Hebron de Barcelona entre 2016 y 2019. También fue validado externamente en 946 casos reportados en dos centros del área metropolitana de Barcelona mostrando un rendimiento diagnóstico excelente. A diferencia de otros modelos, la calculadora de riesgo de Barcelona permite seleccionar de forma personalizada el umbral de probabilidad de csPCa deseado, optimizando así la sensibilidad o especificidad según el escenario clínico y la categoría PI-RADS del paciente.

Una de las aportaciones diferenciales del BCN-MRI PM es su análisis estratificado según categorías PI-RADS, que demostró que su utilidad clínica es máxima en los grupos con PI-RADS <3 y PI-RADS 3, donde el juicio clínico es más incierto. Por el contrario, en pacientes con PI-RADS 4 o 5, el modelo confirma que la indicación de biopsia es prácticamente ineludible, debido a la alta prevalencia de csPCa. Con un umbral del 15 % de probabilidad de csPCa, el modelo de Barcelona logró evitar el 40 % de las biopsias prostáticas innecesarias, con una tasa de no detección de csPCa del 5,4 % en la cohorte de desarrollo y del 11,5 % en la cohorte de validación externa. Estos resultados superan claramente a la mpMRI sola, cuya especificidad en escenarios similares fue significativamente inferior. A diferencia de otros modelos con rangos limitados, el modelo de Barcelona permite incorporar valores clínicos reales sin restricción. Además, evita el uso directo del PSAD, al descomponerlo en sus componentes individuales, PSA y volumen prostático, eliminando así la necesidad de cálculos previos por parte del usuario (163).

2. JUSTIFICACIÓN DEL PROYECTO

El cáncer de próstata (PCa) es la neoplasia maligna más frecuentemente diagnosticada en varones y la tercera causa de muerte por cáncer. Clásicamente, su sospecha se ha basado en la combinación de la determinación sérica del antígeno prostático específico (PSA) y del tacto rectal (DRE), mientras la confirmación diagnóstica se ha establecido a través de la biopsia prostática. El European Randomized Study of Screening for Prostate Cancer (ERSPC) demostró una reducción sostenida de hasta un 30% en la mortalidad específica por PCa a partir del séptimo año de seguimiento, a expensas de la detección del PCa clínicamente significativo (csPCa). No obstante, la metodología clásica empleada en este estudio evidenció limitaciones en términos de especificidad, lo que derivó en un elevado número de biopsias innecesarias y la sobredetección de cánceres insignificantes (iPCa) y su sobretratamiento.

El paradigma de detección precoz del PCa ha cambiado, focalizándose en la detección del csPCa. Esta evolución ha sido posible gracias a la introducción de la resonancia magnética (MRI) prostática y del Prostate Imaging-Reporting and Data System (PI-RADS), que permite clasificar las lesiones detectadas según el riesgo de csPCa. El valor predictivo negativo de la MRI (PI-RADS < 3) supera el 90% evitando un número relevante de biopsias prostáticas. Además, la MRI ha permitido desarrollar la biopsia prostática dirigida a las lesiones sospechosas de csPCa (PI-RADS > 3) aumentando su detección. En este nuevo escenario, el *European Council of Cancer Screening* recomendó el cribado poblacional del csPCa en 2022, y la *European Association of Urology* (EAU) lo hace estratificando el riesgo de csPCa a través herramientas predictivas, con el objetivo de racionalizar el uso de la MRI y reducir el número de biopsias innecesarias. El protocolo actual de biopsia prostática sugiere obtener entre 3 y 5 muestras de cada lesión sospechosa mediante biopsias dirigidas realizadas con fusión de imágenes (MRI-TRUS) a las lesiones PI-RADS > 3 y complementariamente obtener entre 10 y 12 muestras de la zona periférica a través de la clásica biopsia sistemática. La vía para realizar la biopsia prostática recomendada actualmente es la transperineal con el objetivo de limitar las complicaciones sépticas y el consumo de antibióticos cuando se utiliza la vía transrectal. Sin embargo, este nuevo enfoque sigue presentando un elevado número de biopsias innecesarias, especialmente en lesiones PI-RADS 3 donde la tasa de detección de csPCa oscila entre el 8 y 14% y la sobredetección de iPCa alcanza hasta el 50%.

Los modelos predictivos son más eficaces que la densidad de PSA, ya que la incluyen entre sus variables predictivas, y más eficientes que los nuevos marcadores tumorales.

Los modelos predictivos permiten individualizar el riesgo del csPCa; sin embargo, deben disponer de una calculadora de riesgo accesible para ser utilizados ágilmente en la práctica clínica y de forma gratuita. El modelo predictivo de Barcelona de csPCa, que incorpora la MRI (BCN-MRI PM) además de seis variables clínicas, fue desarrollado después de analizar las deficiencias del modelo de Rotterdam que incorporaba la MRI, pero había sido adaptado al PI-RADS v 1.0, limitaba el rango de edad entre 50 y 75 años y de PSA entre 0.4 y 50 ng/mL. El BCN-MRI PM se desarrolló con el PI-RADS v 2.0, no presenta limitación en los rangos de edad y PSA, y también dispone de un calculador de riesgo accesible. El análisis comparativo entre ambos modelos predictivos en nuestro medio demostró una superioridad de BCN-MRI PM.

La evidencia científica actual sugiere que la lectura experta de la MRI puede tener un impacto clínico en la selección de candidatos a biopsia prostática. Existen numerosos intentos infructuosos para limitar el uso de la biopsia sistemática. Existen dudas respecto de cuáles son las plataformas más apropiadas para realizar la biopsia prostática transperineal mediante fusión de imágenes (MRI-TRUS), y el protocolo más adecuado para obtener la máxima efectividad de la biopsia prostática. Respecto del BCN-MRI PM, debe ser validado en pacientes con sospecha de PCa tratados con 5-ARI por hiperplasia benigna de próstata, cuando se utiliza el PI-RADS v 2.1, y también cuando se utiliza la vía transperineal y un protocolo de biopsia por saturación de las lesiones sospechosas y áreas perilesionales. Estos aspectos deben permitir una la optimización de la detección precoz del csPCa y constituyen la justificación de nuestra hipótesis de trabajo.

3. HIPÓTESIS

La presente tesis plantea la hipótesis de que una estrategia diagnóstica integrada basada en la interpretación experta de la resonancia magnética prostática, la utilización de modelos predictivos basados en MRI, el abordaje transperineal y la realización de biopsias dirigidas mediante un protocolo de saturación de las lesiones sospechosas y áreas perilesionales permite optimizar el diagnóstico precoz del cáncer de próstata clínicamente significativo, aumentando su detección y reduciendo las biopsias innecesarias y el sobrediagnóstico de tumores clínicamente insignificantes. Asimismo, se postula que el modelo predictivo BCN-MRI PM mantiene su capacidad discriminativa y su utilidad clínica cuando se aplica en pacientes tratados con inhibidores de la 5-alfa reductasa, evaluados mediante la clasificación PI-RADS v2.1 y sometidos a biopsia prostática por vía transperineal utilizando un protocolo de saturación de lesiones sospechosas y áreas perilesionales.

4. OBJETIVOS

OBJETIVO PRINCIPAL

Optimizar el diagnóstico precoz del cáncer de próstata clínicamente significativo mediante la evaluación de una estrategia diagnóstica integrada basada en la interpretación experta de la resonancia magnética prostática, la utilización de modelos predictivos basados en MRI, el abordaje transperineal y la biopsia dirigida mediante protocolos de saturación de las lesiones sospechosas y áreas perilesionales, así como mediante la validación del modelo predictivo BCN-MRI PM en distintos escenarios clínicos.

OBJETIVOS SECUNDARIOS

1. Analizar el impacto clínico de la lectura experta de la MRI y limitar las biopsias sistemáticas a partir de un modelo predictivo.
2. Comparar la efectividad de la biopsia prostática, realizada por vía transrectal y transperineal para detectar csPCa.
3. Comparar la eficacia de un protocolo de biopsia dirigida por saturación (*mapping* cada 0.5 mm) a las lesiones sospechosas y áreas perilesionales frente al protocolo actualmente recomendado, analizando además la utilidad clínica de las plataformas de fusión MRI-TRUS empleadas en el abordaje transperineal para la detección de csPCa
4. Validar el BCN-MRI PM en pacientes tratados con 5-ARI, clasificados con el PI-RADS v 2.1, utilizando la vía transperineal y un protocolo de biopsia dirigida por saturación, *mapping* cada 0.5 mm, a las lesiones sospechosas y áreas perilesionales en una plataforma apropiada.

5. COMPENDIO DE PUBLICACIONES

Esta Tesis se presenta como compendio de nueve publicaciones que se exponen a continuación.

5.1. PUBLICACIÓN 1

Título: Concordance Between the Expert Reading of Biparametric-MRI and the Nonexpert Multiparametric-MRI for the Detection of Clinically Significant Prostate Cancer: Clinical Implications

Revista: Clinical Genitourinary Cancer

Año de publicación: 2024

Volumen: 22

Páginas: 2374

DOI: <https://doi.org/10.1016/j.clgc.2024.102233>

Autores: Nahuel Paesano, María José Gutiérrez Vallecillo, Violeta Catalá, Larisa Tcholakian, Xavier Alomar, Miguel Barranco, Abel González-Huete, Jonathan Hernández Mancera, Enric Trilla, Juan Morote.

Factor de impacto (JCR): 2.7

Cuartil (JCR): 2 (Área de Urología y Nefrología)



Concordance Between the Expert Reading of Biparametric-MRI and the Nonexpert Multiparametric-MRI for the Detection of Clinically Significant Prostate Cancer: Clinical Implications

Nahuel Paesano,^{1,2} María José Gutiérrez Vallecillo,² Violeta Catalá,^{1,2} Larisa Tcholakian,^{1,2} Xavier Alomar,¹ Miguel Barranco,¹ Abel González-Huete,³ Jonathan Hernández Mancera,^{1,4} Enric Trilla,^{5,6} Juan Morote^{5,6}

Abstract

This study analyzes the concordance between nonexpert radiologists' readings of multiparametric MRI (mpMRI) and expert readings of biparametric MRI (bpMRI) in the detection of clinically significant prostate cancer. A low concordance (49.1%) was found, with expert reclassification potentially reducing prostate biopsies by 27% and the over-detection of insignificant cancers, without compromising the detection of clinically significant cancers.

Purpose: Prostate-magnetic resonance imaging (MRI) interpretation is challenging, with expertise playing a crucial role. Biparametric MRI (bpMRI) is gaining popularity in experienced centers due to its time and cost advantages over multiparametric MRI (mpMRI). We aim to analyze concordance between nonexpert radiologist PI-RADS from mpMRI and expert radiologist PI-RADS from bpMRI, and its clinical implications. **Material and Methods:** 222 men suspected of having prostate cancer (PCa) and mpMRI reported by nonexpert radiologists were referred to a reference center for transperineal MRI-TRUS fusion biopsy where an expert radiologist reported bpMRI PI-RADS 2.1 and segmentation, blinded to external mpMRI. Mapping targeted suspected lesions and 12-core systematic biopsies were performed. Clinically significant PCa (csPCa) was diagnosed when ISUP-grade group was ≥ 2 . **Results:** Concordance between both PI-RADS existed in 49.1% of cases (Kappa index 0.288). In 102 cases (45.9%), expert reclassification to lower PI-RADS existed, while an increase existed in 11 cases (5.0%), $P < .001$. Agreement existed in 30.8% of nonexpert PI-RADS 3, 43.6% of PI-RADS 4, and 83.7% of PI-RADS 5, $P < .001$. Potential clinical implications included 27% reduction in prostate biopsies when using expert bpMRI readings compared to nonexpert mpMRI readings ($P < 0.001$), while undetected csPCa were 4.2% and 3.4%, respectively, $P = .669$. Over-detection reduction of insignificant PCa was 29.4% and 0%, respectively, $P = .034$. **Conclusions:** Concordance between nonexpert PI-RADS mpMRI and expert PI-RADS bpMRI was low, increasing with nonexpert PI-RADS. Expert reclassification would reduce prostate biopsies by more than one quarter and over-detection of iPCa, while csPCa detection remained similar.

Clinical Genitourinary Cancer, Vol. 22, No. xxx, 102233 © 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Keywords: Biopsy, Radiologist expertise, Prostate Biopsy

Introduction

Prostate cancer (PCa) is the most common malignancy and the third leading cause of cancer mortality in men in the United States and European Union.¹ In 2020, about 1.4 million men worldwide were diagnosed with PCa, representing 15% of male cancers.^{2,3}

¹ Creu Blanca Clinic, Barcelona, Spain

² Uroima, Barcelona, Spain

³ Department of Radiology, Ramón y Cajal University Hospital, Madrid, Spain

⁴ Department of Radiology, Fundació Puigvert, Barcelona, Spain

⁵ Department of Urology, Vall d'Hebron University Hospital, Barcelona, Spain

⁶ Department of Surgery, Universitat Autònoma de Barcelona, Bellaterra, Spain

Submitted: Aug 13, 2024; Revised: Sep 24, 2024; Accepted: Sep 27, 2024; Epub: 5 October 2024

Address for correspondence: Nahuel Paesano, MD, PhD, Creu Blanca Clinic, Av. Josep Vicenç Foix 71, Barcelona, 08034, Spain

1558-7673/\$ - see front matter © 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

<https://doi.org/10.1016/j.clgc.2024.102233>

E-mail contact: npaesa@gmail.com

Expert Versus Nonexpert MRI Readings in Prostate Cancer Detection

The suspicion of PCa remains based on the serum measurement of prostate-specific antigen (PSA) level and digital rectal examination (DRE); diagnosis requires a prostate biopsy.⁴ Screening is contentious due to excessive biopsies and the over-detection of insignificant tumors (iPCa), leading to over-treatment.⁵

Clinically significant Prostate cancer (csPCa) is commonly defined as Gleason pattern 3+4 or higher, equivalent to grade groups 2 to 5 by the International Society of Urologic Pathology (ISUP).⁶

Recent advancements propose complementary tools to reduce unnecessary biopsies and over-detection of iPCa, including new molecular markers, predictive models, and classic PSA density. However, the most significant progress in early csPCa detection has come from prostate magnetic resonance imaging (MRI) and targeted biopsies of suspicious areas.⁷ The evolution of multiparametric MRI techniques (mpMRI) and overall improvement in interpretation through the Prostate Imaging-Report and Data System (PI-RADS) have been essential to identifying the semi-quantitative risk of csPCa in suspicious areas.⁸

Dynamic contrast-enhanced (DCE) MRI has a limited role in PI-RADS categorization, primarily enhancing peripheral zone findings with a diffusion-weighted image (DWI) score of 3. For improved visibility of csPCa, multiparametric MRI (mpMRI) is preferred, aiding in focal therapy planning and active surveillance.⁹ However, DCE-MRI with gadolinium chelate raises concerns due to potential gadolinium retention, nephrogenic systemic fibrosis risk, longer examination time, and higher costs.^{10,11} Interest is growing in abbreviated prostate MRI protocols without DCE-MRI, known as biparametric MRI (bpMRI). Several studies using PI-RADS v2 report that the diagnostic accuracy of bpMRI for detecting csPCa is comparable to that of mpMRI.^{12,13}

These innovations and PI-RADS score evolution for categorizing prostate lesions, ranging from very low to high csPCa suspicion, led to software development merging MRI findings with real-time transrectal ultrasound (TRUS) images.¹⁴

Inter-reader MRI variability and radiologist experience are variables that determine the correct detection of csPCa. The literature lacks a single definition of an expert radiologist, with criteria ranging from a minimum of 1000 cases or three years in prostate imaging to board-certified uro-radiologists with 5 to 12 years of prostate MRI experience.¹⁵⁻¹⁷

Our main objective is to analyze the concordance degree of PI-RADS scores of index lesions reported from the nonexpert mpMRI and the expert bpMRI reading, in men suspected of having PCa undergoing transperineal MRI-TRUS fusion and systematic prostate biopsies. Secondly, we aim to assess the influence of the concordance degree on the number of biopsies needed, and the rates of csPCa detection and iPCa over-detection. Additionally, we aim to assess predictive factors influencing the concordance degree between both PI-RADS categories.

Material and Methods

Design, Setting, and Participants

This retrospective analysis was based on the first-year prospective trial validating Barcelona risk calculators for detecting csPCa^{18,19} at Creu Blanca Clinic, Barcelona, Spain—a specialized center for

transperineal MRI-TRUS fusion prostate biopsy. From January 1, 2022 to December 31, 2022, 222 men with suspected PCa (PSA >3.0 ng/mL and/or abnormal DRE) were referred for biopsy based on mpMRI findings interpreted by general radiologists. A prebiopsy bpMRI, segmented and classified on PI-RADS v2.1, was performed independently of external mpMRI. The study adhered to START guidelines,²⁰ used anonymized data, and received Vall d'Hebron Ethics Committee approval (PRAG-02/2021), supported by Instituto de Salud Carlos III of Spain (PI20/01666).

Intervention

To Analyze the concordance between PI-RADS scores from general radiologist-reported mpMRI at the index lesion and experienced radiologist-reported prebiopsy bpMRI for lesion segmentation and PI-RADS v2.1 reclassification. Evaluate potential clinical implications of this reclassification.

MRI Image Acquisition Data and Segmentation

The prebiopsy bpMRI at Creu Blanca Clinic used a Siemens Verio™ 3 Tesla MRI Scanner with a pelvic-phased array. The protocol comprised TSG-SET2 transversal sections, coronal and sagittal TSET2 sequences (2D and 3D), DWI (b-values: 1600-2000-3000 s/mm²), and ADC mapping. An experienced uro-radiologist, with 15+ years and 1,500+ annual MRI readings, reclassified external mpMRI lesions using PI-RADS v2.1 based on bpMRI for segmentation.²¹ The ProFuse™ system aided semi-automatic segmentation of up to three suspicious lesions, meeting European Society of Urogenital Radiology criteria²². Men with suspected PCa and lesions reclassified to PI-RADS score 2 underwent the same biopsy protocol as those who had targeted and systematic biopsies. The Prostate Imaging Quality (PI-QUAL) scores of the external mpMRI were of sufficient diagnostic quality, scoring ≥ 3.^{23,24}

Transperineal Prostate Biopsy

Prostate biopsies were performed transperineally in the lithotomy position under general anesthesia by four experienced urologists. MRI-TRUS image fusion was performed with the ARTEMIS™ robotic system (Eigen, California, USA). Core biopsy samples were obtained using the BARD Magnum™ gun with 18-gauge x 20-cm prostate biopsy needles (Bard Care, Crawley, UK) under ultrasound vision (HITACHI ALOKA NOBLUS™, HITACHI, Connecticut, USA).

The biopsy protocol included mapping-targeted biopsies, obtaining a maximum of three samples from suspicious areas through 0.5-mm mapping per lesion and perilesional region. A subsequent systematic biopsy, following the ARTEMIS™ platform scheme, comprised 12 cores, excluding suspicious areas. Systematic biopsy cores were individually numbered as independent samples 1 to 12, while cores from suspicious areas were grouped as samples 13 to 15.

Histopathological Diagnosis

A urologic pathologist with over 10 years of prostatic pathology experience analyzed the material. The pathology report included the number of positive cores, tumor length, and the International Society of Urologic Pathology (ISUP) grade group. CsPCa was defined as ISUP-GG 2 or higher.^{6,25}

Available Variables for the Study

Age, family history of PCa (first degree), biopsy type (initial vs. repeated), DRE result (normal vs. suspicious), DRE prostate volume category (small, medium, large), PSA level (ng/mL), MRI prostate volume, number of suspicious areas, external PI-RADS score, expert PI-RADS v2.1 score, maximum lesion diameter (mm), lesion site (right vs. left), and location (peripheral base-center, peripheral apex, central-transition zone, or anterior zone). Pathology findings covered ISUP grade group, length per affected core, total core count, and positive samples categorized by location in systematic and mapping-targeted biopsies.

Endpoint Variables of the Study

The main endpoint variable of this study was the reclassification of PI-RADS score. Additionally, we examined the hypothetical decrease of prostate biopsies, the impact on detecting csPCa, and the potential over-detection of iPCa.

Statistical Analysis

Quantitative variables were presented as medians and interquartile ranges (IQR: 25th-75th percentile), while qualitative variables were expressed as percentages. Pearson's chi-square test assessed the association among qualitative variables. Concordance between PI-RADS categories from nonexpert and expert MRI readings was evaluated using the Kappa index. Binary logistic regression identified independent predictive variables for concordance, providing odds ratios (OR) and 95% confidence intervals (95% CI). Significance was considered for P values $< .05$. Statistical analysis utilized SPSS v.25 (IBM Corp., Armonk, NY, USA).

Results

The characteristics of the 222 men included in this study are shown in Table 1. The median age at biopsy was 67 years (IQR: 61-72) with a median serum PSA level of 6.8 ng/mL (IQR: 5.0-9.2). The median prostate volume, as reported from MRI, was 47 cc (IQR: 35-65). In 29 men (13.6%), a family history of PCa existed, and 40 men (18.8%) had undergone at least one previous negative biopsy. DRE was suspicious in 24 men (11.3%). In 169 cases, only one suspicious lesion existed (76.1%), in 43 (19.4%) two, and in 10 cases, three (4.5%). PI-RADS score reported from the external mpMRI of the index lesion was 2 in 4 men (1.8%), 3 in 26 (11.7%), 4 in 149 (67.1%) and 5 in 43 (19.4%). The median cores obtained for each patient was 21 (IQR: 19-24). In total, 152 (68.5%) patients have been diagnosed with PCa, of which 118 (53.2%) were csPCa and 34 (15.3%) were iPCa.

When considering the correlation between PI-RADS scores for index lesions reported by general radiologists in mpMRI conducted at external centers and those reported by an experienced radiologist in prebiopsy bpMRI at the study center, we observed concurrence in 109 cases (49.1%) with a Kappa index of 0.288, Figure 1. Overall, in 102 cases (45.9%), experienced radiologists reduced the PI-RADS score, while in 11 (5.0%) increased the PI-RADS score ($P < .001$). Correlation between expert and nonexpert reading according to the nonexpert PI-RADS is summarized in Table 2. Concordance between nonexpert and expert reading was greater as the PI-

Table 1 Characteristics of Men With Suspected PCa Referred for Prostate Biopsy at the Study Center.

Characteristic	Measurement
Number of men	222
Median age (IQR), years	67 (61-72)
Median PSA (IQR), ng/mL	6.8 (5.0-9.2)
Suspicious DRE, n (%)	24 (11.3)
Repeated biopsy, n (%)	40 (18.8)
PCa family history, n (%)	29 (13.6)
Median Prostate volume (IQR), cc	47 (35-65)
mpMRI lesions, n (%)	
1	169 (76.1)
2	43 (19.4)
3	10 (4.5)
PI-RADS of the index lesion, n (%)	
2	4 (1.8)
3	26 (11.7)
4	149 (67.1)
5	43 (19.4)
Median larger diameter of the index lesion, mm (IQR)	11 (9-15)
Location of index lesions, n (%)	
Peripheral zone	157 (70.7)
Transitional-central zone	60 (27.0)
Anterior zone	5 (2.3)
Apical zone	65 (29.3)
Median cores obtained, n (IQR)	21 (19-24)
PCa detection, n (%)	152 (68.5)
csPCa detection, n (%)	118 (53.2)
iPCa detection, n (%)	34 (15.3)

Abbreviations: n = number, IQR = interquartile range; PSA = prostate-specific antigen; DRE = digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = prostate imaging-report and data system; PCa = prostate cancer; cs = clinically significant; i = insignificant.

RADS score increased. It was 30.8% in PI-RADS 3, 43.6% in PI-RADS 4 and 83.7% in PI-RADS 5, Figure 2.

Characteristics of the relationship between the histopathological results corresponding to the index lesion biopsies and the PI-RADS score of the MRIs read in the study center and external centers are detailed in Table 3. Of the 64 men with an index lesion categorized by the expert center as PI-RADS 2, 49 men (76.6%) did not have PCa and 10 (15.6%) were diagnosed with GG1 PCa. The over-detection of iPCa was lower with expert reading in suspected PI-RADS 4 lesions, while no differences were found between both readings in PI-RADS 5 lesions. Detection of csPCa increased along with increasing PI-RADS score in expert readings. In contrast, this correlation was not observed in the evaluations performed by general radiologists. Following expert criteria, 64 (28.8%) suspicious images reported by external centers as PI-RADS score ≥ 3 were lowered to PI-RADS category 2. Considering that prostate biopsy could be avoided in men with PI-RADS < 3 , expert reading could have avoided 28.8% of prostate biopsies while reading by general radiologists could have avoided 4 biopsies (1.8%), $P = .021$. If they had not been biopsied, 5 (4.2%) of csPCa would have been missed by

Expert Versus Nonexpert MRI Readings in Prostate Cancer Detection

Figure 1 Correlation between the PI-RADS score in the index lesion reported in the mpMRI performed at external centers, and the PI-RADS reported by an experienced radiologist in the prebiopsy bpMRI performed at the study center.

PI-RADS reported at external centers, n (%)	PI-RADS reported at the study center, n (%)						
		1	2	3	4	5	All
	1	0	0	0	0	0	0 (0)
	2	0	0	0	3	1	4 (1.8)
	3	0	14	8	3	1	26 (11.7)
	4	0	47	34	65	3	149 (67.1)
	5	0	3	2	2	36	43 (19.4)
	All	0	64 (28.8)	44 (19.8)	73 (32.9)	41 (18.5)	222 (100)

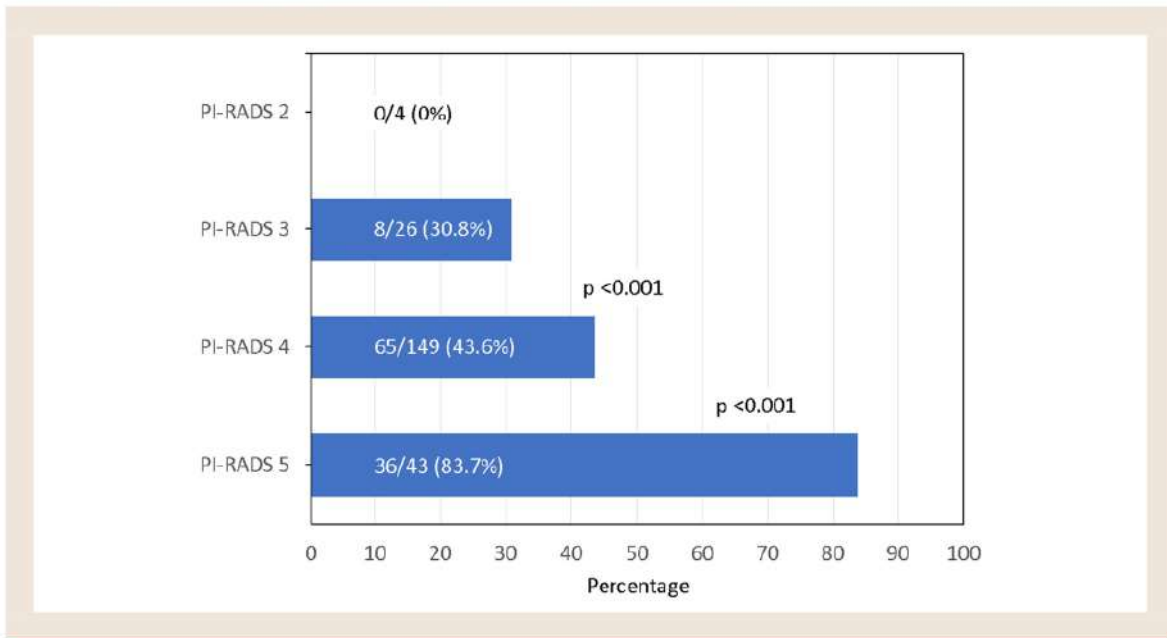
Concordance between PI-RADS = 109/222 (49.1%); Kappa index = 0.288; $p < 0.001$ **Table 2** Correlation of PI-RADS Scores Between General and Expert Radiologists Across Different Centers.

PI-RADS from external centers	Number of cases, (%)	PI-RADS from the study center, n (%)			P Value
		Decrease	Concordance	Increased	
1	0 (0)	0 (0)	0 (0)	0 (0)	-
2	4 (1.9)	0 (0)	0 (0)	4 (100)	-
3	26 (11.7)	14 (53.8)	8 (30.8)	4 (15.4)	< .001
4	149 (67.1)	81 (54.4)	65 (43.6)	3 (2.0)	< .001
5	43 (19.4)	7 (16.3)	36 (83.7)	0 (0)	-
All	222 (100)	102 (45.9)	109 (49.1)	11 (5.0)	< .001

Table 3 Prostate Biopsy Results and PI-RADS Scores From External and Study Center MRI Exams.

PI-RADS	Center	Cases, n (%)	No PCa, n (%)	GG 1 n (%)	GG 2 n (%)	GG 3 n (%)	GG 4 n (%)	GG 5 n (%)
1	External centers	0	0	0	0	0	0	0
	Study center	0	0	0	0	0	0	0
2	External centers	4 (1.8)	0 (0)	0 (0)	3 (75.0)	0 (0)	0 (0)	1 (25.0)
	Study center	64 (28.8)	49 (76.6)	10 (15.6)	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)
3	External centers	26 (11.7)	13 (50)	5 (19.2)	6 (23.1)	0 (0)	2 (7.2)	0 (0)
	Study center	44 (19.8)	17 (38.6)	16 (36.4)	9 (20.5)	2 (4.5)	0 (0)	0 (0)
4	External centers	149 (67.1)	52 (34.9)	26 (17.4)	43 (28.9)	19 (12.8)	7 (4.7)	2 (1.3)
	Study center	73 (32.9)	3 (4.1)	5 (6.8)	41 (56.2)	15 (20.5)	8 (11.0)	1 (1.4)
5	External centers	43 (19.4)	5 (11.6)	3 (7.0)	13 (30.2)	12 (27.9)	3 (7.0)	7 (16.3)
	Study center	41 (18.5)	1 (2.4)	3 (7.3)	13 (31.7)	13 (31.7)	3 (7.3)	8 (19.5)
All	All	222 (100)	70 (31.5)	34 (15.3)	65 (29.3)	31 (14.0)	12 (5.4)	10 (4.5)

Abbreviations: PI-RADS = prostate imaging-report and data system; PCa = prostate cancer; GG = ISUP grade group significant PCa.

Figure 2 Concordance degree between the PI-RADS score reported in the index lesion of mpMRI performed at external centers and that reported at the study center, according to the referred PI-RADS.**Table 4** Analysis of Biopsy Approaches Affecting csPCa Detection and iPCa Over-Detection.

Parameter	Strategy for Prostate biopsy:			P Value
	All referred men	Only referred PI-RADS ≥ 3	Only study center PI-RADS ≥ 3	
Prostate biopsies, n (%)	222 (100)	↓ 4 (1.8)	↓ 64 (28.8)	= .021
csPCa detection, n (%)	118 (53.2)	↓ 4 (3.4)	↓ 5 (4.2)	= .669
iPCa over-detection, n (%)	34 (15.3)	↓ 0 (0)	↓ 10 (29.4)	= .034

Abbreviations: csPCa = clinically significant prostate cancer; iPCa = insignificant prostate cancer; PI-RADS = prostate imaging-report and data system.

the expert reading compared to 4 (3.4%) by nonexpert reading, $P = .669$. Regarding the over-detection of iPCa, the reclassification of PI-RADS by expert reading would reduce the detection of 10 (29.4%) iPCa while none by nonexpert reading, $P = .034$, Table 4. The four men (100%) in whom nonexpert reading suggested as PI-RADS 2, had aggressive PCa, in three an ISUP grade group 2 was found and 5 in one, Figure 3. An example of the disagreement between expert and nonexpert readings is shown in Figure 4A, Figure 4B.

The multivariate analysis conducted using the available variables in this study revealed that the nonexpert PI-RADS score, and prostate volume independently predicted the concordance between nonexpert and expert PI-RADS, Table 5. Specifically, the level of concordance increased with the rise of the nonexpert PI-RADS, OR 3.925 (95% CI 1.888-8.160), $P < 0.001$. Concerning prostate volume, concordance increased as its volume decreased, OR 0.359 (95% CI 0.162-0.795), $P = 0.012$. A notable impact of prostate volume on concordance was observed exclusively in nonexpert PI-RADS 4, with no significant influence in PI-RADS 3 and 5.

Discussion

Expertise in prostate MRI interpretation lacks a standardized definition. Some suggest a radiologist becomes experienced after interpreting at least 500 cases, while others set the threshold at 1000 cases.^{15,26} Alternatively, experience may be measured in years, with three, five, or twelve years in prostate imaging considered as experienced.^{13,16} Histopathological feedback and case volume are crucial for expertise.²⁷

There is a notable absence of studies comparing nonexpert mpMRI reading with expert bpMRI reading, especially with PI-RADS v2.1. Our study aimed at investigating the concordance degree between both nonexpert reading using mpMRI and the reclassification of lesions through expert reading using bpMRI. We also aimed to understand the impact of different readings on the detection of csPCa. Literature recognizes bpMRI for its speed, cost-effectiveness, and security, prompting our interest in evaluating expert reading in bpMRI.^{28,29}

We observed agreement between expert and nonexpert report of PI-RADS score of index lesions readings in less than half of cases

Expert Versus Nonexpert MRI Readings in Prostate Cancer Detection

Figure 3 CsPcCa detection according to the PI-RADS reported at external centers and study center.

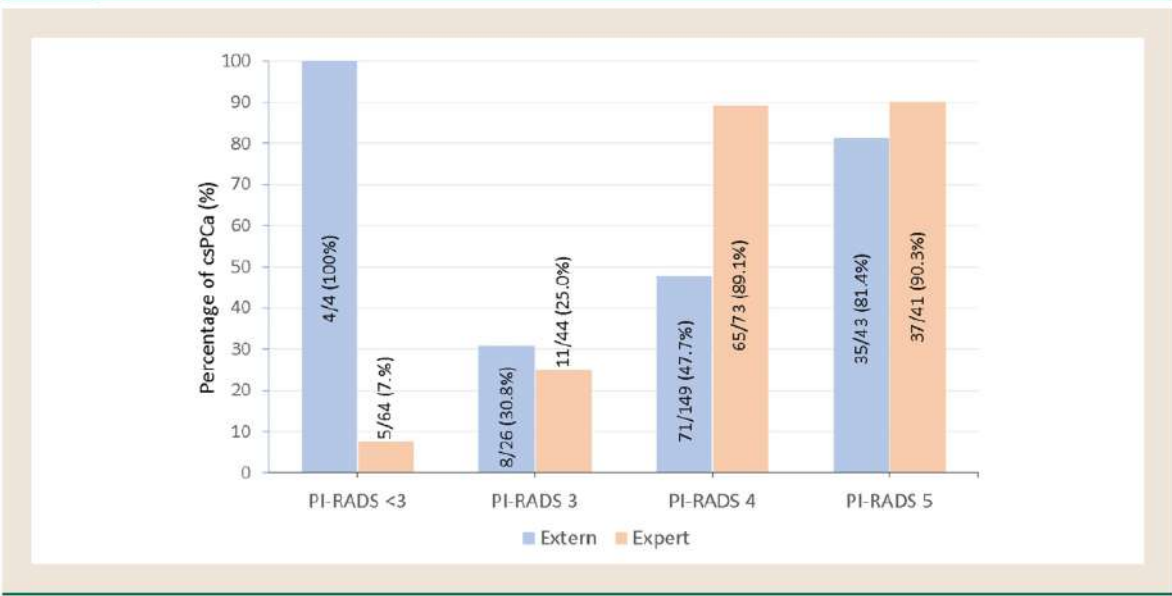


Figure 4A External Center Report: A 14 mm lenticular-shaped area located in the transition zone, left lobe, mid-region, posterior segment, shows signal hypointensity on T2-weighted sequences and diffusion restriction, consistent with PIRADS 4. Study Center Report: An area of hypointensity on T2-weighted sequences is found within a nodule, with mild restriction similar to the adjacent transition zone, which is therefore recategorized as PIRADS 2. Biopsy result: Negative for malignant prostate neoplasia in both systematic biopsies and Target biopsy.

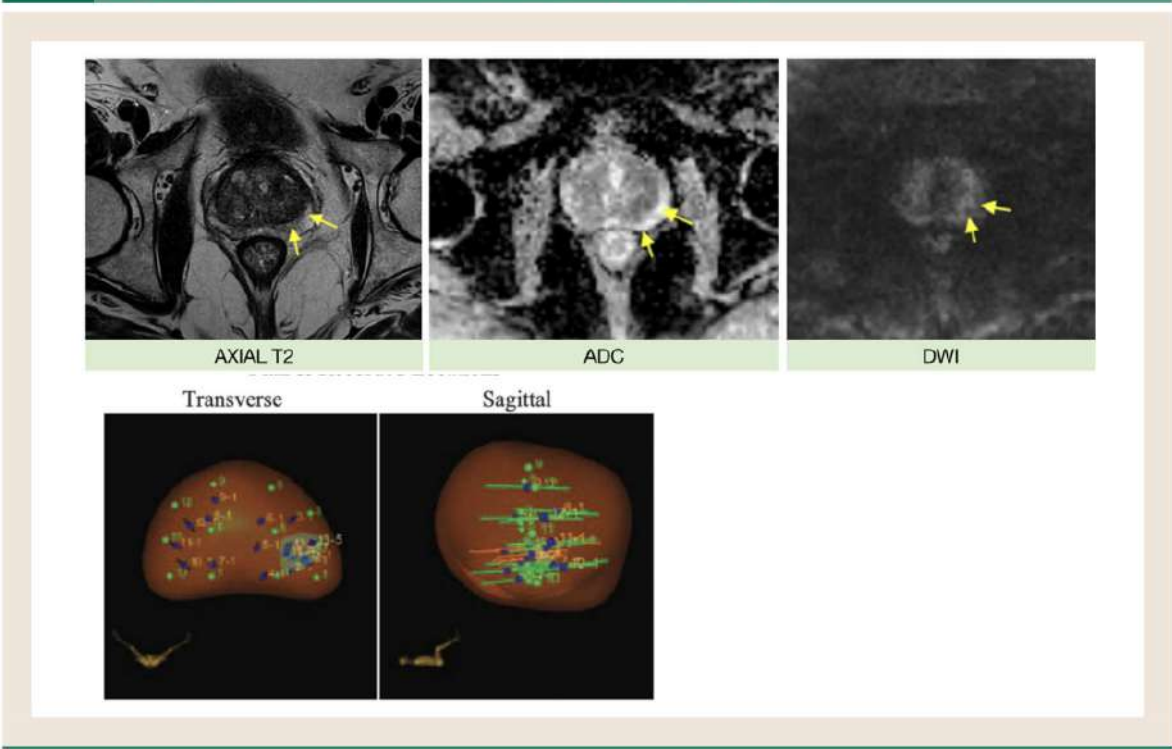
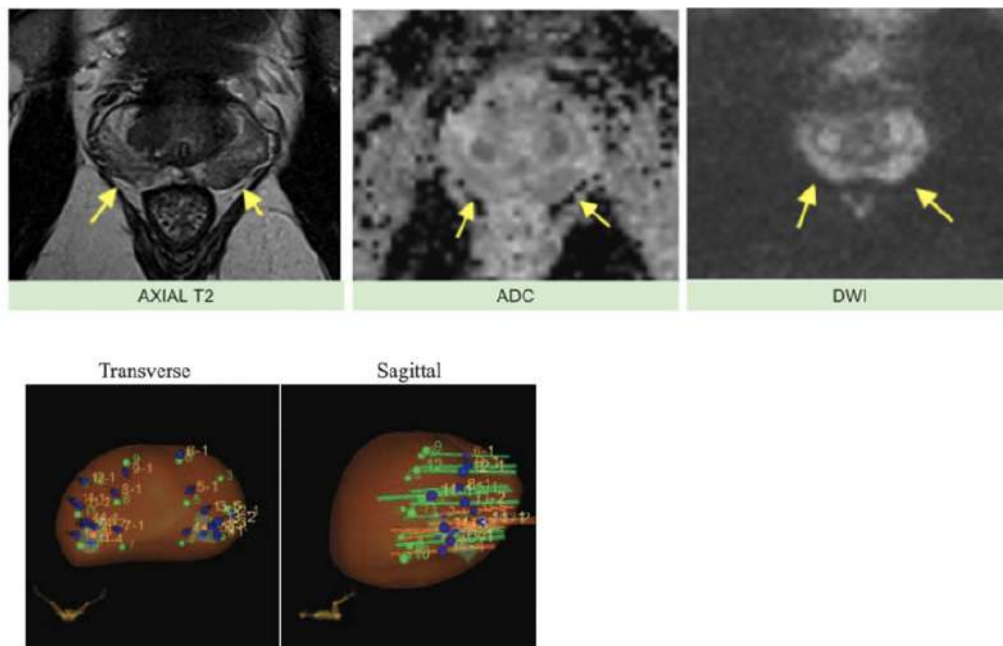


Figure 4B External Center Report: A 10 mm area located in the peripheral zone, left lobe, mid-region, posteromedial segment, showing signal hypointensity on T2-weighted sequences and marked diffusion restriction, consistent with PIRADS 4; an 8 mm lesion with similar characteristics in the peripheral zone, right lobe, mid-region, posteromedial segment. Study Center Report: An area of signal hypointensity on T2-weighted sequences with linear margins, showing mild restriction on diffusion sequences, findings suggestive of prostatitis, recategorized to PIRADS 2. Biopsy result: Negative for malignant prostate neoplasia in both systematic biopsies and Target biopsy.



(49.1%) with a low grade of concordance. Consistent with our results, other studies have reported fair agreement between readers and differences among radiologists in lesion characterization.^{29–31} Gatti et al. emphasized the importance of reader experience in assessing bpMRI, aligning with our results.¹⁵ Among 64 men with lesions recategorized by the expert reading with bpMRI as PIRADS 2, 49 patients (76.6%) did not have PCa, and 10 (15.6%) were diagnosed with GG1 PCa. In a recent study, results paralleled ours in terms of expert reading. Out of 116 index lesions, 45 were reclassified with a PI-RADS score 2 or less, exempting them from prostate biopsy. The study also highlighted discrepancies between nonexpert and expert readings, corroborating our findings.³² Notably, all men with a reclassified PI-RADS score of 2 underwent prostate biopsy, with a low csPCa rate (4.2%), and those with an external PI-RADS score of 2 were reclassified to higher PI-RADS, all having csPCa (100%). The detection of csPCa increased with rising PI-RADS scores in expert readings, contrary to assessments by general radiologists. This contradicts findings by Boschheidgen et al., who reported increased csPCa detection with higher PI-RADS scores in both readings.³¹ Kang et al. and Soon et al. also reported correlations between higher Likert scores or PI-RADS scores and increased csPCa detection, especially in experienced group readings.^{29,33}

Improving reader experience significantly reduces the tendency to over-detect iPCa. Boschheidgen et al. conducted a study comparing readings from experts and nonexperts in prostate MRI imaging for 45-year-old men, revealing a 71% reduction in iPCa detection when using PI-RADS ≥ 4 as the biopsy threshold.³¹

In the context of prostate volume, it becomes evident that prostate size influences the accuracy of nonexpert readings. Gatti et al. reported that in cases of PI-RADS 4, smaller prostatic volumes were associated with undetected lesions among readers with intermediate experience (young radiologists with 300 cases). The cancer detection rate significantly decreases in small and heterogeneous prostates, emphasizing the impact of experience on accurate readings.¹⁵

Based on the criteria of avoiding prostate biopsy when PI-RADS category is less than three,⁴ expert reading reduced the need for prostate biopsies by 28.8%, compared to 1.8% with nonexpert reading of mpMRI. This aligns with findings by Boschheidgen et al. who observed a 20% reduction in biopsies for PI-RADS 3 to 5 in expert reading.³¹

The PI-RADS v. 2.1 reading model can be applied without the use of contrast for PI-RADS 3 lesions in the peripheral zone, as the dominant sequence in this region is the diffusion-weighted

Expert Versus Nonexpert MRI Readings in Prostate Cancer Detection

Table 5 Univariate and Multivariate Analysis of Variables Predicting PI-RADS Score Correspondence Across Different Centers.

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	P Value	Odd ratio (95% CI)	P Value
Age, Ref. ≤ 68 years	1.997 (1.167-3.418)	= .011	2.171 (0.960-4.913)	= .063
PCa family history, Ref. no	0.975 (0.446-2.131)	= .950	0.776 (0.283-2.132)	= .623
Previous negative prostate biopsy, Ref. no	1.003 (0.491-2.048)	= .993	0.761 (0.310-1.886)	= .551
Serum PSA, Ref. ≤ 6.8 ng/mL	2.497 (1.455-4.287)	< .001	1.703 (0.789-3.677)	= .175
Digital rectal examination, Ref. normal	3.088 (1.265-7.533)	= .010	2.623 (0.868-7.929)	= .088
Prostate volume, Ref. ≤ 47 cc	0.371 (0.216-0.638)	< .001	0.359 (0.162-0.795)	= .012
mpMRI, Ref. PI-RADS ≤ 3	3.052 (1.295-7.194)	= .008	3.925 (1.888-8.160)	< .001
Number of suspicious lesions, Ref. one	2.785 (1.451-5.346)	= .002	1.703 (0.792-3.662)	= .173
Largest diameter of index lesion, Ref. ≤ 11 mm	2.596 (1.509-4.464)	< .001	1.122 (0.496-2.539)	= .783
Central zone location of index lesion, Ref. no	0.549 (0.300-1.006)	= .051	0.606 (0.243-1.514)	= .284
Apical zone location of index lesion, Ref. no	1.705 (0.950-3.060)	= .073	1.559 (0.580-3.569)	= .294

Abbreviations: PCa = prostate cancer; PSA = Prostate specific antigen; mpMRI = multiparametric magnetic resonance imaging.

sequence. Contrast material is only relevant for a potential upgrade to PI-RADS 4 in those PI-RADS 3 lesions that show enhancement after contrast administration. For this reason, in our study, there might be a higher proportion of PI-RADS 3 lesions in the expert interpretation using bpMRI.^{34,35}

To our knowledge, this is the first study comparing nonexpert mpMRI reading with expert bpMRI reading using PI-RADS V 2.1. We assess the clinical impact by comparing with histopathological results. A strength is the blind reporting of bpMRI by an expert without prior exposure to mpMRI. Limitations include a retrospective, single-center design with a limited patient cohort. The absence of intravenous contrast may impact lesion upgrading, affecting biopsy considerations for PI-RADS 4 or higher lesions. The high expertise of our radiologists may limit study reproducibility.

Further studies are warranted to assess the agreement between expert and nonexpert radiologists in reading bpMRI, validate bpMRI, and understand the clinical impact of reducing biopsies through expert bpMRI reading. Additionally, investigations should explore whether a bpMRI without contrast, coupled with expert reading, suffices in a prebiopsy setting.

Conclusion

Concordance between nonexpert PI-RADS mpMRI and expert PI-RADS bpMRI was low and it increased as the PI-RADS mpMRI score was higher. The reclassification of PI-RADS category with expert reading would reduce the need of prostate biopsies more than one quarter, without reducing csPCa detection, and decreasing the over-detection of iPCa.

Clinical Practice Points

- **Patient Summary:** The experience of radiologists plays a crucial role in accurately interpreting magnetic resonance imaging (MRI) findings and categorizing lesions based on PI-RADS scores. Expert reading of bpMRI improves the early detection of csPCa compared with nonexpert reading of mpMRI.
- **What the Study Adds:** The study highlights the clinical importance of expert bpMRI readings in guiding patient management

decisions. By reducing unnecessary biopsies without compromising csPCa detection rates, expert interpretation of bpMRI offers potential benefits in optimizing resource utilization and minimizing unnecessary biopsies.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Nahuel Paesano: Writing – original draft, Investigation, Data curation, Conceptualization. **María José Gutiérrez Vallecillo:** Writing – original draft, Data curation. **Violeta Catalá:** Methodology, Investigation, Conceptualization. **Larisa Tcholakian:** Data curation. **Xavier Alomar:** Data curation. **Miguel Barranco:** Data curation. **Abel González-Huete:** Conceptualization. **Jonathan Hernández Mancera:** Conceptualization. **Enric Trilla:** Supervision, Conceptualization. **Juan Morote:** Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72:7–33. doi:10.3322/caac.21708.
2. Bertuccio P, Santucci C, Carioli G, Malvezzi M, La Vecchia C. Mortality trends from urologic cancers in Europe over the period 1980–2017, and a projection to 2025. *Eur Urol Oncol.* 2021;4:677–696. doi:10.1016/j.euo.2021.05.005.
3. Sung H, Feday J, Siegel RL, et al. Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–249. doi:10.3322/caac.21660.
4. Mottet N, van den Bergh RCN, Briers E, et al. EAU–EANM–ESTRO–ESUR–SIOG guidelines on prostate cancer–2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2021;79:243–262. doi:10.1016/j.eururo.2020.09.042.
5. Draisma G, Boer R, Otto SJ, et al. Lead times and overdiagnosis due to prostate specific antigen screening: estimates from the European randomized study of screening for prostate cancer. *J Natl Cancer Inst.* 2003;95:868–878. doi:10.1093/jnci/95.12.868.

6. Epstein JI, Egevad L, Amin MB, et al. Grading committee the 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol*. 2016;40:244–252. doi:10.1097/PAS.0000000000000530.
7. Stabile A, Giganti F, Rosenkrantz AB, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. *Nat Rev Urol*. 2020;17:41–61. doi:10.1038/s41585-019-0212-4.
8. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging - reporting and data system: 2015, version 2. *Eur Urol*. 2016;69:16–40. doi:10.1016/j.eururo.2016.04.016.
9. Huebner NA, Korn S, Resch I, et al. Visibility of significant prostate cancer on multiparametric magnetic resonance imaging (MRI)-do we still need contrast media? *Eur Radiol*. 2021;31:3754–3764. doi:10.1007/s00330-020-07494-1.
10. Mathur M, Jones JR, Weinreb JC. Gadolinium deposition and nephrogenic systemic fibrosis: a radiologist's primer. *Radiographics*. 2020;40:153–162. doi:10.1148/rp.2020190110.
11. Tamada T, Kido A, Yamamoto A, et al. Comparison of biparametric and multiparametric MRI for clinically significant prostate cancer detection with PI-RADS version 2.1. *J Magn Reson Imaging*. 2021;53:283–291. doi:10.1002/jmri.27283.
12. Tavakoli AA, Hielscher T, Badura P, et al. Contribution of dynamic contrast-enhanced and diffusion MRI to PI-RADS for detecting clinically significant prostate cancer. *Radiology*. 2023;306:186–199. doi:10.1148/radiol.212692.
13. Thais WM, Moser S, Hepp T, et al. Head-to-head comparison of biparametric versus multiparametric MRI of the prostate before robot-assisted transperineal fusion prostate biopsy. *World J Urol*. 2022;40:2431–2438. doi:10.1007/s00345-022-04120-1.
14. Jue JS, Rastinehad AR. MRI Fusion Transperineal Prostate Biopsy Instructions and Troubleshooting. *J Endourol*. 2021;35:S2–S6. doi:10.1089/end.2020.1075.
15. Gatti M, Faletti R, Calleri G, et al. Prostate cancer detection with biparametric magnetic resonance imaging (bpMRI) by readers with different experience: performance and comparison with multiparametric (mpMRI). *Abdom Radiol (NY)*. 2019;44:1883–1893. doi:10.1007/s00261-019-01934-3.
16. Mullerad M, Hedvig H, Liang W, et al. Prostate cancer: detection of extracapsular extension by genitourinary and general body radiologists at MR imaging. *Radiology*. 2004;232:140–146. doi:10.1148/radiol.2321031254.
17. de Rooij M, Israel B, Tummers M, et al. ESUR/ESUI consensus statements on multi-parametric MRI for the detection of clinically significant prostate cancer: quality requirements for image acquisition, interpretation and radiologists' training. *Eur Radiol*. 2020;5404–5416. doi:10.1007/s00330-020-06929-z.
18. Morote J, Borque-Fernando A, Triquell M, et al. The Barcelona predictive model of clinically significant prostate cancer. *Cancers (Basel)*. 2022;14:1589. doi:10.3390/cancers14061589.
19. Morote J, Borque-Fernando A, Triquell M, et al. Comparison of Rotterdam and Barcelona magnetic resonance imaging risk calculators for predicting clinically significant prostate cancer. *Eur Urol Open Sci*. 2023;53:46–54. doi:10.1016/j.euro.2023.03.013.
20. Moore CM, Kasivisvanathan V, Eggeger S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an international working group. *Eur Urol*. 2013;64:544–552. doi:10.1016/j.eururo.2013.03.030.
21. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol*. 2019;76:340–351. doi:10.1016/j.eururo.2019.02.033.
22. Roethke MC, Kuru TH, Schultze S, et al. Evaluation of the ESUR PI-RADS scoring system for multiparametric MRI of the prostate with targeted MR/TRUS fusion-guided biopsy at 3.0 Tesla. *European Radiol*. 2014;24:344–352. doi:10.1007/s00330-013-3017-5.
23. Giganti F, Kirkham A, Kasivisvanathan V, et al. Understanding PI-QUAL for prostate MRI quality: a practical primer for radiologists. *Insights Imag*. 2021;12:59. <https://doi.org/10.1186/s13244-021-00956-6>
24. Giganti F, Allen C. Imaging quality and prostate MRI: it is time to improve. *Br J Radiol*. 2021;94(1118):20200934. doi:10.1259/bjr.20200934.
25. Epstein JI, Zelefsky MJ, Sjöberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol*. 2016;69:428–435. doi:10.1016/j.eururo.2015.06.046.
26. Pickersgill NA, Vetter JM, Raval NS, et al. The accuracy of prostate magnetic resonance imaging interpretation: impact of the individual radiologist and clinical factors. *Urology*. 2019;127:68–73. doi:10.1016/j.urol.2019.01.035.
27. Kang HC, Jo N, Bamashmos AS, et al. Accuracy of prostate magnetic resonance imaging: reader experience matters. *Eur Urol Open Sci*. 2021;27:53–60. doi:10.1016/j.euro.2021.03.004.
28. Kuhl CK, Bruhn R, Krämer N, Nebelung S, Heidenreich A, Schrading S. Abbreviated biparametric prostate MR imaging in men with elevated prostate-specific antigen. *Radiology*. 2017;285:493–505. doi:10.1148/radiol.2017170129.
29. Kang Z, Min X, Weinreb J, Li Q, Feng Z, Wang L. Abbreviated biparametric versus standard multiparametric MRI for diagnosis of prostate cancer: a systematic review and meta-analysis. *AJR Am J Roentgenol*. 2019;212:357–365. doi:10.2214/AJR.18.20103.
30. Józwiak R, Sobiecki P, Lorenc T. Intraobserver and interobserver agreement between six radiologists describing mpMRI features of prostate cancer using a PI-RADS 2.1 structured reporting scheme. *Life (Basel)*. 2023;13:580. doi:10.3390/life13020580.
31. Boschheidgen M, Albers P, Schlemmer HP, et al. Multiparametric magnetic resonance imaging in prostate cancer screening at the age of 45 years: results from the first screening round of the PROBASC trial. *Eur Urol*. 2024;85:105–111. doi:10.1016/j.eururo.2023.09.027.
32. Stabile A, Sorce G, Barletta F, et al. Impact of prostate MRI central review over the diagnostic performance of MRI-targeted biopsy: should we routinely ask for an expert second opinion? *World J Urol*. 2023;41:3231–3237. doi:10.1007/s00345-023-04365-4.
33. Sonn GA, Fan RE, Ghanouni P, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. *Eur Urol Focus*. 2019;5:592–599. doi:10.1016/j.euf.2017.11.010.
34. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol*. 2019;76:340–351. doi:10.1016/j.eururo.2019.02.033.
35. Asif A, Nathan A, Ng A, et al. Comparing biparametric to multiparametric MRI in the diagnosis of clinically significant prostate cancer in biopsy-naïve men (PRIME): a prospective, international, multicentre, non-inferiority within-patient, diagnostic yield trial protocol. *BMJ Open*. 2023;13:070280. doi:10.1136/bmjopen-2022-070280.

5.2. PUBLICACIÓN 2

Título: A Diagnostic Accuracy Study of Targeted and Systematic Biopsies to Detect Clinically Significant Prostate Cancer, including a Model for the Partial Omission of Systematic Biopsies

Revista: Cancers

Año de publicación: 2023

Volumen: 15

Páginas: 4543

DOI: <https://doi.org/10.3390/cancers15184543>

Autores: Juan Morote, Natàlia Picola, Jesús Muñoz-Rodríguez, Nahuel Paesano, Xavier Ruiz-Plazas, Marta V. Muñoz-Rivero, Anna Celma, Gemma García-de Manuel, Ignacio Aisian, Pol Servian and José M. Abascal

Factor de impacto (JCR): 4.5

Cuartil (JCR): 1 (Área de Oncología)



Article

A Diagnostic Accuracy Study of Targeted and Systematic Biopsies to Detect Clinically Significant Prostate Cancer, including a Model for the Partial Omission of Systematic Biopsies

Juan Morote ^{1,2,*}, Natàlia Picola ³, Jesús Muñoz-Rodríguez ⁴, Nahuel Paesano ⁵, Xavier Ruiz-Plazas ⁶, Marta V. Muñoz-Rivero ⁷, Anna Celma ^{1,2}, Gemma García-de Manuel ⁸, Ignacio Aisian ⁹, Pol Servian ^{10,†} and José M. Abascal ^{11,12,†}

¹ Department of Urology, Vall d'Hebron Hospital, 08035 Barcelona, Spain; ana.celma@vallhebron.cat

² Department of Surgery, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

³ Department of Urology, Hospital Universitari de Bellvitge, 08907 Hospitalet de Llobregat, Spain; npicola@bellvitgehospital.cat

⁴ Department of Urology, Hospital Universitari Parc Taulí, 08208 Sabadell, Spain; jmunoz@tauli.cat

⁵ Clínica Creu Blanca, 08034 Barcelona, Spain; nahuel.paesano@creublancas.es

⁶ Department of Urology, Hospital Universitari Joan XXIII, 43005 Tarragona, Spain; xruiz.tarragona.ics@gencat.cat

⁷ Department of Urology, Hospital Arnau de Vilanova, 25198 Lleida, Spain; mvmunoz.lleida.ics@gencat.cat

⁸ Department of Urology, Hospital Universitari Josep Trueta, 17007 Girona, Spain; gemmagarcia.girona.ics@gencat.cat

⁹ Department of Urology, Hospital Clinic, 08036 Barcelona, Spain; iasiain@clinic.cat

¹⁰ Department of Urology, Hospital Germans Trias i Pujol, 08916 Badalona, Spain; pservian.germanstrias@gencat.cat

¹¹ Department of Urology, Parc de Salut Mar, 08003 Barcelona, Spain; jabascal@psmar.cat

¹² Department of Medicine and Health Science, Universitat Pompeu Fabra, 08003 Barcelona, Spain

* Correspondence: juan.morote@vallhebron.cat

† Equal contribution as last author.



Citation: Morote, J.; Picola, N.; Muñoz-Rodríguez, J.; Paesano, N.; Ruiz-Plazas, X.; Muñoz-Rivero, M.V.; Celma, A.; Manuel, G.G.-d.; Aisian, I.; Servian, P.; et al. A Diagnostic Accuracy Study of Targeted and Systematic Biopsies to Detect Clinically Significant Prostate Cancer, including a Model for the Partial Omission of Systematic Biopsies. *Cancers* **2023**, *15*, 4543. <https://doi.org/10.3390/cancers15184543>

Academic Editor: Emmanuel S. Antonarakis

Received: 22 June 2023

Revised: 16 August 2023

Accepted: 12 September 2023

Published: 13 September 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Simple Summary: Targeted biopsies of suspicious lesions on multiparametric magnetic resonance imaging (mpMRI) improve the sensitivity of systematic biopsies for clinically significant prostate cancer (csPCa) detection. However, systematic biopsies are still recommended, since a small, albeit significant, percentage of csPCa is only detected in them. In a contemporary series, 13.9% of csPCa cases were only detected in systematic biopsies, which represented 6.7% of its overall detection rate. The finding of independent predictive factors for csPCa detection in targeted biopsies allowed the possibility to develop a predictive model for avoiding systematic biopsies with a low risk of missing csPCa.

Abstract: The primary objective of this study was to analyse the current accuracy of targeted and systematic prostate biopsies in detecting csPCa. A secondary objective was to determine whether there are factors predicting the finding of csPCa in targeted biopsies and, if so, to explore the utility of a predictive model for csPCa detection only in targeted biopsies. We analysed 2122 men with suspected PCa, serum PSA > 3 ng/mL, and/or a suspicious digital rectal examination (DRE), who underwent targeted and systematic biopsies between 2021 and 2022. CsPCa (grade group 2 or higher) was detected in 1026 men (48.4%). Discrepancies in csPCa detection in targeted and systematic biopsies were observed in 49.6%, with 13.9% of csPCa cases being detected only in systematic biopsies and 35.7% only in targeted biopsies. A predictive model for csPCa detection only in targeted biopsies was developed from the independent predictors age (years), prostate volume (mL), PI-RADS score (3 to 5), mpMRI Tesla (1.5 vs. 3.0), TRUS-MRI fusion image technique (cognitive vs. software), and prostate biopsy route (transrectal vs. transperineal). The csPCa discrimination ability of targeted biopsies showed an AUC of 0.741 (95% CI 0.721–0.762). The avoidance rate of systematic prostate biopsies went from 0.5% without missing csPCa to 18.3% missing 4.6% of csPCa cases. We conclude

that the csPCa diagnostic accuracy of targeted biopsies is higher than that of systematic biopsies. However, a significant rate of csPCa remains detected only in systematic biopsies. A predictive model for the partial omission of systematic biopsies was developed.

Keywords: clinically significant prostate cancer detection; systematic biopsy; targeted biopsy; prostate biopsy concordance

1. Introduction

Prostate cancer (PCa) is the leading malignant tumour in men from industrialised countries [1]. The European Randomised Screening for Prostate Cancer (ERSPC) trial has shown a persistent decrease in PCa-specific mortality over more than 20 years of follow-up due to the early detection and treatment of clinically significant PCa (csPCa) in the Göteborg section of ERSPC [2]. The early detection of PCa has evolved towards csPCa due to the spread of multiparametric magnetic resonance imaging (mpMRI) and targeted biopsies of suspicious lesions [3]. The high negative predictive value of mpMRI has allowed for a reduction in the number of unnecessary biopsies [4], and targeted biopsies have increased the sensitivity of systematic biopsies for csPCa [5]. However, systematic biopsies remain the only way to biopsy men with high risks of csPCa and negative mpMRI, with some csPCa cases only detected in systematic biopsies still being mpMRI-positive [6,7]. A recent study based on the Göteborg prostate cancer screening trial suggested that targeted biopsies are sufficient in men with a prostate imaging report and data system (PI-RADS) score of 3 or higher [8], while 20% of csPCa cases are missed [9]. In contrast, other studies have suggested that targeted biopsies could be avoided in men with serum prostate-specific antigen (PSA) levels over 10 ng/mL and an abnormal digital rectal examination (DRE) result in order to decrease the demand for mpMRI, given that almost all csPCa cases are detected in systematic biopsies carried out in these men at high risk of csPCa [10,11]. The transperineal route has recently been recommended for reducing the infectious complications of the transrectal route [12–15]. Systematic biopsy currently includes twelve needle sticks, often detecting insignificant cancer lesions, causing pain and other adverse effects. Targeted biopsies include few needle sticks, and they detect more significant cancer lesions and fewer insignificant cancer lesions than systematic biopsies [6,7,16].

The Barcelona predictive models and risk calculators were developed to predict the risk of csPCa detection just after PCa suspicion to avoid unnecessary mpMRI exams and before mpMRI to improve candidate selection for prostate biopsy. Both predictive models were developed at our centre and externally validated in the metropolitan area of Barcelona [17,18]. Currently, both models are being validated in Catalonia, a country with 7,900,000 inhabitants, in a prospective trial. The main objective of this study is to analyse the accuracy of targeted and systematic biopsies for the detection csPCa in a current population of suspected PCa. We also aim to identify independent predictive factors for the detection of csPCa in targeted biopsies and to develop a predictive model for the partial omission of systematic biopsies.

2. Materials and Methods

2.1. Design, Setting, and Participants

Among 3,557 men with suspected PCa, due to serum PSA > 3 ng/mL and/or a suspicious DRE result, enrolled in a prospective trial for the validation of the Barcelona risk calculators [17,18] at 10 centres in Catalonia (Spain), 2122 men underwent TRUS-MRI fusion targeted biopsy and systematic prostate biopsy consecutively between 1 January 2021 and 31 December 2022.

2.2. MRI and Prostate Biopsy

MpMRI exams were always performed at each participant centre and reported with PI-RADS v.2.0 by an experienced radiologist. A pelvic phased-array surface coil was always used as a 1.5 or 3.0 Tesla MRI magnetic field strength.

MRI-TRUS fusion images were obtained using the cognitive or software technique. TRUS-assisted prostate biopsy was performed via the transrectal or transperineal route. Targeted biopsies of suspected lesions (PI-RADS ≥ 3) were performed, obtaining between 2 and 6 cores, and 12-core TRUS systematic prostate biopsy was also conducted. Prostate biopsies were performed by an experienced urologist at each centre.

Biopsy material was analysed in the pathology department of each participant centre by an experienced pathologist using the International Society of Urologic Pathology grade group (GG) to classify PCa. csPCa was reported when GG was 2 or higher [19].

2.3. Outcome Variable

CsPCa detection in systematic and targeted biopsies was the outcome variable for this study.

2.4. Candidate Predictive Variables for the Concordance Degree of csPCa Detection between Systematic and Targeted Biopsies

The candidate predictive variables for the concordance between the systematic and targeted biopsies were age (years), serum PSA level (ng/mL), the type of biopsy (initial vs. repeat), PCa family history (no vs. yes), DRE (normal vs. abnormal), prostate volume (mL), PI-RADS v.2 score (3 vs. 4 vs. 5), the magnetic field strength of mpMRI (1.5 vs. 3 Tesla), TRUS-MRI image fusion technique (cognitive vs. software), and the type of biopsy route (transrectal vs. transperineal). If independent predictive variables were found, the clinical utility of a predictive model developed to predict csPCa in targeted biopsies could be verified.

2.5. Statistical Analysis

A statistical analysis was carried out through the harmonisation of the anonymised data sets provided by each participant centre. Quantitative variables are defined as medians and interquartile ranges (IQR: 25–75 percentile). Qualitative variables are defined as percentages. The recodification of quantitative to qualitative variables was performed to estimate the complementarity of the systematic and targeted biopsies. Odds ratios (ORs) and 95% of confidence intervals (CIs) were calculated. The concordance degree of the systematic and targeted biopsies was assessed with the Pearson chi-square test. Independent predictive variables of the concordance between the systematic and targeted biopsies were assessed in a binary logistic regression analysis. A predictive model for the ability to detect csPCa in targeted biopsies was developed from the identified independent predictors of csPCa detection in targeted biopsies. A receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to assess the discrimination ability of targeted biopsies to detect csPCa. The corresponding specificities to 100, 97.5, and 95% sensitivity threshold likelihoods were assessed, and the rates of avoided unnecessary systematic biopsies for csPCa were undetected. Significant differences were considered when p values were lower than 0.05. SPSS v.25 was used to perform this statistical analysis.

3. Results

3.1. Characteristics of the Study Cohort

The characteristics of the men with suspected PCa selected for this study are presented in Table 1. We found a median age of 68 years and a median serum PSA level of 7.3 ng/mL. The percentage of men with an abnormal DRE was 26.9%, that of repeat prostate biopsies was 33.4%, and that of PCa family history was 7.3%. The median prostate volume was 53 mL. mpMRI was performed with a 3 Tesla scan in 70.5% of cases, whereas for 29.5%

of cases, we performed a 1.5 Tesla scan. The percentage of men with a PI-RADS score of 3 was 22.9%, and the percentages of those with PI-RADS scores of 4 and 5 were 54% and 23.1%, respectively. The TRUS-MRI image fusion technique used for targeted biopsies was cognitive in 42.3% of cases, and the software technique was used in 57.7%. The route of prostate biopsy was transperineal in 60.6% of cases and transrectal in 39.4%.

PCa was detected in 1424 men (67.1%), with csPCa in 1026 (48.4%) and insignificant PCa in 398 (18.7%).

Table 1. Characteristics of men subjected to systematic and targeted biopsies.

Characteristic	Measurement
Number of men, n	2122
Median age, years (IQR)	68 (62–73)
Median serum PSA, ng/mL (IQR)	7.3 (5.2–11.0)
Abnormal DRE, n (%)	570 (26.9)
Repeat prostate biopsy, n (%)	708 (33.4%)
PCa family history, n (%)	154 (7.3)
Median prostate volume, mL (IQR)	53 (39–95)
3 Tesla mpMRI, n (%)	1493 (70.5)
PI-RADS 3, n (%)	485 (22.9)
PI-RADS 4, n (%)	1146 (54.0)
PI-RADS 5, n (%)	491 (23.1)
Software TRUS-MRI image fusion, n (%)	1224 (57.7)
Transperineal route, n (%)	1286 (60.6)
ISUP grade group of detected tumours, n (%)	
1	398 (27.9)
2	522 (36.7)
3	184 (12.9)
4	172 (12.1)
5	148 (10.4)
PCa, n (%)	1424 (67.1)
csPCa, n (%)	1026 (48.4)

PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; csPCa = clinically significant PCa; IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = prostate imaging report and data system; TRUS-MRI = transrectal ultrasound–magnetic resonance imaging; n = number; ISUP = international society of urologic pathology.

3.2. Analysis of Concordance between Systematic and Targeted Biopsies according to the Detection of csPCa

The overall concordance–discordance between the systematic and targeted biopsies reporting csPCa is presented in Table 2. Among 2122 suspected PCa cases, the concordance of the systematic and targeted biopsies was observed in 1613 (76%). In 517 cases (24.4%), both biopsies detected csPCa, whereas in 1096 cases (51.6%), csPCa was not found at all, with $p < 0.001$. Discordance between the results reported in the systematic and targeted biopsies was observed in 509 cases (24%). CsPCa was detected only in targeted biopsies in 366 cases (17.3%), whereas it was only detected in systematic biopsies in 143 cases (6.7%), $p < 0.001$.

Table 2. Analysis of overall concordance–discordance of csPCa detection rate in systematic and targeted biopsies.

Number of Men	Discordance n (%)	CsPCa in Systematic and Targeted Biopsies n (%)			
		– –	– +	+ –	++
2122	509 (24.0)	1096 (51.6)	366 (17.3)	143 (6.7)	517 (24.4)
$p < 0.001$					

Considering the 1026 cases of detected csPCa, in 517 cases (50.4%), csPCa was detected in both types of biopsies. In 366 (35.7%) cases, csPCa was detected only in targeted biopsies,

whereas in 143 (13.9%) cases, csPCa was only detected in systematic biopsies. The ISUP-GG of csPCa detected only in targeted biopsies corresponded to GG 2 in 233 cases (60.9%), GG 3 in 68 (18.6%), GG 4 in 51 (13.9%), and GG 5 in 24 (6.6%). The ISUP-GG of csPCa detected only in systematic biopsies corresponded to GG 2 in 99 cases (69.2%), GG 3 in 21 (14.7%), GG 4 in 15 (10.5), and GG 5 in 8 (5.6%). After Recoding the ISUP-GG in high-grade csPCa ($GG \geq 3$) resulted in 44 cases (30.8%) being detected only in systematic biopsies and 143 cases (39.1%) being detected only in targeted biopsies, $p = 0.129$.

3.3. Univariate and Multivariate Analyses of Candidate Predictive Variables for the Concordance Degree of csPCa in Systematic and Targeted Biopsies

The odds ratios and 95% confidence intervals of the candidate predictive variables for the concordance between the systematic and targeted biopsies are presented in Table 3. A univariate analysis showed significant associations between the results of the two types of biopsies and age (≤ 68 years), $p < 0.001$; prostate volume (≤ 53 mL), $p < 0.001$; the MRI Tesla scanner (1.5 vs. 3.0 Tesla); PI-RADS score (3 vs. 4 vs. 5), $p < 0.001$; the TRUS-MRI image fusion technique (cognitive vs. software), $p < 0.001$; and biopsy route (transrectal vs. transperineal), $p < 0.001$.

Table 3. Univariate and multivariate analyses of candidate predictive variables for the concordance between systematic and targeted biopsies in detecting csPCa.

Predictive Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Age, ref. ≤ 68 years	1.464 (1.119–1.789)	<0.001	1.480 (1.182–1.803)	<0.001
Serum PSA, ref. ≤ 7.3 ng/mL	0.972 (0.786–1.186)	0.777	0.893 (0.722–1.105)	0.299
DRE, ref. normal	1.233 (0.989–1.536)	0.066	1.087 (0.856–1.379)	0.493
Type of biopsy, ref. initial	1.112 (0.901–1.371)	0.323	1.176 (0.939–1.473)	0.159
PCa family history, ref. no	1.205 (0.833–1.744)	0.312	1.306 (0.888–1.921)	0.175
Prostate volume, ref. ≤ 53 mL	0.570 (0.465–0.698)	<0.001	0.582 (0.470–0.720)	<0.001
Type of mpMRI, ref. 1.5 Tesla	1.274 (1.017–1.596)	<0.001	1.463 (1.148–1.865)	0.002
PI-RADS category, ref. 3	1.690 (1.431–1.956)	<0.001	1.590 (1.352–1.870)	<0.001
Type of TRUS-MRI fusion technique, ref. visual	1.483 (1.206–1.823)	<0.001	1.333 (1.046–1.701)	0.020
Prostate biopsy approach, ref. transrectal	1.592 (1.288–1.968)	<0.001	1.335 (1.052–1.694)	0.018

PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = prostate imaging report and data system; CI = confidence interval; TRUS-MRI = transrectal ultrasound–MRI.

The binary logistic regression confirmed that age (ref. ≤ 68 years) presented a concordance OR of 1.480 (1.182–1.803), $p < 0.001$. Prostate volume (ref. ≤ 53 mL) presented an OR of 0.582 (0.480–0.720), $p < 0.001$. The MRI Tesla scan (ref. 1.5 Tesla) presented an OR of 1.463 (1.148–1.865), $p = 0.002$. The PI-RADS score (ref. 3) presented an OR of 1.590 (1.352–1.870), $p < 0.001$. The TRUS-MRI image fusion technique (ref. cognitive) presented an OR of 1.333 (1.046–1.701), $p = 0.020$. The biopsy route (ref. transrectal) presented an OR of 1.335 (1.052–1.694), $p = 0.018$. Age and prostate volume were clinical characteristics of suspected PCa in men for predicting concordance between systematic and targeted biopsies. The magnetic field strength of MRI and the PI-RADS score were characteristics of MRI, whereas the TRUS-MRI fusion technique and biopsy route were characteristics associated with prostate biopsy.

The discordance between the systematic and targeted biopsies, according to the findings of the csPCa clinical predictors, is presented in Table 4. We always noted an increasing trend in the rate of csPCa detected in the targeted biopsies but not in the systematic biopsies. However, a significant difference was found in terms of age and prostate volume. The rate of discordance from an age ≤ 68 years to >68 years increased from 20.6 to 27.5%, $p < 0.001$. However, from a prostate volume ≤ 53 mL to >53 mL, the discordance rate decreased from 29 to 18.9%, $p < 0.001$ (Table 4).

Table 4. Overall discordance of systematic and targeted biopsies for the detection of csPCa and its detection in systematic or targeted biopsies alone, according to the clinical characteristics of the analysed population.

According to:	Number of Men	Discordance	<i>p</i> Value	Only in TB	Only in SB	<i>p</i> Value
Age:						
≤68 years, n (%)	1087	224 (20.6)	<0.001	162 (14.9)	62 (5.7)	<0.001
>68 years, n (%)	1035	285 (27.5)		204 (19.7)	81 (7.8)	<0.001
Serum PSA:						
≤7.3 ng/mL, n (%)	1064	258 (24.2)	0.777	191 (18.0)	67 (6.3)	<0.001
>7.3 ng/mL, n (%)	1058	251 (23.7)		175 (16.5)	76 (7.2)	<0.001
DRE:						
Normal, n (%)	1552	356 (22.9)	0.062	268 (17.3)	88 (5.7)	<0.001
Abnormal, n (%)	570	153 (26.8)		98 (17.2)	55 (9.6)	<0.001
Type of biopsy:						
Initial, n (%)	1414	330 (23.3)	0.323	238 (16.8)	92 (6.5)	<0.001
Repeat, n (%)	708	179 (15.6)		128 (18.1)	51 (7.2)	<0.001
PCa family history:						
No	1968	467 (23.7)	0.328	330 (16.8)	127 (7.0)	<0.001
Yes	154	42 (27.3)		36 (23.4)	6 (3.9)	<0.001
Prostate volume:						
≤53 mL, n (%)	1064	309 (29.0)	<0.001	225 (21.1)	84 (7.3)	<0.001
>53 mL, n (%)	1058	200 (18.9)		141 (13.3)	59 (5.6)	<0.001

TB = targeted biopsy; SB = systematic biopsy; PSA = prostate-specific antigen; DRE = digital rectal examination.

An analysis of the overall discordance between the systematic and targeted biopsies and the detection of csPCa in the systematic or targeted biopsies alone, according to the characteristics of mpMRI and prostate biopsy, is presented in Table 5. The detection of csPCa in the targeted biopsies alone was always significantly higher than that in the systematic biopsies alone. The discordance between the two biopsy types increased from 21 to 25.3% regarding the use of 1.5 vs. 3 Tesla mpMRI, $p < 0.001$; from 11.5 to 31% according to a PI-RADS score of 3 vs. 5, $p < 0.001$; and from 19 to 27.2% according to the transrectal vs. transperineal route and the cognitive vs. software MRI-TRUS image fusion technique, $p < 0.001$.

Table 5. Overall discordance in csPCa detection between systematic and targeted biopsies and its detection in systematic or targeted biopsies alone according to the characteristics of mpMRI and prostate biopsy.

According to:	Number of Men	Discordance	<i>p</i> Value	Only in TB	Only in SB	<i>p</i> Value
MRI Tesla scan						
1.5 Tesla	625	131 (21.0)	0.035	84 (13.4)	47 (7.5)	<0.001
3.0 Tesla	1497	378 (25.3)		282 (18.8)	96 (6.4)	<0.001
PI-RADS score:						
PI-RADS 3, n (%)	485	56 (11.5)	<0.001	24 (4.9)	32 (6.6)	<0.001
PI-RADS 4, n (%)	1146	301 (26.3)		215 (18.8)	86 (7.5)	<0.001
PI-RADS 5, n (%)	491	152 (31.0)		127 (25.9)	25 (5.1)	<0.001
Biopsy route:						
Transrectal, n (%)	836	159 (19.0)	<0.001	85 (10.2)	74 (8.9)	<0.001
Transperineal, n (%)	1286	350 (27.2)		281 (21.9)	69 (5.4)	<0.001
MRI-TRUS fusion technique:						
Cognitive, n (%)	836	159 (19.0)	<0.001	103 (11.5)	76 (8.5)	<0.001
Software, n (%)	1286	350 (27.0)		263 (21.5)	67 (5.5)	<0.001

TB = targeted biopsy; SB = systematic biopsy; PI-RADS = prostate imaging report and data system.

3.4. Development of a Predictive Model for the Discrimination Ability of Targeted Biopsies to Detect csPCa

Due to the findings of predictive variables for the detection of csPCa in targeted biopsies, a predictive model including age, prostate volume, the type of MRI, PI-RADS, the type of TRUS-MRI image fusion technique, and the type of biopsy route was developed, and probabilities of csPCa detection in targeted biopsies were generated. Figure 1 represents the ROC curve of the developed model, showing the discrimination ability of targeted biopsies for csPCa.

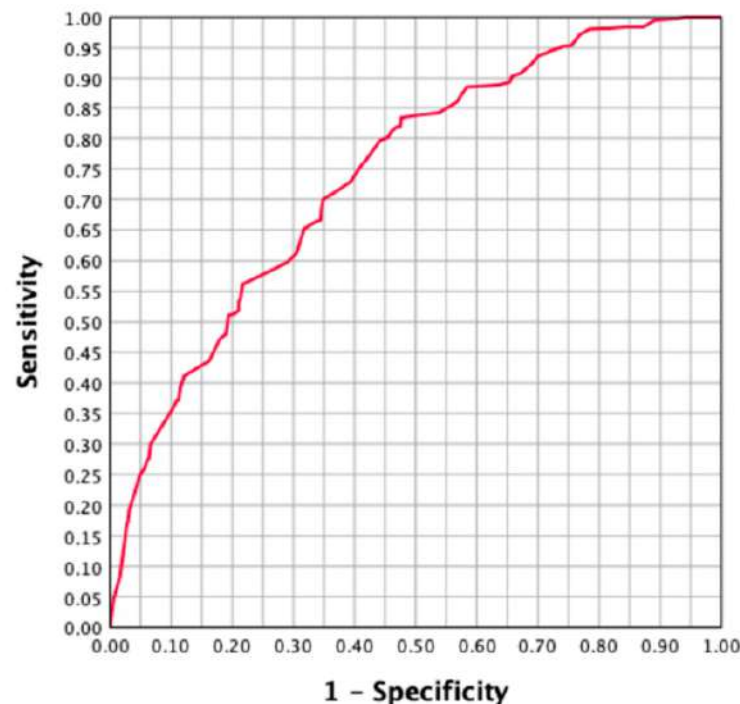


Figure 1. ROC curve showing the csPCa discrimination ability of targeted biopsies.

The AUC of the ROC curve was 0.741 (95% CI 0.721–0.762). After assessing the thresholds with 100, 97.5, and 95% sensitivity thresholds for csPCa detection, the corresponding specificities were 5.8, 22.5, and 27.4%. Using these parameters, we observed that 11 systematic biopsies were avoided without missing csPCa at 100% sensitivity. In total, 312 systematic biopsies were avoided (14.7%) and 25 csPCa cases were undetected (2.4%) in the targeted biopsies at the 97.5% sensitivity threshold. At 95% sensitivity, 368 systematic biopsies were avoided (18.3%) and 47 csPCa cases (4.6%) were undetected (Table 6).

Table 6. Specificities corresponding to the 100, 97.5, and 95% sensitivity thresholds for csPCa detection in targeted biopsies and potential reductions in systematic biopsies and undetected csPCa.

Threshold	Sensitivity (%)	Specificity (%)	Avoided SB (%)	Undetected csPCa (%)
0.038	100	5.8	11 (0.5)	0
0.061	97.5	22.5	312 (14.7)	25 (2.4)
0.071	95.0	27.4	388 (18.3)	47 (4.6)

4. Discussion

The present study confirms that targeted biopsies are more sensitive than systematic biopsies for detecting csPCa. However, 6.7% of csPCa cases were detected only in systematic

biopsies, whereas 17.2% of csPCa cases were detected only in targeted biopsies. Among 1026 csPCa cases, 13.9% were identified only in systematic biopsies, 35.7% were detected only in targeted biopsies, and 50.4% were identified in both. CsPCa cases detected only in targeted biopsies showed an increasing trend of higher GG, but this was not significant regarding those observed in systematic biopsies. These results are in line with other results previously reported, which supports the need for systematic biopsies [20–27].

The detection of csPCa in systematic biopsies alone is mainly due to non-visible MRI lesions containing this type of tumour [16]. This is the reason for the 9.2% (95% CI 6.9–11.9%) csPCa detection rate in systematic biopsies carried out in men with negative mpMRI (PI-RADS < 3) [4]. Discordance between systematic and targeted biopsies in csPCa detection is defined as the amount of csPCa detected only in one type of biopsy. The reasons for detecting csPCa in only systematic biopsies include the fact that the multifocality of csPCa is not always visible on mpMRI, the fact that there are errors associated with lesion targeting, and the fact that MRI lesions can be missed by radiologists [16].

In 2009, Ahmed et al. suggested that men undergoing systematic biopsy are at risk of the underdiagnosis of csPCa and overdiagnosis of clinically insignificant PCa [28]. In 2017, PROMIS was the trial first providing level-one evidence on the underdiagnosis of csPCa in systematic biopsies. In this trial, a prospective, multicentre, and paired cohort of 576 biopsy-naïve men with suspected PCa was subjected to transperineal 12-core TRUS-guided systematic biopsy; targeted biopsies of the visible lesions on MRI were performed, and prostate mapping biopsy performed every 5 mm served as the reference test. The 48% (95% CI 42–55%) csPCa sensitivity of systematic biopsies increased to 93% (95% CI 88–96%) in targeted biopsies [29]. The PRECISION study was a multicentre and randomised trial, also reported in 2017, including 500 biopsy-naïve men with suspected PCa referred for prostate biopsy. CsPCa was detected in 38% of 245 men who finally underwent MRI and TRUS-guided targeted biopsies, compared to 26% of 235 men who underwent TRUS-guided systematic biopsy. Biopsies were performed evenly via the transrectal or transperineal route. The PRECISION trial generated level-one evidence supporting the notion that targeted biopsies show increased sensitivity compared to systematic biopsies [30]. In 2018, the MRI-First study, a prospective, multicentre, and paired trial, enrolled 251 men with suspected PCa, of whom 53 with PI-RADS < 3 underwent systematic biopsy alone, whereas 198 men with PI-RADS ≥ 3 underwent systematic and targeted biopsies. CsPCa was detected in 29.9% (95% CI 24.3–36%) of systematic biopsies and in 32.3% (95% CI 26.5–38.4%) of targeted biopsies. The percentage of csPCa detected in systematic biopsies alone was 5.2% (95% CI 2.8–8.7%), whereas it was only detected in 7.6% (95% CI 4.6–11.6%) of targeted biopsies, with this difference not being significant. The authors of the MRI-First trial concluded that systematic and targeted biopsies had similar sensitivities for csPCa detection [26]. In 2019, the PAIREDCAP trial included 248 biopsy-naïve men with MRI-visible lesions who underwent systematic biopsy followed by cognitive or software TRUS-MRI fusion targeted biopsy. The csPCa detection rate was 62.1% in systematic biopsies, 46.8% in cognitive TRUS-MRI fusion targeted biopsies, and 60.1% in software TRUS-MRI fusion targeted biopsies, whereas 70% of csPCa cases were detected with all these methods. The authors concluded that both systematic and targeted biopsies are required since csPCa was undetected in between 11.5% and 33.3% of cases using any method alone [31].

Brisbane et al. observed that, in 2048 men with suspected PCa and PI-RADS ≥ 3, from two US institutions, 90% (95% CI 89–91%) of the csPCa cases detected were located within a radius of 10 mm from the nearest lesion. In total, 65% (95% CI 63–67%) of csPCa cases were detected within the region of interest identified on mpMRI, whereas 26% (95% CI 24–27%) of csPCa cases were detected in the perilesional area [32]. Recently, Williams et al. retrospectively analysed 41 csPCa cases among 2103 men (1.9%) with suspected PCa, in which csPCa was missed in targeted biopsies and detected in systematic biopsies. The authors reported that 21 csPCa cases (51.2%) were missed in targeted biopsies due to errors in lesion targeting, with 17 (40.5%) being missed due to MRI-invisible lesions and 3 (7%) being overlooked due to MRI lesions missed by the radiologist. They also compared the

characteristics of 425 men with suspected PCa in whom csPCa was detected in targeted biopsies and those of 45 men in whom csPCa was missed in targeted biopsies. They reported lower serum PSA levels, higher prostate volumes, lower numbers of core-targeted biopsies, and lower PI-RADS scores in men with undetected csPCa in targeted biopsies, although the multivariate analysis only found an association of lower PI-RADS scores with undetected csPCa in the targeted biopsies [33].

Our study reported predictive variables for the concordance between systematic and targeted biopsies in csPCa detection. We observed that older age and a larger prostate volume increased the discordance between systematic and targeted biopsies, as also observed by Williams et al. [34]. Regarding the characteristics of mpMRI, we reported an increased discordance when the magnetic field strength was 3 Tesla compared with 1.5 Tesla, with this mainly being due to an increased number of csPCa cases detected only in targeted biopsies. Such data have not been reported previously, beyond the finding that csPCa detection is not increased using 3 Tesla mpMRI [28]; however, more lesions with csPCa may be detected when a higher magnetic field strength is used. As reported by Williams et al. [34], we also observed how the complementarity between systematic and targeted biopsies increased with the PI-RADS score. We observed that the detection rate of csPCa in targeted biopsies alone increased from 4.9% in men with PI-RADS 3 to 18.8% in those with PI-RADS 4 and to 25.9% in those with PI-RADS 5. However, the rate of csPCa detected in systematic biopsies alone remained stable (5.1–7.5%) from PI-RADS 3 to 5. The reason for this finding may be related to the increased visibility of csPCa detected when the PI-RADS score increases. The PAIREDCAP trial also supports our finding of the higher csPCa sensitivity of software TRUS-MRI image fusion compared to cognitive TRUS-MRI image fusion [24]. Finally, we observed that 10.2% of csPCa cases were only detected in targeted biopsies when the transrectal route was used, while 21.9% were only detected when the transperineal route was used. This percentage of csPCa cases detected only in systematic biopsies decreased from 8.9 to 5.4%. Such data have not been reported previously, beyond the overall increased sensitivity reported for the transperineal route, which is also influenced by the location of the lesions [35].

Because independent predictive factors of the csPCa discrimination ability of targeted biopsies were found (age, prostate volume, the type of MRI, PI-RADS, the type of TRUS-MRI image fusion technique, and the type of biopsy route), a model for the prediction of csPCa in targeted biopsies was developed. The AUC of the model was only 0.741 (95% CI 0.721–0.762); however, the ROC curve presented good performance in the high-sensitivity zone, which allowed for 11 systematic biopsies (0.5%) to be avoided without missing csPCa at 100% sensitivity, whereas 14.7% of systematic biopsies were avoided, missing 2.4% of csPCa at 97.5% sensitivity, and 18.3% systematic biopsies were avoided, missing 4.6% of csPCa at 95% sensitivity. No predictive model for avoiding systematic biopsies in men with suspected PCa and PI-RADS ≥ 3 has been reported previously. We summarise that, currently, targeted biopsies are more sensitive than systematic biopsies for detecting csPCa. However, systematic biopsies are still needed to detect all csPCa cases. The newly developed predictive model could increase the avoidance rate from a small number of systematic biopsies without missing csPCa to up to 18.3% of systematic biopsies missing less than 5% of csPCa.

The main limitation of our study is the definition of csPCa in prostate biopsies, which may not represent the true pathology of the entire prostate gland. The recent recruitment of selected men prevented knowing the evolution of detected tumours. This study is a post hoc analysis of a cohort of men who underwent systematic and targeted biopsies in a prospective trial designed to validate the Barcelona risk calculations in Catalonia. The prediction of the csPCa discrimination ability of targeted biopsies could be improved through other independent predictive variables not included in our study (e.g., the location and size of visible lesions).

Improvements in MRI, based on future increases in magnetic field strength, could enhance the visibility of csPCa. The combination of MRI with Ga⁶⁸PSMA-PET (Ga⁶⁸PSMA-

PET-MRI) is promising. The metabolic activity detected in MRI-visible lesions or in areas without visible lesions can improve the effectiveness of targeted biopsies. The specificity of MRI could also be increased by differentiating visible lesions with no or low metabolic activity [35,36]. Additionally, future improvements in TRUS-MRI fusion images and robotic targeted biopsies will also help to avoid systematic biopsies and decrease the current over-detection of insignificant PCa [8,9].

5. Conclusions

Targeted biopsies currently remain more sensitive than systematic biopsies for detecting csPCa. However, 13.9% of csPCa cases were only detected in systematic biopsies, which represented 6.7% of the overall csPCa detection rate. The disagreement between the systematic and targeted biopsies for csPCa detection was multifactorial, with age, prostate volume, MRI magnetic field strength, PI-RADS score, TRUS-MRI image fusion technique, and biopsy route being independent predictive variables. The predictive model developed for csPCa detection in targeted biopsies was able to increase the omission rate of systematic biopsies from 0.5% without missing csPCa to 18.3% missing 4.6% of csPCa cases.

Author Contributions: Conceptualisation, J.M., P.S. and J.M.A.; methodology, J.M.; software, J.M., P.S. and J.M.A.; formal analysis, J.M.; resources, J.M., P.S. and J.M.A.; data curation, J.M., N.P. (Natàlia Picola), N.P. (Nahuel Paesano), J.M.-R., X.R.-P., M.V.M.-R., A.C., G.G.-d.M., I.A., P.S. and J.M.A.; writing—original draft preparation, J.M.; writing—review and editing, J.M., P.S. and J.M.A.; supervision, J.M.; project administration, J.M.; funding acquisition, J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Instituto de Salut Carlos III (SP) and the European Union, grant number PI20/01666.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Vall Hebron Hospital and Research Institute (protocol PRAG02/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We acknowledge M.J. Ribal and Lorente from the Catalan Society of Urology for their support in organising this multicentre study group.

Conflicts of Interest: The authors declare no conflict of interest. The funder had no role in the design of the study; in the collection, analyses, or interpretation of the data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)] [[PubMed](#)]
2. Fränlund, M.; Månsson, M.; Godtman, R.A.; Aus, G.; Holmberg, E.; Kollberg, K.S.; Lodding, P.; Pihl, C.G.; Stranne, J.; Lilja, H.; et al. Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial. *J. Urol.* **2022**, *208*, 292–300. [[CrossRef](#)] [[PubMed](#)]
3. Van Poppel, H.; Albrecht, T.; Basu, P.; Hogenhout, R.; Collen, S.; Roobol, M. Serum PSA-based early detection of prostate cancer in Europe and globally: Past, present and future. *Nat. Rev. Urol.* **2022**, *19*, 562–572. [[CrossRef](#)] [[PubMed](#)]
4. Wagaskar, V.G.; Levy, M.; Ratnani, P.; Moody, K.; Garcia, M.; Pedraza, A.M.; Parekh, S.; Pandav, K.; Shukla, B.; Prasad, S.; et al. Clinical Utility of Negative Multiparametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer and Clinically Significant Prostate Cancer. *Eur. Urol. Open Sci.* **2021**, *28*, 9–16. [[CrossRef](#)] [[PubMed](#)]
5. Kasivisvanathan, V.; Stabile, A.; Neves, J.B.; Giganti, F.; Valerio, M.; Shanmugabavan, Y.; Clement, K.D.; Sarkar, D.; Philippou, Y.; Thurtell, D.; et al. Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis. *Eur. Urol.* **2019**, *76*, 284–303. [[CrossRef](#)]

6. Drost, F.J.H.; Osses, D.; Nieboer, D.; Bangma, C.H.; Steyberg, E.W.; Roobol, M.J.; Shoots, I.G. Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. *Eur. Urol.* **2020**, *77*, 78–94. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Morote, J.; Celma, A.; Planas, J. Re: Frank-Jan H. Drost, Daniel Osses, Daan Nieboer; et al. Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. *Eur. Urol.* **2020**; *77*:78–94: Are Targeted Prostate Biopsies Enough in Men with a Previous Negative Biopsy? *Eur. Urol.* **2020**, *77*, 138–139. [\[CrossRef\]](#)
8. Hugosson, J.; Månsson, M.; Wallström, J.; Axcróna, U.; Carlsson, S.V.; Egevad, L.; Geterud, K.; Khatami, A.; Kohestani, K.; Pihl, C.G.; et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. *N. Engl. J. Med.* **2022**, *387*, 2126–2137. [\[CrossRef\]](#)
9. Morote, J. Re: Jonas Hugosson, Marianne Månsson, Jona Wallström; et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. *N. Engl. J. Med.* **2022**, *387*:2126–37. *Eur. Urol. Oncol.* **2023**, *6*, 234. [\[CrossRef\]](#)
10. Morote, J.; Celma, A.; Roche, S.; de Torres, I.M.; Mast, R.; Semedey, M.E.; Regis, L.; Planas, J. Who Benefits from Multiparametric Magnetic Resonance Imaging After Suspicion of Prostate Cancer. *Eur. Urol. Oncol.* **2019**, *2*, 664–669. [\[CrossRef\]](#)
11. Morote, J.; Triquell, M.; Campistol, M.; Abascal, J.M.; Servian, P.; Trilla, E. Stratifying the initial prostate cancer suspicion to avoid magnetic resonance exams by sequencing men according to serum prostate-specific antigen, digital rectal examination and the prostate-specific antigen density based on digital rectal prostate volume category. *BJUI Compass* **2023**, *4*, 266–268. [\[PubMed\]](#)
12. Loeb, S.; Vellekoop, A.; Ahmed, H.U.; Catto, J.; Emberton, M.; Nam, R.; Rosario, D.J.; Scattoni, V.; Lotan, Y. Systematic review of complications of prostate biopsy. *Eur. Urol.* **2013**, *64*, 876–892. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Bennett, H.Y.; Roberts, M.J.; Doi, S.A.; Gardiner, R.A. The global burden of major infectious complications following prostate biopsy. *Epidemiol. Infect.* **2016**, *144*, 1784–1791. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Borghesi, M.; Ahmed, H.; Nam, R.; Schaeffer, E.; Schiavina, R.; Taneja, S.; Weidner, W.; Loeb, S. Complications After Systematic, and Image-guided Prostate Biopsy. *Eur. Urol.* **2017**, *71*, 353–365. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Pepeljonovic, L.; Tan, G.H.; Huang, S.; Mann, S.; Frydenberg, M.; Moon, D.; Haneghi, U.; Landau, A.; Snow, R.; Grummet, J. Zero hospital admissions for infection after 577 transperineal prostate biopsies using single-dose cephazolin prophylaxis. *World J. Urol.* **2017**, *35*, 1199–1203. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Connor, M.J.; Gorin, M.A.; Eldred-Evans, D.; Bass, E.J.; Desai, A.; Dudderidge, T.; Winkler, M.; Ahmed, H.U. Landmarks in the evolution of prostate biopsy. *Nat. Rev. Urol.* **2023**, *20*, 241–258. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Morote, J.; Borque-Fernando, Á.; Triquell, M.; Campistol, M.; Celma, A.; Regis, L.; Abascal, J.M.; Servian, P.; Planas, J.; Mendez, O.; et al. A Clinically Significant Prostate Cancer Predictive Model Using Digital Rectal Examination Prostate Volume Category to Stratify Initial Prostate Cancer Suspicion and Reduce Magnetic Resonance Imaging Demand. *Cancers* **2022**, *14*, 5100. [\[CrossRef\]](#)
18. Morote, J.; Borque-Fernando, A.; Triquell, M.; Celma, A.; Regis, L.; Escobar, M.; Mast, R.; de Torres, I.M.; Semidey, M.E.; Abascal, J.M.; et al. The Barcelona Predictive Model of Clinically Significant Prostate Cancer. *Cancers* **2022**, *14*, 1589. [\[CrossRef\]](#)
19. Epstein, J.I.; Egevad, L.; Amin, M.B.; Delahunt, B.; Srigley, J.R.; Humphrey, P.A.; Grading, C. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am. J. Surg. Pathol.* **2016**, *40*, 244–252. [\[CrossRef\]](#)
20. Kasivisvanathan, V.; Rannikko, A.S.; Borghi, M.; Panebianco, V.; Mynderse, L.A.; Vaarala, M.H.; Briganti, A.; Budäus, L.; Hellawell, G.; Hindley, R.G.; et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N. Engl. J. Med.* **2018**, *378*, 1767–1777. [\[CrossRef\]](#)
21. Rouvière, O.; Puech, P.; Renard-Penna, R.; Claudon, M.; Roy, C.; Mège-Lechevallier, F.; Decaussin-Petrucci, M.; Dubreuil-Chambardel, M.; Magaud, L.; Remontet, L.; et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): A prospective, multicentre, paired diagnostic study. *Lancet Oncol.* **2018**, *20*, 100–109. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Elkhoury, F.F.; Felker, E.R.; Kwan, L.; Sisk, A.E.; Delfin, M.; Natarajan, S.; Marks, L.S. Comparison of Targeted vs. Systematic Prostate Biopsy in Men Who Are Biopsy Naïve: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. *JAMA Surg.* **2019**, *154*, 811–818. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Fourcade, A.; Payrard, C.; Tissot, V.; Perrouin-Verbe, M.A.; Demany, N.; Serey-Effeil, S.; Callerot, P.; Coquet, J.B.; Doucet, L.; Deruelle, C.; et al. The combination of targeted and systematic prostate biopsies is the best protocol for the detection of clinically significant prostate cancer. *Scand. J. Urol.* **2018**, *52*, 174–179. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Celma, A.; López, R.; Roche, S.; Planas, J.; Regis, L.; Placer, J.; Borque, A.; Esteban, L.M.; de Torres, I.; Morote, J. Are targeted prostate biopsies ready to replace systematic prostate biopsies. *Actas Urol. Esp.* **2019**, *43*, 573–578. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Borghesi, M.; Bianchi, L.; Barbaresi, U.; Vagnoni, V.; Corcioni, B.; Gaudiano, C.; Fiorentino, M.; Giunchi, F.; Chessa, F.; Garofalo, M.; et al. Diagnostic performance of MRI/TRUS fusion-guided biopsies vs. systematic prostate biopsies in biopsy-naïve, previous negative biopsy patients and men undergoing active surveillance. *Minerva Urol. Nephrol.* **2021**, *73*, 357–366. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Eklund, M.; Jäderling, F.; Discacciati, A.; Bergman, M.; Annerstedt, M.; Aly, M.; Glacsgen, A.; Carlsson, S.; Grönberg, H.; Nordström, T.; et al. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. *N. Engl. J. Med.* **2021**, *385*, 908–920. [\[CrossRef\]](#) [\[PubMed\]](#)

27. Zhang, L.L.; Li, W.C.; Xu, Z.; Jiang, N.; Zang, S.M.; Xu, L.W.; Huang, W.B.; Wang, F.; Sun, H.B. ^{68}Ga -PSMA PET/CT targeted biopsy for the diagnosis of clinically significant prostate cancer compared with transrectal ultrasound guided biopsy: A prospective randomized single-centre study. *Eur. J. Nucl. Med. Mol. Imaging* **2021**, *48*, 483–492. [\[CrossRef\]](#)
28. Ahmed, H.U.; Kirkham, A.; Arya, M.; Illing, R.; Freeman, A.; Allen, C.; Emberton, M. Is it time to consider a role for MRI before prostate biopsy? *Nat. Rev. Clin. Oncol.* **2009**, *6*, 197–206. [\[CrossRef\]](#)
29. Ahmed, H.U.; El-Shater Bosaily, A.; Brown, L.C.; Gabe, R.; Kaplan, R.; Parmar, M.K.; Collaco-Moraes, Y.; Ward, K.; Hindley, R.G.; Freeman, A.; et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. *Lancet* **2017**, *389*, 815–822. [\[CrossRef\]](#)
30. Kato, D.; Ozawa, K.; Takeuchi, S.; Kawase, M.; Kawase, K.; Nakai, C.; Takai, M.; Iinuma, K.; Nakane, K.; Kato, H.; et al. The Utility of Combined Target and Systematic Prostate Biopsies in the Diagnosis of Clinically Significant Prostate Cancer Using Prostate Imaging Reporting and Data System Version 2 Based on Biparametric Magnetic Resonance Imaging. *Curr. Oncol.* **2021**, *28*, 1294–1301. [\[CrossRef\]](#)
31. Günzel, K.; Magheli, A.; Busch, J.; Baco, E.; Cash, H.; Heinrich, S.; Edler, D.; Schostak, M.; Borgmann, H.; Schlegel, J.; et al. Evaluation of systematic prostate biopsies when performing transperineal MRI/TRUS fusion biopsy with needle tracking—What is the additional value. *Int. Urol. Nephrol.* **2022**, *54*, 2477–2483. [\[CrossRef\]](#)
32. Brisbane, W.G.; Priester, A.M.; Ballon, J.; Kwan, L.; Delfin, M.K.; Felker, E.R.; Sisk, A.E.; Hu, J.C.; Marks, L.S. Targeted Prostate Biopsy: Umbra, Penumbra, and Value of Perilesional Sampling. *Eur. Urol.* **2022**, *82*, 303–310. [\[CrossRef\]](#)
33. Williams, C.; Ahdoot, M.; Daneshvar, M.A.; Hague, C.; Wilbur, A.R.; Gomella, P.T.; Shih, J.; Khondakar, N.; Yerram, N.; Mehralivand, S.; et al. Why Does Magnetic Resonance Imaging-Targeted Biopsy Miss Clinically Significant Cancer. *J. Urol.* **2022**, *207*, 95–107. [\[CrossRef\]](#)
34. Zattoni, F.; Marra, G.; Kasivisvanathan, V.; Grummet, J.; Nandurkar, R.; Ploussard, G.; Olivier, J.; Chiu, P.K.; Valerio, M.; Contero, P.; et al. The Detection of Prostate Cancer with Magnetic Resonance Imaging-Targeted Prostate Biopsies is Superior with the Transperineal vs. the Transrectal Approach. A European Association of Urology-Young Academic Urologists Prostate Cancer Working Group Multi-Institutional Study. *J. Urol.* **2022**, *208*, 830–837.
35. Chen, M.; Zhang, Q.; Zhang, C.; Zhao, X.; Marra, G.; Gao, J.; Lv, X.; Zhang, B.; Fu, Y.; Wang, F.; et al. Combination of ^{68}Ga -PSMA PET/CT and Multiparametric MRI Improves the Detection of Clinically Significant Prostate Cancer: A Lesion-by-Lesion Analysis. *J. Nucl. Med.* **2019**, *60*, 944–949. [\[CrossRef\]](#)
36. Chen, M.; Qiu, X.; Zhang, Q.; Zhang, C.; Zhou, Y.H.; Zhao, X.; Fu, Y.; Wang, F.; Guo, H. PSMA uptake on ^{68}Ga -PSMA-11-PET/CT positively correlates with prostate cancer aggressiveness. *Q. J. Nucl. Med. Mol. Imaging* **2022**, *66*, 67–73. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

5.3. PUBLICACIÓN 3

Título: Efficacy of Prostate Biopsies via Transperineal and Transrectal Routes for Significant Prostate Cancer Detection: A Multicenter Paired–Matched Study

Revista: Diagnostics

Año de publicación: 2025

Volumen: 15

Páginas: 288

DOI: <https://doi.org/10.3390/diagnostics15030288>

Autores: Nahuel Paesano, Natàlia Picola, Jesús Muñoz-Rodríguez, Xavier Ruiz-Plazas, Marta V. Muñoz-Rivero, Ana Celma, Gemma García-de Manuel, Berta Miró, Pol Servian, José M. Abascal, Enrique Trilla and Juan Morote.

Factor de impacto (JCR): 3.4

Cuartil (JCR): 1 (Área de Medicina - general e interna)

Article

Efficacy of Prostate Biopsies via Transperineal and Transrectal Routes for Significant Prostate Cancer Detection: A Multicenter Paired–Matched Study

Nahuel Paesano ^{1,2,*}, Natàlia Picola ³, Jesús Muñoz-Rodríguez ⁴, Xavier Ruiz-Plazas ⁵,
Marta V. Muñoz-Rivero ⁶, Ana Celma ⁷, Gemma García-de Manuel ⁸, Berta Miró ⁹, Pol Servian ¹⁰,
José M. Abascal ^{11,12}, Enrique Trilla ^{2,7,†} and Juan Morote ^{2,7,†}

¹ Clínica Creu Blanca, 08018 Barcelona, Spain

² Department of Surgery, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain; enrique.trilla@vallhebron.cat (E.T.); juan.morote@uab.cat (J.M.)

³ Department of Urology, Hospital Universitari de Bellvitge, 08907 Hospitalet de Llobregat, Spain; npicola.bellvitge@gencat.cat

⁴ Department of Urology, Hospital Universitari Parc Taulí, 08208 Sabadell, Spain; jmunoz@tauli.cat

⁵ Department of Urology, Hospital Universitari Joan XXIII, 43005 Tarragona, Spain; xruiz.tarragona.ics@gencat.cat

⁶ Department of Urology, Hospital Universitari Arnau de Vilanova, 25198 Lleida, Spain; mvmunoz.lleida.ics@gencat.cat

⁷ Department of Urology, Hospital Univeritari Vall d'Hebron, 08035 Barcelona, Spain; ana.celma@vallhebron.cat

⁸ Department of Urology, Hospital Universitari Josep Trueta, 17007 Girona, Spain; gemmagarcia.girona.ics@gencat.cat

⁹ Statistic Unit, Vall d'Hebron Research Institute, 08035 Barcelona, Spain; berta.miro@vhir.org

¹⁰ Department of Urology, Hospital Univeritari Germans Trias i Pujol, 08916 Badalona, Spain; pservian.germanstrias@gencat.cat

¹¹ Department of Urology, Parc de Salut Mar, 08003 Barcelona, Spain; jabascal@psmar.cat

¹² Department of Medicine and Health Sciences, Universitat Pompeu Fabra, 08002 Barcelona, Spain

* Correspondence: npaesano@gmail.com; Tel.: +34-691-127-234

† These authors contributed equally to this work.



Academic Editor: Francesca Senguedolce

Received: 1 January 2025

Revised: 16 January 2025

Accepted: 23 January 2025

Published: 26 January 2025

Citation: Paesano, N.; Picola, N.; Muñoz-Rodríguez, J.; Ruiz-Plazas, X.; Muñoz-Rivero, M.V.; Celma, A.; García-de Manuel, G.; Miró, B.; Servian, P.; Abascal, J.M.; et al. Efficacy of Prostate Biopsies via Transperineal and Transrectal Routes for Significant Prostate Cancer Detection: A Multicenter Paired–Matched Study. *Diagnostics* **2025**, *15*, 288. <https://doi.org/10.3390/diagnostics15030288>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Background: A transperineal approach to prostate biopsy is now recommended to reduce the risk of infectious complications associated with the transrectal route. Our aim is to compare the efficacy of transrectal- and transperineal-guided biopsies involving the magnetic resonance imaging (MRI) of index lesions in detecting significant prostate cancer (sPCa), and to evaluate the role of systematic biopsies. **Methods:** In a prospective and multicenter trial conducted in an opportunistic early detection program for sPCa in Catalonia (Spain), between 2021 and 2023, 4029 men suspected of having PCa underwent multiparametric MRI followed by guided and systematic biopsies. From this cohort, we retrospectively selected 1376 men with reports of the size and localization of their index lesions. A matched group of 325 pairs of men subjected to transrectal and transperineal biopsy were chosen to account for confounding variables. We compared sPCa detection rates determined via index lesions and systematic biopsies, as well as by lesion localization. **Results:** Transperineal and transrectal biopsies detected sPCa in 49.5% vs. 40.6% overall ($p = 0.027$), 44.6% vs. 30.8% from index lesions ($p = 0.001$), and 24.3% vs. 35.1% from systematic biopsies ($p = 0.003$). sPCa detection rates were higher in transperineal biopsies across all index lesion localizations, with significant increases in the anterior zone (47.8% vs. 20.8% at the mid-base, $p = 0.039$, and 52.9% vs. 24.2% at the apex, $p = 0.024$) and central zone (33.3% vs. 5.9%, $p = 0.003$). With regards to sPCa detected only in systematic biopsies, 10.5% of cases were detected in transrectal biopsies and 4.9% of cases were detected in transperineal biopsies ($p = 0.012$). **Conclusions:** Targeted biopsies conducted via the transperineal route showed higher sPCa detection rates than transrectal biopsies, particularly for anterior and apical lesions, with systematic biopsies showing reduced utility.

Keywords: prostate biopsy; magnetic resonance imaging; target biopsy; transperineal; transrectal; prostate cancer

1. Introduction

Prostate cancer (PCa) is the second leading cause of mortality among men [1]. The introduction of multiparametric magnetic resonance imaging (MRI) has significantly improved early PCa detection, especially significant PCa (sPCa), thereby reducing morbidity and mortality through timely intervention [2]. Confirming the diagnosis of PCa typically involves a prostate biopsy, with techniques such as MRI-ultrasound (MRI-US) fusion-guided biopsy being employed to reduce false negatives [3]. However, the widespread global use of the transrectal approach presents considerable risks, including severe complications such as prostatitis, sepsis, and rectal bleeding [4]. In this scenario, Transperineal Prostate Biopsy (TPB) has emerged as an alternative to overcome some of the limitations of Transrectal Prostate Biopsy (TRB) that may increase the safety profile of the prostate biopsy procedure [5]. Concerns regarding infection risks and the prevalence of multidrug-resistant bacterial strains have led the European Association of Urology (EAU) to recommend a shift towards the transperineal route [6]. Reports indicate sepsis rates as low as zero with the transperineal approach [7], leading international groups to advocate for discontinuing the use of TRB as soon as possible [8]. However, a randomized trial conducted in the U.S., involving men undergoing either transrectal or transperineal prostate biopsy under local anesthesia, found complication rates of 2.6% and 2.7%, respectively. Importantly, no participants developed sepsis in either group [9]. The transperineal approach offers benefits, particularly in terms of anterior and apical sampling, whereas the far field suffers from degraded TRB resolution, making visualization challenging [10]. A study analyzing a modified transrectal-guided sextant biopsy, including anteriorly directed cores at the prostate apex, revealed the identification of 17% of tumors in the anterior and apical zones [11]. This critical consideration is currently being evaluated in the ongoing TRANSLATE trial, which randomly selects men suspected of having PCa to undergo MRI-targeted and systematic TRUS-guided biopsy via transrectal or transperineal routes, with the endpoint of diagnosing sPCa [12]. The targeted biopsy of index lesions, areas of the highest oncological suspicion, has proven to be highly effective, being capable of identifying more than 95% of sPCas. This highlights the importance of focusing evaluations on these critical areas [13]. In the era of MRI-targeted biopsy, controversies remain regarding the effectiveness of TPB and TRB. However, only a few studies have assessed the rates of detection of PCa and sPCa between these two approaches.

We hypothesize that the transperineal route for prostate biopsies is more effective than the transrectal route in targeting index lesions for sPCa detection in men suspected of having PCa. Our first objective is to analyze the efficacy of guided biopsies of the index lesion for detecting sPCa in a matched-paired group to avoid the influence of confounding variables. Secondly, we aim to compare the additional role of systematic biopsies in detecting sPCa according to the biopsy route. Finally, we seek to determine if specific localizations of index lesions benefit from either the transrectal or transperineal biopsy route.

2. Materials and Methods

2.1. Design, Setting, and Participants

This is a retrospective analysis of a prospective, multicenter trial conducted as part of the sPCa opportunistic screening program in Catalonia (Spain), between 2021 and 2023, in ten participating centers. The study involved 4029 men with serum prostate-specific

antigen (PSA) levels higher than 3.0 ng/mL and/or a suspicious digital rectal examination (DRE), who underwent multiparametric magnetic resonance imaging (mpMRI), reported using the Prostate Imaging Reporting and Data System v. 2.1, followed by two-to-four-core-guided biopsies and/or twelve-core systematic biopsies. Exclusion criteria were applied in cases where data were unavailable regarding pathology in the index lesion and systematic biopsies, age (years), serum PSA levels (ng/mL), DRE (suspicious vs. normal), type of biopsy (initial vs. repeated), family history of PCa (no vs. yes), prostate volume (mL), Tesla scanner strength (1.5 vs. 3.0), PI-RADS (2–5), size of the index lesion (mm), index lesion location (posterior vs. anterior, and mid-base vs. apex), and type of fusion (cognitive vs. software-based). From this cohort, 1376 men were selected after index lesion size and localization were reported as well after the pathology of index lesions and that of systematic biopsies were separately determined. A 1:1 matched group of 325 pairs of men subjected to transrectal and transperineal biopsy was finally selected to account for confounding variables. The patient selection strategy is represented in Figure 1. The study received approval from the review board of the Vall d’Hebron Hospital coordinator center (PRAG-02/2021). All study participants signed written consent forms.

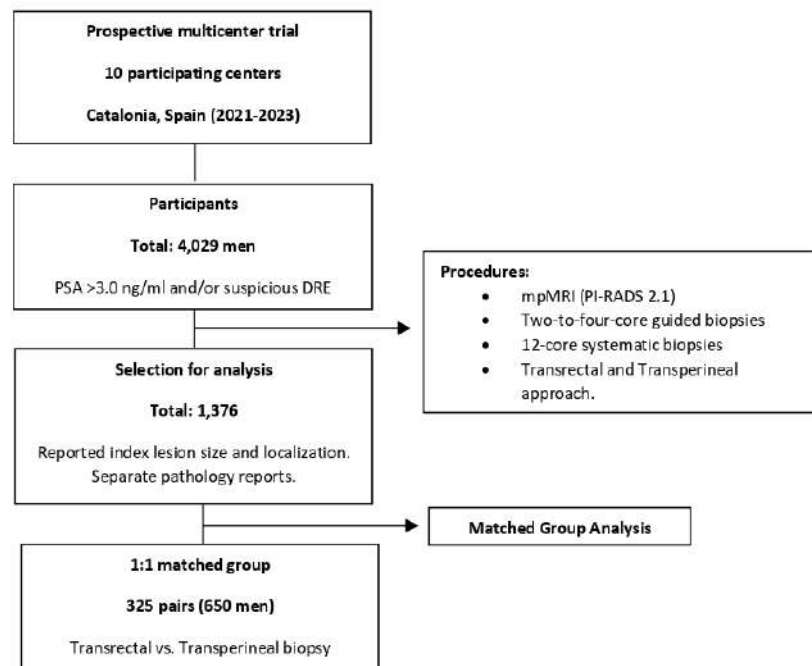


Figure 1. Flowchart of the patient selection strategy.

2.2. PCa Diagnostic Approach

Men suspected of having PCa were initially selected based on the recommendation of urologists at the primary health setting after tests showed serum prostate-specific antigen (PSA) levels higher than 3.0 ng/mL and/or a suspicious DRE. The men were then referred to the nearest participant centers. The MRI systems had magnetic field strengths of 1.5 Tesla in four centers and 3.0 Tesla in six centers, where an expert radiologist reported findings using PI-RADS v2.1 [14]. For all prostate biopsies, MRI-TRUS image fusion was performed, utilizing cognitive techniques and software techniques in five centers. Lesions with the highest PI-RADS scores and of the largest sizes were defined as MRI index lesions [13]. Biopsies were carried out transrectally in four centers and transperineally in six centers.

Each suspected lesion underwent two-to-four-targeted cores according to their size, in addition to a twelve-core systematic biopsy using the classic sextant method per lobule, avoiding suspicious lesions in all men. Experienced operators conducted the biopsies in each center, and experienced uropathologists analyzed the biopsy materials, using the International Society of Urologic Pathology grade groups (ISUP-GGs). Insignificant PCa (iPCa) was defined by an ISUP-GG of 1, while sPCa was considered when the ISUP-GG was 2 or higher [15].

2.3. Variables in the Study

Age (years), serum PSA (ng/mL), digital rectal exam (DRE) characteristics (normal vs. suspicious), type of prostate biopsy (initial vs. repeated), first degree of PCa family history (no vs. yes), MRI prostate volume (mL), PI-RADS score (2–5), Tesla (1.5 vs. 3.0), number of suspicious lesions (1–3), length of index lesion (mm), posterior–anterior localization of index lesion (peripheral, central, and anterior zone), cranio-caudal localization of index lesion (mid-base vs. apex), type of fusion TRUS-MRI images (cognitive vs. software), type of biopsy approach (transrectal vs. transperineal), PCa, sPCa, and iPCa detected in the targeted biopsy of the index lesion and in systematic biopsy were all outcome variables.

2.4. Statistical Analysis

Participating centers provided anonymized datasets which were harmonized for statistical analysis. The study complied with Standards of Reporting for MRI-Targeted Biopsy Studies (START) guidelines [16]. Means and their 95% confidence intervals (CIs), and medians and interquartile ranges (IQR: 25th–75th percentile) described quantitative variables, while numbers and percentages described qualitative ones. Pearson's chi-square and Mann–Whitney U tests compared qualitative and quantitative variables, respectively. Binary logistic regression identified independent predictors for sPCa, accounting for the prostate biopsy route. A 1:1 matching group was selected based on the biopsy route to normalize the effects of the confounding variables: age, serum PSA, suspicious DRE, repeated biopsies, family history of PCa, prostate volume, 3 Tesla scanner, PI-RADS, size of index lesion, index lesion location, and software-based use. R package matching v4.10, a multivariate and propensity score matching software with automated balance optimization (R Foundation for Statistical Computing, Vienna, Austria) was used. Significant differences were at $p < 0.05$; p -values from 0.05 to 0.1 indicated trends. This analysis was conducted with the Statistical Package for the Social Sciences (version 29.0, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Characteristics of Cohort Study

The characteristics of the cohort study are summarized in Table 1. The median age was 68 years (IQR: 62–73), and the median PSA was 7.2 ng/mL (IQR: 5.3–10.8). Abnormal DRE findings were present in 25% of cases, repeated biopsies in 27.4%, and a family history of PCa in 10.8%. The median MRI prostate volume was 52 mL (IQR: 38–73), and the PSA density was 0.14 ng/mL/mL (IQR: 0.09–0.13). A 3 Tesla MRI was performed in 46.4% of cases, with two suspicious lesions identified in 23.9% and three in 3.8%. The PI-RADS score for the index lesion was 2 in 15.1% of cases, 3 in 20.3%, 4 in 43.3%, and 5 in 21.7%. The median index lesion length was 11 mm (IQR: 0.7–15). The index lesion was in the peripheral zone in 64.8% of cases, the central/transitional zone in 14.2%, and the anterior zone in 21%. Regarding the cranio-caudal axis, the index lesion was located at the mid-base in 59.2% of cases and at the apex in 40.8%. Software TRUS-MRI fusion images for targeted biopsies were used in 55.7% of cases. The transperineal route was used in 59.8% of cases,

and the transrectal route in 40.2%. Overall, sPCa was detected in 41.3% of targeted biopsies of the index lesion and in 29.7% of systematic biopsies, while iPCa was detected in 13.1% and 18.5% of cases, respectively.

Table 1. Characteristics of the study population.

Characteristic	Measurement
Number of men	1376
Age, years, mean (95% CI)	67.5 (67.1–68.0)
Serum PSA, ng/mL, mean (95% CI)	9.7 (8.4–9.8)
Abnormal DRE, <i>n</i> (%)	344 (25.0)
Repeated prostate biopsy, <i>n</i> (%)	377 (27.4)
PCa family history, <i>n</i> (%)	149 (10.8)
Prostate volume, cc, mean (95% CI)	58.9 (57.3–60.5)
PSA density, ng/mL/cc, mean (95% CI)	0.14 (0.09–0.13)
3 Tesla mpMRI, <i>n</i> (%)	638 (46.4)
Suspicious lesions, <i>n</i> (%)	
1	1376 (100)
2	329 (23.9)
3	52 (3.8)
Index lesion PI-RADS score, <i>n</i> (%)	
2	355 (15.1)
3	449 (20.3)
4	960 (43.3)
5	468 (21.7)
Index lesion length, mm, mean (95% CI)	11.7 (10.6–13.2)
Postero-anterior index lesion localization, <i>n</i> (%)	
Peripheral zone	891 (64.8)
Central/transitional zone	196 (14.2)
Anterior zone	289 (21.0)
Craniocaudal index lesion localization, <i>n</i> (%)	
Mid-Base	815 (59.2)
Apex	561 (40.8)
Software image TRUS-MRI fusion biopsy, <i>n</i> (%)	767 (55.7)
Transperineal route, <i>n</i> (%)	823 (59.8)
Overall PCa detection, <i>n</i> (%)	867 (63.0)
sPCa	652 (47.4)
iPCa	215 (15.6)
PCa detected at index lesion biopsy, <i>n</i> (%)	749 (54.4)
sPCa	568 (41.3)
iPCa	180 (13.1)
PCa detected at systematic biopsies, <i>n</i> (%)	662 (48.1)
sPCa	408 (29.7)
iPCa	254 (18.5)

CI = confidence interval; PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; sPCa = significant PCa; iPCa = insignificant PCa.

3.2. Binary Logistic Regression for Searching Independent Predictive Variables of sPCa, Selection of a Matched Group to Avoid Confounders, and Characteristics of Paired Groups

Odds ratios (ORs) and 95% confidence intervals (CIs) of the potential independent predictive variables for sPCa are presented in Table 2. It was found that age, serum PSA, DRE, type of biopsy, prostate volume, Tesla, type of TRUS-MRI fusion image, and PI-RADS were independent predictive variables for sPCa. To avoid the influence of these confounders on sPCa detection and normalize the overall influence of the prostate biopsy route according to the localization of the index lesion, a 1:1 matched group of 325 pairs of participants (650 cases) was selected. Table 3 summarizes the comparison of all variables

included in the matched study group. All characteristics of participants, MRI, and biopsy techniques were statistically similar with respect to the peripheral localization vs. other localization of index lesions and the outcome variables sPCa and iPCa. The index lesion was localized in the peripheral zone in 49.2% of men who underwent transrectal biopsy and 50.8% of those who underwent the transperineal route, $p = 0.793$. Central/transitional zone localization was observed in 21.2% and 10.2%, respectively, at $p = 0.032$, and fibromuscular anterior zone localization was observed in 13.2% and 22.8%, respectively, at $p = 0.028$. Regarding the cranio-caudal axis, 48% of index lesions occupied the mid-base in men who underwent TRB and 63.4% occupied the mid-base in those subjected to TPB; index lesions occupied the apex in 52% and 36.6%, respectively, at $p < 0.001$. The overall detection of PCa in guided biopsies of the index lesion and systematic biopsies conducted through the transrectal route was 58.5%, while it was 67.1% when the biopsy was conducted through the transperineal route, $p = 0.028$.

Table 2. Logistic regression analysis for searching independent predictive variables of sPCa detection in index lesions, apart from the prostate biopsy route.

Predictive Variable	Odds Ratio (95% CI)	p Value
Age, Ref. one year	1.054 (1.035–1.073)	<0.001
Serum PSA, Ref. one ng/mL	1.035 (1.013–1.057)	0.001
DRE, Ref. normal	1.581 (1.152–2.170)	0.005
Type of biopsy, Ref. initial	0.627 (0.460–0.857)	0.003
PCa family history, Ref. no	1.472 (0.952–2.275)	0.082
Prostate volume, Ref. one mL	0.978 (0.972–0.983)	<0.001
Tesla, Ref. 1.5	1.296 (1.221–2.728)	<0.001
Number of suspicious lesions, Ref. 1	1.021 (0.943–1.167)	0.671
Length of index lesion, Ref. one mm	1.003 (0.981–1.026)	0.783
PI-RADS score of index lesion, Ref. 2	3.938 (3.201–4.845)	<0.001
Postero-anterior localization of index lesion, Ref. PZ	0.888 (0.777–1.015)	0.081
Cranio-caudal localization of index lesion, Ref. mid-base	0.907 (0.804–1.022)	0.110
Type of guided biopsy, Ref. cognitive	1.911 (1.439–2.539)	<0.001

CI = confidence interval; PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PZ = peripheral zone.

Table 3. Compared characteristics of the matched selected groups based on the prostate biopsy route.

Characteristic	Transrectal	Transperineal	p Value
Number of men	325	325	-
Age, years, mean (95% CI)	67.8 (67.1–68.5)	67.4 (66.8–67.5)	0.896
Serum PSA, ng/mL, mean (95% CI)	9.6 (8.9–9.6)	9.3 (8.7–9.8)	0.988
Abnormal DRE, n (%)	65 (20.0)	68 (20.0)	1.000
Repeated prostate biopsy, n (%)	89 (27.4)	86 (26.5)	0.754
PCa family history, n (%)	39 (12.0)	43 (13.2)	0.838
Prostate volume, cc, mean (95% CI)	61.5 (58.9–59.3)	59.3 (55.3–59.2)	0.678
PSA density, ng/mL/cc, mean (95% CI)	0.17 (0.13–0.19)	0.16 (0.15–0.19)	0.980
3 Tesla mpMRI, n (%)	169 (52.0)	164 (50.5)	0.892
Suspicious lesions, n (%)			
1	375 (100)	375 (100)	1.000
2	81 (21.6)	87 (23.2)	0.894
3	14 (3.7)	16 (4.3)	0.905
Index lesion PI-RADS score, n (%)			
2	3 (0.9)	3 (0.9)	1.000
3	72 (22.2)	72 (22.2)	1.000
4	193 (59.4)	193 (59.4)	1.000
5	57 (15.5)	57 (15.5)	1.000

Table 3. Cont.

Characteristic	Transrectal	Transperineal	p Value
Index lesion length, mm, mean (95% CI)	11.3 (10.8–11.9)	11.6 (11.1–12.1)	0.981
Posteroanterior index lesion localization, n (%)			
Peripheral zone	213 (49.2)	220 (50.8)	0.793
Central (central and transitional) zone	69 (21.2)	33 (10.2)	0.032
Anterior zone	43 (13.2)	72 (22.2)	0.028
Craniocaudal index lesion localization, n (%)			
Mid-base	156 (48.0)	206 (63.4)	<0.001
Apex	169 (52.0)	119 (36.6)	<0.001
Software image TRUS-MRI fusion biopsy, n (%)	164 (49.2)	158 (48.6)	0.897
Overall PCa detection, n (%)	190 (58.5)	218 (67.1)	0.028
sPCa	132 (40.6)	161 (49.5)	0.027
iPCa	58 (17.8)	57 (17.5)	0.997
PCa detected at index lesion biopsy, n (%)	140 (43.1)	200 (61.5)	<0.001
sPCa	100 (30.8)	145 (44.6)	<0.001
iPCa	39 (12.0)	55 (16.9)	0.094
PCa detected at systematic biopsies, n (%)	172 (52.9)	156 (48.0)	0.239
sPCa	114 (35.1)	79 (24.3)	0.003
iPCa	58 (17.8)	77 (23.7)	0.082

CI = confidence interval; PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; sPCa = significant PCa; iPCa = insignificant PCa.

3.3. Overall Efficacy of Systematic Biopsies According to the Prostate Biopsy Route

The overall detection rate of PCa in systematic biopsies when the transrectal route was utilized was 52.9%, while it was 48% when the transperineal route was used, at $p = 0.239$. Regarding sPCa detection, these rates were 35.1% and 24.3%, respectively, at $p = 0.003$; for iPCa detection, the rates were 17.8% and 23.7%, respectively, at $p = 0.082$. We note that 10.5% of sPCas were only detected in systematic biopsies when the transrectal route was conducted, while 4.9% of them were detected when the transperineal route was used, $p = 0.012$ (Table 4).

Table 4. The effectiveness of systematic biopsies and targeted biopsies on the index lesion for detecting overall PCa, sPCa, and iPCa, based on the prostate biopsy route, in the matched selected groups.

Type of PCa	Systematic Biopsies			Targeted Biopsies		
	TR Route (n = 325)	TP Route (n = 325)	p Value	TR Route (n = 325)	TP Route (n = 325)	p Value
sPCa, n (%)	144 (35.1)	79 (24.3)	0.003	100 (30.8)	145 (44.6)	<0.001
iPCa, n (%)	58 (17.8)	77 (23.7)	0.082	39 (12.0)	55 (16.9)	0.094
Overall PCa, n (%)	172 (52.9)	156 (48.0)	0.239	140 (43.1)	200 (61.5)	<0.001

n = number; PCa = prostate cancer; sPCa = significant PCa; iPCa = insignificant PCa; TR = transrectal route; TP = transperineal route.

3.4. Overall Efficacy of Guided Biopsies to the Index Lesion According to the Biopsy Route and Localizations

The overall detection rates of PCa in the index lesion for the transrectal and transperineal routes were 43.1% and 61.5%, respectively, at $p < 0.001$. sPCa detection rates were 30.8% and 44.6%, respectively, at $p < 0.001$, and iPCa detection rates were 12% and 16.9%, respectively, at $p = 0.094$, as shown in Table 3.

The rate of sPCa detection in the recodified localizations of index lesions regarding the posterior–anterior and cranio-caudal axes and the prostate biopsy route are summarized in Table 5. We noted non-significant differences between both biopsy routes when the

index lesion was localized in the peripheral zone, either at the mid-base or apex. TPB detected more sPCas than TRB did in the central and mid-base zones, at 33.3% and 5.9%, respectively, and at $p = 0.003$. In the anterior and mid-base zones, sPCa detection rates were 47.8% and 20.8%, respectively, at $p = 0.039$. In the anterior and apical zones, these rates were 44.6% and 24.2%, respectively, at $p = 0.024$.

Table 5. Detection of sPCa on targeted biopsies of index lesions according to their localization and the prostate biopsy route.

Localization of Index Lesion	sPCa Detection	Transrectal	Transperineal	<i>p</i> Value
PZ-MB, <i>n</i> (%)	102/217 (47.0)	36/81 (44.4)	66/136 (48.5)	0.577
CZ-MB, <i>n</i> (%)	11/75 (14.7)	3/51 (5.9)	8/24 (33.3)	0.003
AZ-MB, <i>n</i> (%)	27/70 (38.6)	5/24 (20.8)	22/46 (47.8)	0.039
PZ-AP, <i>n</i> (%)	79/221 (35.7)	48/136 (35.3)	31/85 (36.5)	0.886
AZ-AP, <i>n</i> (%)	26/67 (37.7)	8/33 (24.2)	18/34 (52.9)	0.024
All localizations, <i>n</i> (%)	245/650 (37.7)	100/325 (30.8)	145/325 (44.6)	>0.001

TR = transrectal; TP = transperineal; PZ = peripheral zone; CZ = central zone; AZ = anterior zone; MB = mid-base; AP = apical.

4. Discussion

Technological advancements in prostate magnetic resonance imaging (MRI) have significantly transformed the diagnostic landscape, leading to higher detection rates of clinically significant prostate cancer (sPCa) [17]. However, direct comparisons of the effectiveness of transperineal biopsy (TPB) and transrectal biopsy (TRB), particularly with MRI/US fusion techniques, remain limited. This study aims to address this gap through a comprehensive analysis of sPCa detection rates, the role of systematic and targeted biopsies, and the impact of lesion localization in TPB and TRB in the MRI era.

Recent studies, such as the PREVENT Randomized Trial, have found no significant differences in sPCa detection between the transperineal and transrectal routes, although transperineal biopsies avoid infectious complications [18]. Similarly, Hoeh et al. concluded that transitioning from transrectal to transperineal MRI-guided prostate biopsy did not compromise the rates of detection of clinically significant prostate cancer (51% vs. 52%) in a tertiary care setting [19]. Conversely, Rai et al. demonstrated higher sPCa detection rates with TPB in a meta-analysis [20]. Similarly, Zattoni et al. reported significantly higher detection rates for TPB, identifying it as an independent predictor of sPCa with a detection rate of 49.1% compared to 35.2% for TRB [21].

Koparal et al., in a multicenter study comparing sPCa detection rates in TPB and TRB, matched 276 men undergoing TPB with 508 patients undergoing TRB by age, DRE, PSA density, and PI-RADS score. The results showed that MRI-targeted TPB and 12-core systematic TPB were significantly superior to TRB, with detection rates of 27.5% vs. 19.5% and 24.6% vs. 16.3%, respectively [22]. Similarly, Diamand et al. recently published a multicenter European study reporting higher detection rates using MRI-guided biopsy in the transperineal approach [23].

Kaneko et al., in a single-center pair-matched study, reported sPCa detection rates of 56% vs. 49%, which were significantly higher for TPB compared to TRB. When combining systematic and targeted biopsies, similar detection rates were observed: 59% for TPB and 60% for TRB [24].

In our multicenter pair-matched study, we observed sPCa detection rates of 30.8% and 44.6% in index lesions under the transrectal and transperineal routes, respectively. For combined systematic and targeted biopsies, the detection rates were 40.6% for TRB and 49.5% for TPB, which showed a significant difference. TPB exhibited significantly higher

sPCa detection rates than TRB, particularly for index lesion targeting. The results obtained in our series are consistent with some of the previously described articles [20–24].

Detecting sPCa requires both systematic and targeted biopsies due to its multifocal nature and the risk of missing lesions with MRI [25]. The 2017 PROMIS trial showed that systematic biopsies alone have 48% sensitivity for sPCa, but combining them with targeted biopsies increases sensitivity to 93% [26]. The PRECISION study found that targeted biopsies detected sPCa in 38% of cases, compared to 26% with systematic biopsies alone [27]. The 2018 MRI-First study reported similar sensitivities for both methods [28]. The 2019 PAIREDCAP trial confirmed the necessity of using both biopsy types, as each method alone fails to detect all sPCa cases [29]. The GÖTEBORG-2 trial indicated that using transrectal MRI-targeted biopsies instead of systematic biopsies for patients with high PSA levels halved the risk of overdiagnosis but delayed the identification of some intermediate-risk tumors [30].

Few studies have compared the effectiveness of systematic biopsies between the transrectal and transperineal approaches in prostate fusion biopsies. In our analysis, systematic biopsies performed via the transrectal route demonstrated a higher detection rate of clinically significant prostate cancer (10.5%) compared to the transperineal route (4.9%). This finding, rarely explored in the literature, contrasts with studies such as those by Koparal et al. [22] and Zattoni et al. [21], which reported advantages of systematic biopsies via the transperineal route, particularly in larger prostates. These discrepancies may be attributed to methodological differences, population characteristics, or predominant prostate volume. In our study, prostates smaller than 30 cc. were associated with a significantly higher detection rates via the transrectal route, while the average prostate volume in both groups was approximately 60 cc., which could have influenced the detection rates observed.

Our analysis also revealed that lesion location influences diagnostic outcomes. Apical and anterior prostate lesions were more effectively sampled in TPB due to better access, while TRB showed superior sampling of posterior lesions due to probe proximity and needle trajectory. No significant differences were noted in sPCa detection between the biopsy approaches for peripheral zone lesions. However, TPB was more effective in detecting sPCa in central and mid-base zones compared to TRB, with detection rates of 33.3% and 5.9%, respectively. Additionally, in the anterior and mid-base zones, detection rates were 47.8% and 20.8%, respectively, which were significant. For anterior and apical zones, the rates of sPCa detection were higher in TPB, with a 44.6% detection rate compared to 24.2% in TRB. This differential impact based on lesion location was further evidenced in subgroup analyses, showing higher sPCa detection rates for anterior and apical lesions with TPB. Consistent with our findings, a meta-analysis published by Uleri et al. found the transperineal approach superior for detecting sPCa in anterior and apical prostate tumors and found that it was equivalent in effectiveness to the transrectal route for peripheral tumors. The former demonstrated better precision for smaller anterior tumors than the transrectal method [31].

While our study benefits from a multicenter design and large sample size, it is not without limitations. The retrospective nature of some data could have introduced inherent selection biases, which we attempted to minimize using a matched-cohort design. Differences in biopsy protocols across various institutions could have generated variability in PCa detection, representing a limitation in this study. Although all centers followed current practice guidelines and terminology, the lack of a centralized review causes heterogeneity in the interpretation of MRIs and in the analysis of biopsies due to the involvement of multiple physicians. However, all MRI analyses were conducted by specialized genitourinary radiologists using version 2.1 of PI-RADS, and biopsy specimens were analyzed by

experienced uropathologists at all centers. Our matched study was insufficient regarding certain locations, as differences were observed in some of them, and it was performed for peripheral locations versus other locations. Another potential limitation of our study is that it did not incorporate the results of secondary biopsied targeted lesions.

Future research should focus on conducting large prospective and randomized trials to determine the optimal biopsy approach in different clinical scenarios. These studies should avoid the influence of confounders, with especial attention to the localization and size of targeted lesions.

5. Conclusions

Targeted biopsies of index lesions performed via the transperineal route demonstrated higher detection rates of sPCa compared to those performed via the transrectal route in our cohort study. This improvement in the efficacy of targeted biopsies using the transperineal route was particularly notable for lesions located in the anterior and apical zones. The efficacy of systematic biopsies decreased when the transperineal route was utilized, especially when detecting sPCa with only them.

Author Contributions: Conceptualization, J.M. and N.P. (Nahuel Paesano); formal analysis J.M., N.P. (Nahuel Paesano) and B.M.; data curation: N.P. (Nahuel Paesano), N.P. (Natàlia Picola), J.M.-R., X.R.-P., M.V.M.-R., A.C., G.G.-d.M., J.M.A. and P.S.; writing—original draft preparation, J.M. and N.P. (Nahuel Paesano); writing—review and editing, E.T.; resources, J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Instituto de Salut Carlos III (SP) and the European Union (PI20/01666).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the coordinating center (PRAG-02/2021, Barcelona 12 February 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: All data obtained and analyzed for this clinical study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Siegel, R.; Miller, K.; Wagle, N.; Jemal, A. Cancer statistics, 2023. *CA Cancer J. Clin.* **2023**, *73*, 17–48. [CrossRef] [PubMed]
2. World Health Organization. *Guide de Cancer Early Diagnosis*; World Health Organization: Geneva, Switzerland, 2017. Available online: <https://apps.who.int/iris/bitstream/handle/10665/254500/9789241511940-eng.pdf?sequence=1&isAllowed=y> (accessed on 12 December 2024).
3. Pepe, P.; Garufi, A.; Priolo, G.; Pennisi, M. Transperineal Versus Transrectal MRI/TRUS Fusion Targeted Biopsy: Detection Rate of Clinically Significant Prostate Cancer. *Clin. Genitourin. Cancer* **2017**, *15*, 33–36. [CrossRef] [PubMed]
4. Derin, O.; Fonseca, L.; Sanchez-Salas, R.; Roberts, M. Infectious complications of prostate biopsy: Winning battles but not war. *World J. Urol.* **2020**, *38*, 2743–2753. [CrossRef] [PubMed]
5. Jacewicz, M.; Günzel, K.; Rud, E.; Sandbæk, G.; Magheli, A.; Busch, J.; Hinz, S.; Baco, E. Antibiotic prophylaxis versus no antibiotic prophylaxis in transperineal prostate biopsies (NORAPP): A randomised, open-label, non-inferiority trial. *Lancet Infect. Dis.* **2022**, *22*, 1465–1471. [CrossRef]
6. Mottet, N.; van den Bergh, R.; Briers, E.; Van den Broeck, T.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillesen, S.; Comford, P.; et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part I: Screening, diagnosis, and local treatment with curative intent. *Eur. Urol.* **2021**, *79*, 243–262. [CrossRef]
7. Loeb, S.; Vellekoop, A.; Ahmed, H.; Catto, J.; Emberton, M.; Nam, R.; Rosario, D.; Scattoni, V.; Lotan, Y. Systematic review of complications of prostate biopsy. *Eur Urol.* **2013**, *64*, 876–892. [CrossRef]

8. Grummet, J.; Gorin, M.; Popert, R.; O'Brien, T.; Lamb, A.; Hadaschik, B.; Radtke, J.P.; Wagenlehner, F.; Baco, E.; Moore, C.; et al. "TREXIT 2020": Why the time to abandon transrectal prostate biopsy starts now. *Prostate Cancer Prostatic Dis.* **2020**, *23*, 62–65. [\[CrossRef\]](#)
9. Stefanova, V.; Buckley, R.; Flax, S.; Spevack, L.; Hajek, D.; Tunis, A.; Lai, E.; Loblaw, A. Transperineal Prostate Biopsies Using Local Anesthesia: Experience with 1,287 Patients. Prostate Cancer Detection Rate, Complications and Patient Tolerability. *J. Urol.* **2019**, *201*, 1121–1126. [\[CrossRef\]](#)
10. Takashima, R.; Egawa, S.; Kuwano, S.; Baba, S. Anterior distribution of Stage T1c nonpalpable tumors in radical prostatectomy specimens. *Urology* **2002**, *59*, 692–697. [\[CrossRef\]](#)
11. Wright, J.; Ellis, W. Improved prostate cancer detection with anterior apical prostate biopsies. *Urol. Oncol.* **2006**, *24*, 492–495. [\[CrossRef\]](#)
12. Bryant, R.; Yamamoto, H.; Eddy, B.; Kommu, S.; Narahari, K.; Omer, A.; Leslie, T.; Catto, J.; Rosario, D.; Good, D.; et al. Protocol for the TRANSLATE prospective, multicentre, randomised clinical trial of prostate biopsy technique. *BJU Int.* **2023**, *131*, 694–704. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Paesano, N.; Catalá, V.; Tcholakian, L.; Alomar, X.; Barranco, M.; Trilla, E.; Morote, J. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. *Int. Braz. J. Urol.* **2024**, *50*, 296–308. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Turkbey, B.; Rosenkrantz, A.; Haider, M.; Padhani, A.; Villeirs, G.; Macura, K.; Tempany, C.; Choyke, P.; Cornud, F.; Margolis, D.; et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur. Urol.* **2019**, *76*, 340–351. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Epstein, J.; Zelefsky, M.; Sjoberg, D.; Nelson, J.; Egevad, L.; Magi-Galluzzi, C.; Vickers, A.; Parwani, A.; Reuter, V.; Fine, S.; et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur. Urol.* **2016**, *69*, 428–435. [\[CrossRef\]](#)
16. Moore, C.M.; Kasivisvanathan, V.; Eggener, S.; Gill, I.S.; Emberton, M.; Fütterer, J.; Grubb, R.L.; Hadaschik, B.; Klotz, L.; Simon, R.; et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: Recommendations from an International Working Group. *Eur. Urol.* **2013**, *64*, 544–552. [\[CrossRef\]](#)
17. Petov, V.; Azilgareeva, C.; Shpikina, A.; Morozov, A.; Krupinov, G.; Kozlov, V.; Singla, N.; Rivas, J.G.; Moreno-Sierra, J.; Rodler, S.; et al. Robot-Assisted Magnetic Resonance Imaging-Targeted versus Systematic Prostate Biopsy: Systematic Review and Meta-Analysis. *Cancers* **2023**, *15*, 1181. [\[CrossRef\]](#)
18. Hu, J.C.; Assel, M.; Allaf, M.E.; Ehdaie, B.; Vickers, A.; Cohen, A.J.; Ristau, B.T.; Green, D.A.; Han, M.; Rezaee, M.E.; et al. Transperineal Versus Transrectal Magnetic Resonance Imaging-targeted and Systematic Prostate Biopsy to Prevent Infectious Complications: The PREVENT Randomized Trial. *Eur. Urol.* **2024**, *86*, 61–68. [\[CrossRef\]](#)
19. Hoeh, B.; Wenzel, M.; Humke, C.; Cano Garcia, C.; Siech, C.; Schneider, M.; Lange, C.; Traumann, M.; Köllermann, J.; Preisser, F.; et al. Transition from Transrectal to Transperineal MRI-Fusion Prostate Biopsy Does Not Compromise Detection Rates of Clinically Significant Prostate Cancer at a Tertiary Care Center. *Diagnostics* **2024**, *14*, 1184. [\[CrossRef\]](#)
20. Rai, B.; Mayerhofer, C.; Somani, B.; Kallidonis, P.; Nagele, U.; Tokas, T. Magnetic Resonance Imaging/Ultrasound Fusion-guided Transperineal Versus Magnetic Resonance Imaging/Ultrasound Fusion-guided Transrectal Prostate Biopsy—A Systematic Review. *Eur. Urol. Oncol.* **2021**, *4*, 904–913. [\[CrossRef\]](#)
21. Zattoni, F.; Marra, G.; Kasivisvanathan, V.; Grummet, J.; Nandurkar, R.; Ploussard, G.; Olivier, J.; Chiu, P.K.; Valerio, M.; Moon, D.; et al. The Detection of Prostate Cancer with Magnetic Resonance Imaging-Targeted Prostate Biopsies is Superior with the Transperineal vs the Transrectal Approach. A European Association of Urology-Young Academic Urologists Prostate Cancer Working Group Multi-Institutional Study. *J. Urol.* **2022**, *208*, 830–837.
22. Koparal, M.; Sözen, T.; Karşıyakalı, N.; Aslan, G.; Akdoğan, B.; Şahin, B.; Türkeri, L. Comparison of transperineal and transrectal targeted prostate biopsy using Mahalanobis distance matching within propensity score caliper method: A multicenter study of Turkish Urooncology Association. *Prostate* **2022**, *82*, 425–432. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Diamand, R.; Guenzel, K.; Mjaess, G.; Lefebvre, Y.; Ferriero, M.; Simone, G.; Fourcade, A.; Fournier, G.; Bui, A.P.; Taha, F.; et al. Transperineal or Transrectal Magnetic Resonance Imaging-targeted Biopsy for Prostate Cancer Detection. *Eur. Urol. Focus.* **2024**, published online. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Kaneko, M.; Medina, L.; Lenon, M.; Hemal, S.; Sayegh, A.S.; Jadvar, D.S.; Ramacciotti, L.S.; Paralkar, D.; Cacciamani, G.E.; Lebastchi, A.H. Transperineal vs transrectal magnetic resonance and ultrasound image fusion prostate biopsy: A pair-matched comparison. *Sci. Rep.* **2023**, *13*, 13457. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Morote, J.; Picola, N.; Muñoz-Rodríguez, J.; Paesano, N.; Ruiz-Plazas, X.; Muñoz-Rivero, M.V.; Celma, A.; Manuel, G.G.; Aislan, I.; Servian, P.; et al. A Diagnostic Accuracy Study of Targeted and Systematic Biopsies to Detect Clinically Significant Prostate Cancer, including a Model for the Partial Omission of Systematic Biopsies. *Cancers* **2023**, *15*, 4543. [\[CrossRef\]](#)
26. Ahmed, H.; El-Shater Bosaily, A.; Brown, L.; Gabe, R.; Kaplan, R.; Parmar, M.; Collaco-Moraes, Y.; Ward, K.; Hindley, R.G.; Freeman, A.; et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (Promis): A paired validating confirmatory study. *Lancet* **2017**, *389*, 815–822. [\[CrossRef\]](#)

27. Kasivisvanathan, V.; Rannikko, A.S.; Borghi, M.; Panebianco, V.; Mynderse, L.A.; Vaarala, M.; Briganti, A.; Budäus, L.; HELLAWELL, G.; Hindley, R.G.; et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N. Engl. J. Med.* **2018**, *378*, 1767–1777. [\[CrossRef\]](#)
28. Rouvière, O.; Puech, P.; Renard-Penna, R.; Claudon, M.; Roy, C.; Mège-Lechevallier, F.; Decaussin-Petrucci, M.; Dubreuil-Chambardel, M.; Magaud, L.; Remontet, L.; et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): A prospective, multicentre, paired diagnostic study. *Lancet Oncol.* **2018**, *20*, 100–109. [\[CrossRef\]](#)
29. Elkhoury, F.; Felker, E.; Kwan, L.; Sisk, A.; Delfin, M.; Natarajan, S.; Marks, L.S. Comparison of Targeted vs. Systematic Prostate Biopsy in Men Who Are Biopsy Naïve: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. *JAMA Surg.* **2019**, *154*, 811–818. [\[CrossRef\]](#)
30. Hugosson, J.; Månsson, M.; Wallström, J.; Axcróna, U.; Carlsson, S.; Egevad, L.; Geterud, K.; Khatami, A.; Kohestani, K.; Pihl, C.G.; et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. *N Engl. J. Med.* **2022**, *387*, 2126–2137. [\[CrossRef\]](#)
31. Uleri, A.; Baboudjian, M.; Tedde, A.; Gallioli, A.; Palou, J.; Long-Depaquit, T.; Palou, J.; Basile, G.; Gaya, J.M.; Briganti, A.; et al. Is There an Impact of Transperineal Versus Transrectal Magnetic Resonance Imaging-targeted Biopsy in Clinically Significant Prostate Cancer Detection Rate? A Systematic Review and Meta-analysis. *Eur. Urol. Oncol.* **2023**, *6*, 621–628. [\[CrossRef\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

5.4. PUBLICACIÓN 4

Título: The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies

Revista: Int Braz J Urol.

Año de publicación: 2024

Volumen: 50

Páginas: 296-308

DOI: <https://doi.org/10.1590/S1677-5538.IBJU.2023.0558>

Autores: Nahuel Paesano, Violeta Catalá, Larisa Tcholakian, Xavier Alomar, Miguel Barranco, Enric Trilla, Juan Morote

Factor de impacto (JCR): 4.5

Cuartil (JCR): 2 (Área de Urología y Nefrología)



The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies

Nahuel Paesano¹, Violeta Catalá¹, Larisa Tcholakian¹, Xavier Alomar¹, Miguel Barranco¹, Enric Trilla^{2,3}, Juan Morote^{2,3}

¹ Creu Blanca Clinic Barcelona, Catalunya, Spain; ² Department of Urology Vall d'Hebron University Hospital Barcelona, Catalunya, Spain; ³ Department of Surgery, Universitat Autònoma de Barcelona, Barcelona, Catalunya, Spain

ABSTRACT

Purpose: To evaluate the effectiveness of mapping-targeted biopsies (MTB) on the index lesion for the detection of clinically significant prostate cancer (csPCa) in transperineal fusion-image prostate biopsies.

Materials and Methods: A retrospective analysis was conducted on 309 men with suspected PCa who underwent prostate biopsies at the Creu Blanca reference center in Barcelona, Spain. The Prostate Imaging-Reporting and Data System (PI-RADS v2.1) of the magnetic resonance images (MRI) were reclassified by an expert radiologist reading of pre-biopsy biparametric MRI used for segmentation of suspected lesions. Transperineal MTB of suspicious lesions and 12-core systematic biopsies were performed using the Artemis™ platform. CsPCa was defined as International Society of Urological Pathology grade group ≥ 2 .

Results: CsPCa was detected in 192 men (62.1%), with detection rates of 6.3% for PI-RADS 2, 26.8% for PI-RADS 3, 87.3% for PI-RADS 4, and 93.1% for PI-RADS 5. MTB of the index lesion identified 185 csPCa (96.3%). CsPCa was detected solely in systematic biopsies in three cases (1.6%), while an additional four cases (2.1%) were identified only in the second suspected lesion. A predictive model for csPCa detection in MTB of the index lesion was developed, with an AUC of 0.918 (95% CI 0.887-0.950).

Conclusions: This model had the potential to avoid 23.3% of prostate biopsies without missing additional csPCa cases. MTB of the index lesion was highly effective for identifying csPCa in fusion transperineal prostate biopsies. A developed predictive model successfully reduced the need for almost one quarter of biopsies without missing csPCa cases.

ARTICLE INFO

 Nahuel Paesano

<https://orcid.org/0000-0001-9278-5543>

Keywords:

Prostatic Neoplasms; Prostate; Retrospective Studies

Int Braz J Urol. 2024; 50: 296-308

Submitted for publication:
November 15, 2023

Accepted after revision:
February 05, 2024

Published as Ahead of Print:
March 10, 2024

INTRODUCTION

Prostate cancer (PCa) currently stands as the most prevalent malignancy and the third leading cause of cancer-related deaths among men in both the United States (US) and the European Union (EU) (1, 2). PCa screening has remained controversial due to the adverse consequences of unnecessary prostate biopsies and the over-detection of insignificant tumors (iPCa) (3). Clinically significant PCa (csPCa) in prostate biopsies can have various definitions. It is most defined when the current grade groups of the International Society of Urologic Pathology (ISUP-GG) are grade 2 or higher (4). In recent years, additional tools have been proposed to mitigate the need for unnecessary biopsies and to reduce the over-detection of iPCa. These include new tumor markers, predictive models, and the traditional prostate-specific antigen density (PSA D). However, the most significant contribution has arisen from prostate magnetic resonance imaging (MRI) and the possibility of performing targeted biopsies of suspicious areas (5).

The implementation of multiparametric MRI (mpMRI) and the enhanced interpretation provided by the Prostate Imaging-Reporting and Data System (PI-RADS) have been essential in identifying suspicious csPCa and assessing its semi-quantitative risk (6, 7). These innovations, coupled with the evolution of PI-RADS for categorizing prostate lesions on a scale ranging from very low to high suspicion of harboring csPCa, have prompted the development of software solutions that facilitate the fusion of MRI-observed areas with real-time transrectal ultrasound (TRUS) images (8).

Image-fusion prostate biopsy is an effective procedure that not only enhances the detection of csPCa but also reduces the likelihood of over-detecting iPCa, regardless of the transrectal or transperineal route (9). The transrectal approach has been the most used method for prostate biopsies on a global scale for many decades (10). However, in 2019, the European Association of Urology (EAU) PCa guidelines made the primary recommendation for transperineal biopsies over transrectal biopsies based on a meta-analysis of

seven studies involving 1,330 biopsied men. This analysis demonstrated a significant reduction in infective complications associated with the transperineal approach compared to transrectal biopsies (11).

The fusion software platforms allow targeted biopsies of suspicious areas previously identified by mpMRI. These biopsies are usually combined with systematic biopsies in the rest of the prostate gland. In cases where an MRI reveals more than one PI-RADS lesion ≥ 3 , the lesion with the highest degree of aggressiveness according to PI-RADS is considered the index lesion, or the largest lesion in the case of two lesions with the same PI-RADS score (12).

The complementarity of systematic and targeted biopsies, defined as the amount of csPCa detected only in one of them, can be attributed to multifocal csPCa, MRI-invisible lesions, errors in lesion targeting, and MRI lesions being missed by radiologists (13). The complementarity of targeted and systematic biopsies has been analyzed using the transrectal approach in a systematic review by the Cochrane organization (14), and currently, the EUA recommends performing both types of biopsies (11).

Due to the current trend of reducing the aggressiveness of prostate biopsies to decrease procedure complications and overdiagnosis of iPCa, it is crucial to continue generating evidence on the effectiveness of targeted transperineal biopsies with image fusion (15). The optimal biopsy strategy, in terms of spatial distribution and the number of cores required, has not yet been clearly defined. Specifically, at least eight systematic biopsy cores should be taken bilaterally, depending on prostate volume, while three to five biopsy cores guided by magnetic resonance imaging are needed to compensate for the risk of target imprecision (11, 16, 17). Conversely, recent studies suggested that distant systematic biopsy cores in relation to the index lesion on magnetic resonance imaging play a limited role in detecting csPCa (18).

We hypothesize that prostate biopsies from the index lesion are sufficient to appropriately diagnose clinically significant prostate cancer. Our objective is to assess the efficacy of exclusively utilizing targeted biopsies by mapping the index lesion in the

detection of clinically significant prostate cancer, and to evaluate the effectiveness of index biopsies compared to systematic biopsies through the transperineal approach.

MATERIAL AND METHODS

Design, Setting, and Participants

This retrospective analysis relates to the first-year prospective trial aimed at validating the Barcelona risk calculators (BCN-RCs) (19, 20). The study was conducted at a reference center specializing in transperineal MRI-TRUS fusion prostate biopsy, located at Creu Blanca in Barcelona, Spain. From January 1 to December 31, 2022, a total of 309 consecutive men with suspected prostate cancer—defined by a serum PSA level >3.0 ng/mL and/or an abnormal digital rectal examination (DRE), along with a positive mpMRI (PI-RADS ≥ 3)—were referred for prostate biopsy. Prostate biopsies in PI-RADS 2 lesions, are not typically referred for biopsy. However, prostate biopsies of PI-RADS 2 lesions were performed in those patients at high risk of cPca, for example, if the PSAD is >0.15 . The study was executed in accordance with the Standards of Reporting for MRI-Targeted Biopsy Studies (START) guidelines (21). The analysis was performed using an anonymized database, and the project received approval from the Vall d'Hebron Ethics Committee (PRAG-02/2020). Furthermore, it was supported by the Instituto de Salut Carlos III of Spain (PI20/01666).

MRI Image Acquisition Data and Segmentation

The studies conducted at the Creu Blanca center were carried out using a Siemens Verio™ 3 Tesla MRI Scanner (Siemens Inc, Munich, Germany) equipped with a pelvic-phased array. The mpMRI protocol included transversal sections in SET1 and TSG-SET2 sequences, as well as coronal and sagittal TSET2 sequences in both 2D and 3D. Diffusion studies (ADC and DWI calculated at 1600-2000-3000) and perfusion during contrast injection were also performed. Lesions were reported in accordance with PI-RADS v.2.1 (22).

For patients referred with mpMRIs performed at other centers, an expert radiologist reclassified the lesions to PI-RADS v.2.1 based on a biparametric MRI (bpMRI) conducted for lesion segmentation. All studies adhered to the criteria established by the European Society of Uro-radiology (ESUR) (23). Up to three suspicious lesions were included. Segmentation of suspicious lesions was achieved using the ProFuse™ semi-automatic system (Eigen, California, USA). Suspected PCa men with reclassified lesions to PI-RADS score 2 received targeted biopsies of these lesions.

Transperineal prostate biopsy

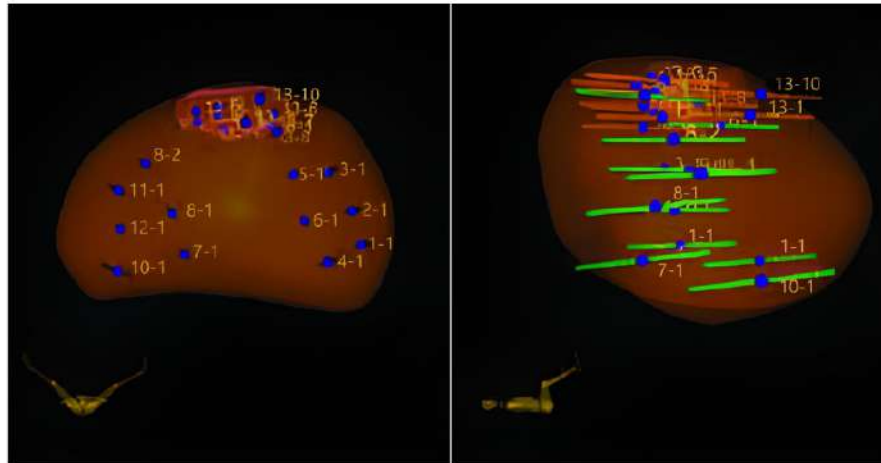
All prostate biopsies were performed transperineally in the lithotomy position under general anesthesia by four urologists with extensive experience in this technique. MRI-TRUS image fusion was performed with the ARTEMIS™ robotic system (Eigen, California, USA). Core biopsy samples were obtained using the BARD Magnum™ gun with 18-gauge x 20-cm prostate biopsy needles (Bard Care, Crawley, UK) under ultrasound vision (HITACHI ALOKA NOBLUS™, HITACHI, Connecticut, USA).

The prostate biopsy protocol included first obtaining mapping-targeted biopsies of a maximum of three suspicious areas by 0.5-mm mapping of each lesion and perilesional area. Thereafter, a systematic biopsy was performed to obtain 12 cores according to the scheme suggested by the ARTEMIS™ platform, excluding the suspicious areas. Each core of the systematic biopsy was numbered and analyzed as an independent sample (1 to 12). The cores of each suspected area were grouped as samples 13 to 15. The mapping-targeted biopsies scheme used is illustrated in Figure-1.

Histopathological diagnosis

A urologic pathologist with more than 10 years of experience in prostatic pathology analyzed the obtained material. The pathology report considered the number of positive cores, length of tumor, and International Society of Urologic Pathology (ISUP) grade group. iPCa was defined with an ISUP-GG of 1, while csPCa was considered when the ISUP-GG was 2 or higher (4, 24).

Figure 1 - Biopsy method. Cores were obtained from a systematic template and MRI lesion.



Variables in the study

Age (years), PCa family history (first degree), type of biopsy (initial vs. repeated), DRE (normal vs. suspicious), DRE prostate volume category (small, medium, large), PSA (ng/mL), MRI prostate volume, the number of suspicious areas, PI-RADS v2.1 score, maximum diameter of lesions (mm), site of lesions (right vs. left), and location (peripheral base-center, peripheral apex, central-transition zone, or anterior zone). Pathology findings were reported as follows: ISUP grade group (GG) of tumors detected and its length in each core affected, the total number of cores submitted, and positive samples according to their location in the systematic biopsy and mapping-targeted biopsies.

Endpoint variables

The endpoint variable was the detection of csPCa.

Statistical Analysis

Quantitative variables were described as medians and interquartile ranges (IQRs: 25th-75th percentile). Qualitative variables were described as percentages. The association between qualitative variables was analyzed using Pearson's chi-square

test. The concordance between systematic and targeted biopsies was assessed using the Kappa index. Independent predictive variables for csPCa detection in mapping-targeted biopsies of the index lesion were identified using binary logistic regression. A predictive model for csPCa detection was developed, and probabilities of csPCa were calculated. The discrimination ability of the model was assessed using receiver operating characteristic (ROC) analysis, and the area under the curve (AUC) and 95% confidence interval were calculated. The net benefit of the model over biopsying all men was analyzed using decision curve analysis (DCA), and specificities corresponding to 100%, 97.5%, and 95% sensitivity thresholds were analyzed. Significant differences were considered when the p values were less than 0.05. Statistical analysis was performed using SPSS v.25 (IBM Corp., Armonk, NY, USA).

RESULTS

The characteristics of the 309 men included in this study are shown in Table-1. The median age at biopsy was 67 years (61-72) with a median serum PSA level of 6.3 ng/mL (4.8-9.3). The median prostate volume, as reported from MRI, was 53 cc (39-75). The median PSA density was 0.14 ng/mL/cc. In 52 men (16.8%),

Table 1 - Suspected PCa Men Characteristics.

Characteristic	Measurement
Number of men	309
Median age (IQR), years	67 (61-72)
Median PSA (IQR), ng/mL	6.3 (4.8-9.3)
Suspicious DRE, n (%)	47 (15.2)
Repeated biopsy, n (%)	78 (25.2)
PCa family history, (%)	52 (16.8)
Median prostate volume (IQR), cc	53 (39-75)
mpMRI lesions, n (%)	
1	309 (100)
2	75 (24.2)
3	11 (3.6)
PI-RADS of lesion 1 (index), n (%)	309
2	48 (15.5)
3	71 (23.0)
4	118 (38.2)
5	72 (23.3)
PI-RADS of lesion 2, n (%)	75
2	5 (6.7)
3	23 (30.7)
4	41 (54.7)
5	6 (8.0)
PI-RADS of lesion 3, n (%)	11
3	3 (36.4)
4	7 (63.6)
PCa detection, n (%)	230 (74.4)
csPCa detection, n (%)	192 (62.1)
iPCa, n (%)	38 (12.3)
csPCa-iPCa detection according to index lesion PI-RADS	
2, n (%)	3 (6.3) - 7 (14.6)
3, n (%)	19 (26.8) - 19 (26.8)
4, n (%)	103 (87.3) - 7 (5.9)
5, n (%)	67 (93.1) - 5 (6.9)

IQR = interquartile range; PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer; PI-RADS = Prostate imaging-report and data system; csPCa = clinically significant PCa; iPCa = insignificant PCa

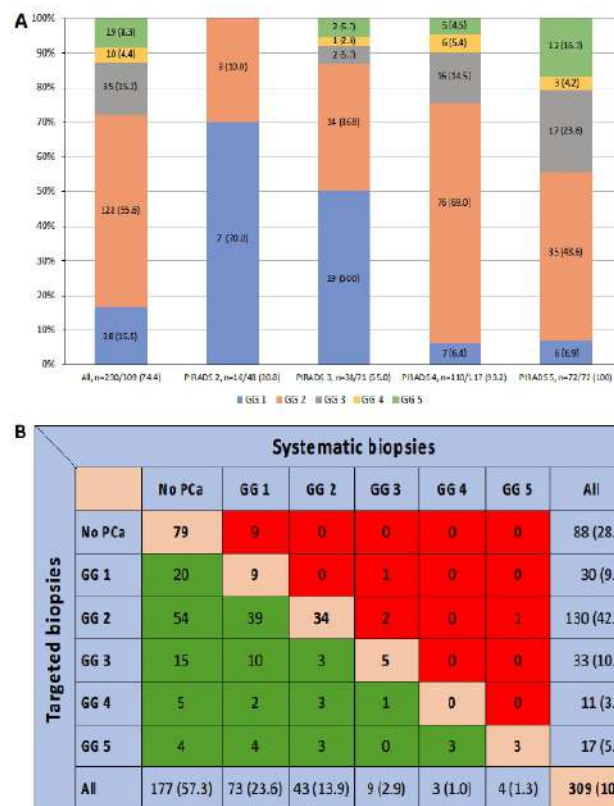
a family history of PCa existed, and 78 men (25.2%) had undergone at least one previous negative biopsy. The digital rectal examination (DRE) was suspicious in 47 men (15.2%). In 223 cases, only one suspicious lesion existed (72.2%), in 75 (24.2%), two, and in 11 cases, three (3.6%). After the biparametric MRI expert reading of the PI-RADS v.2.1, the index lesion was classified as 2 in 48 cases (15.5%), 3 in 71 (23%), 4 in 118 (38.2%), and 5 in 72 (23.3%). Within the second lesions, 5 (6.7%) were PI-RADS 2, 23 (30.7%) PI-RADS 3, 41 (54.7%) PI-RADS 4, and 6 (8.0%) PI-RADS 5. Among the 11 third lesions, 4 (36.4%) were PI-RADS 3, and 7 (63.6%) were PI-RADS 4. A median of 22 total cores (15-30) were obtained from mapping-targeted biopsies of suspicious

and systematic biopsies. PCa was detected in 230 men (74.4%), with 192 (62.1%) identified as csPCa, and 38 (12.3%) as iPCa.

The distribution rates of csPCa and iPCa according to the PI-RADS v.2.1 categories are shown in Table-1. The csPCa detection rate was 6.3% in PI-RADS 2, 26.8% in PI-RADS 3, 87.3% in PI-RADS 4, and 93.1% in PI-RADS 5 ($p < 0.001$). The iPCa over-detection rates were 14.6% in PI-RADS 2, 26.8% in PI-RADS 3, 5.9% in PI-RADS 4, and 6.9% in PI-RADS 5 ($p < 0.001$).

The distribution of ISUP-GGs in all PCa detected according to the PI-RADS categories in the index lesion is presented in Figure-2A. The over-detection

Figure 2 - Distribution of grade groups in all PCa detected and according to the PI-RADS category of the index lesion (A), and correlation of biopsy findings (from no PCa to the highest-grade group) observed in targeted and systematic biopsies (B).



tion of iPCa decreased, and the detection of csPCa increased as the PI-RADS category became higher ($p < 0.001$). The correlation between the ISUP-GG of PCa detected in targeted and systematic biopsies is presented in Figure-2B. We observed that 9 ISUP-GG 1 cases were detected in the systematic biopsies in men without PCa detected in targeted biopsies. One ISUP-GG 3 case was detected in the systematic biopsies performed in men with ISUP-GG 1 in targeted biopsies. We found 3 cases in which systematic biopsies upgraded the ISUP-GG 2 detected in targeted biopsies (2 cases to GG 3 and 1 to GG 5). No cases with ISUP-GG 3 and 4 in targeted biopsies upgraded in systematic biopsies. In summary, 1 of 30 iPCa cases upgraded to csPCa (3.3%), while 3 of 130 ISUP-GG 2 cases (2.3%) upgraded to GG 3 (2) and GG 5 (1).

CsPCa was detected in both targeted and systematic biopsies in 56 cases (18.1%), solely in targeted biopsies in 133 (43.0%), and only in systematic biopsies in three cases (1.0%) ($p < 0.001$, and Kappa index 0.239). Targeted biopsies of the index lesion identified 185 of the 189 csPCa cases detected within all targeted biopsies (97.9%). Four csPCa cases were additionally detected in the targeted biopsy of the second suspicious lesion (2.1%), while the targeted biopsies of 11 third suspicious lesions did not detect any additional csPCa case (0%). The ISUP-GGs of PCa detected in the index lesion and those additionally detected in the second targeted biopsy are reported in Table-2.

In terms of core samples, if targeted biopsies of the index lesion were solely performed, the total number of core samples obtained, which was 6,573, would be reduced to 2,392 (63.6%). This reduction would result from 3,708 (56.4%) core samples obtained in systematic biopsies, 426 (6.5%) in the second suspicious lesion, and 47 (0.7%) in the third suspicious lesion.

To investigate the development of a predictive model for the detection of clinically significant prostate cancer (csPCa) in mapping-targeted biopsies of the index lesion, we conducted a logistic regression analysis involving 12 independent predictive variables related to the characteristics of the patients, MRI findings, and the number of core samples obtained. Serum PSA, with an odds ratio (OR) of 1.136 (95% confidence interval: 1.010-1.277, $p = 0.033$), prostate volume, with an OR of 0.987 (95% confidence interval: 0.365-0.991, $p < 0.001$), and the PI-RADS score, with an OR of 7.285 (95% confidence interval: 4.455-11.913, $p < 0.001$), emerged as the independent predictors of csPCa, as presented in Table-3.

The ROC curve of the developed predictive model demonstrated an AUC of 0.918 (95% confidence interval: 0.887-0.950), illustrated in Figure 3A. Application of the model revealed a net benefit over the strategy of performing biopsies on all men, as shown in Figure 3B. Specificities were provided for sensitivity thresholds of 100%, 97.5%, and 95%, with values of 239, 52.1, and 64.1%, respectively. Using

Table 2 - CsPCa Detection in Targeted Biopsies. New csPCa Detected Only in Secondary Lesions and its grade group.

Lesion	Number of lesions, n	csPCa n (%)*	New csPCa, n (%)#	Grade group of csPCa			
				2	3	4	5
Index	309	185 (59.9)	185 (97.9)	125	33	9	18
Second	75	40 (53.3)	4 (2.1)	4 [‡]	0	0	0
Third	11	2 (18.2)	0 (0)	0	0	0	0
All	395	227 (100)	189 (100)	131	35	9	17

n = number; csPCa = clinically significant prostate cancer; * percent referred to the number of lesions; # percent referred to all csPCa detected;

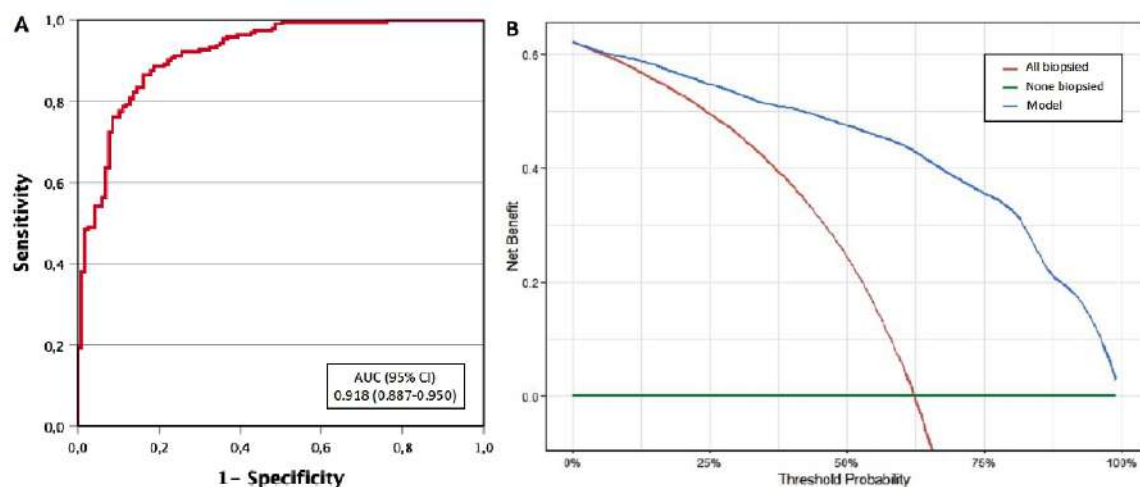
[‡] Three men have GG 1 in the index lesion while one had no PCa.

Table 3 - Multivariate Analysis Searching Independent predictors for csPCa detection.

Candidate predictors	Odds ratio (95% CI)	p Value
Age, Ref. one year	1.039 (0.991-1.090)	= 0.101
PCa family history, Ref. no	2.013 (0.761-5.324)	= 0.159
Repeated biopsy, Ref. no	1.649 (0.734-3.758)	= 0.234
Serum PSA, Ref. one ng/mL	1.136 (1.010-1.277)	= 0.033
DRE, Ref. normal	1.094 (0.354-0.381)	= 0.875
Prostate volume, Ref. one cc	0.978 (0.365-0.991)	< 0.001
Number of MRI lesions, Ref. 1	2.212 (0.848-5.160)	= 0.066
PI-RADS score of index lesion, Ref. 2	7.285 (4.455-11.913)	< 0.001
Diameter of index lesion, Ref. one mm	1.005 (0.930-1.096)	= 0.901
Number of targeted cores to index lesion, Ref. 2 cores2	1.167 (0.993-1.372)	= 0.061
Zone of lesion, Ref. CZ	0.710 (0.265-1.899)	= 0.495
Position of index lesion, Ref. posterior	0.730 (0.255-2.090)	= 0.557

CI = confidence interval; PSA = prostate-specific antigen; MRI = magnetic resonance imaging; PI-RADS = prostate imaging-report and data system; CZ = central zone.

Figure 3 - Discrimination ability for csPCa of the developed model based for performing only targeted biopsy of the index lesion (A), and decision curve analysis showing the benefit of the developed model compared to conduct targeted biopsies of the index lesion in all cases (B).



the 100% sensitivity threshold, it would be possible to avoid 72 (23.3%) mapping-targeted biopsies of the index lesion without missing additional cases of csPCa, beyond the six cases (3.1%) that were only detected in systematic biopsies and targeted biopsies of the second suspicious lesions (note that one case was detected in both types of biopsies).

Following the implementation of the developed model, 602 additional core samples, corresponding to the 72 avoided mapping-targeted prostate biopsies of the index lesion, would be spared. When combined with the previously estimated 63.6% reduction in core samples resulting from exclusively performing mapping-targeted biopsies of index lesions, this would result in a total reduction of 72.8% in core samples.

DISCUSSION

Early detection of csPCa continues to improve with the implementation of new MRI-TRUS image fusion software for performing targeted biopsies (25), new strategies for biopsying (26), and the recent recommendation for the transperineal approach (27). The challenge is to detect the maximum amount of csPCa while minimizing the over-detection of iPCa and secondary side effects (9, 28).

In this study, we report, to the best of our knowledge, the first series of MRI-TRUS fusion image biopsies with the Artemis™ platform through the transperineal route, utilizing mapping-targeted biopsies of suspicious lesions and a 12-core systematic biopsy. The overall PCa detection rate reached 74.4%, with 62.1% for csPCa and 12.3% for iPCa. These detection rates of csPCa and iPCa appear to be well balanced with the expectations in PI-RADS v2.1 and are appropriate when compared with other series (29).

In the current context of precision medicine, the multifocal nature of PCa poses a significant challenge (30). In the quest to determine the best protocol for performing targeted prostate biopsies using fusion images from MRI for the most accurate diagnosis and the lowest aggressiveness, several series have been published with multiple biopsy protocols.

These include sampling only in the peripheral prostate area, avoiding transition zone biopsy (31), performing saturation biopsies in the target area (32), combine PSA D and PI-RADS to exclusively conduct target biopsies in patients with elevated PSA D, eliminating the need for systematic biopsies (33), using Umbra (targeted lesion) and Penumbra (perilesional) samples (34), optimizing the number of cores by obtaining only three or fewer core samples per targeted lesion (35), or conducting only biopsy samples in the target lesion without systematic biopsies (36).

However, the additional value of MRI-guided biopsies of suspicious secondary lesions and systematic biopsies over index lesion mapping-guided biopsies for the detection of csPCa in fusion transperineal prostate biopsies is not yet fully established. Rachubinski et al. (37) evaluated the diagnosis of csPCa in index lesions and secondary lesions of 571 patients who underwent prostate biopsy using transperineal image fusion. This study concluded that targeted biopsy of the secondary lesion can provide valuable diagnostic information in most clinical scenarios and should not be omitted in most fusion biopsy protocols. Previous prospective studies and a meta-analysis indicate an added value of systematic biopsy for detecting csPCa, with rates ranging between 4.3% and 5.2% for the ISUP grade 2 group and between 1.2% and 4.1% for the ISUP grade 3 group in patients without prior biopsy (38, 39). Our study showed that mapping-targeted biopsies of the index lesion identified 96.3% of csPCa, and it was necessary to perform mapping-targeted biopsies of the secondary lesion to detect an additional 2.1% of csPCa cases. Another 1.6% of csPCa was only detected in systematic biopsies (see below). Our findings also revealed that biopsy at the third lesion did not identify any new cases of csPCa.

Regarding the complementarity of systematic biopsies for detecting csPCa, Petov et al. (40) have published a meta-analysis concluding that targeted and systematic biopsies have comparable csPCa detection rates. Marra et al. (41) reported that the PCa detection rate of targeted biopsy was higher than that of systematic biopsies, but their role should not be

overlooked, and the combination of targeted and systematic biopsies is essential. In line with the results of these studies, the Cochrane systematic review makes its position clear regarding the complementarity of systematic biopsies with targeted biopsies via the transrectal route (14). However, the complementarity of both types of biopsies via the transperineal route is not yet well established. Porpiglia et al. (42) compared the detection rate of csPCa between targeted biopsy alone and targeted biopsy complemented with systematic biopsy. This trial was designed as a non-inferiority study and concluded that fusion-targeted biopsy alone was not inferior to the fusion biopsy complemented with systematic biopsy for the detection of csPCa by the transperineal approach. In our study, the complementarity analysis between mapping-targeted biopsy and systematic biopsy showed that csPCa was only detected in systematic biopsy in three cases (1%). Regarding the correlation between mapping-targeted biopsies and systematic biopsies, we observed that nine ISUP-GG 1 tumors were detected in the systematic biopsies in men with no PCa detected in targeted biopsies, which increased the rate of over-detection. In three cases, systematic biopsies did not yield any new diagnosis of csPCa but resulted in an up-grading of targeted biopsies from ISUP-GG 2 to ISUP-GG 3 in two cases, and to ISUP-GG 5 in one case. We consider these findings important for establishing the management of localized PCa with active surveillance or focal therapy (43).

Having established the high effectiveness of mapping-targeted biopsy of the index lesion, identifying 96.3% of csPCa, we developed a new predictive model for detecting csPCa in mapping-targeted biopsies of the index lesion. This model reported a high discrimination ability, allowing us to avoid almost one quarter of prostate biopsies without missing additional csPCa, accounting for seven cases (3.6%); of these, four were detected only in the second suspicious lesion, and three only in the systematic biopsy. Additionally, to reduce almost one quarter of prostate biopsies, the application of this model decreased the aggressiveness of the overall prostate biopsy approach. In summary, the strategy of performing only

mapping-targeted biopsy of the index lesion and applying the developed predictive model avoided almost one quarter of prostate biopsies and reduced the aggressiveness of overall prostate biopsies by reducing 72.8% of the 6,573 core samples obtained.

Our study is affected by several limitations, primarily due to its retrospective and non-randomized design. This study was conducted under a specific biopsy protocol, using the Artemis™ platform in a single center. An expert reading of MRI, reclassifying PI-RADS v.2.1, accurate segmentation of suspicious lesions by an expert radiologist, and a limited number of experienced surgeons performing the procedure may have contributed to the high rate of csPCa detection. Future well-designed studies will be needed to analyze simple and efficient strategies for prostate biopsy while minimizing its aggressiveness.

CONCLUSIONS

Transperineal mapping-targeted biopsy of the index lesion was effective in identifying over 95% of csPCa. Furthermore, the application of a developed predictive model for csPCa detection in mapping-targeted biopsy of the index lesion reduced the number of prostate biopsies by almost one quarter without missing additional csPCa. This combined strategy significantly decreased the aggressiveness of prostate biopsies by reducing almost 75% of core samples obtained, particularly when using the Artemis™ robotic platform.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72:7-33.
2. Bertuccio P, Santucci C, Carioli G, Malvezzi M, La Vecchia C, Negri E. Mortality Trends from Urologic Cancers in Europe over the Period 1980-2017 and a Projection to 2025. *Eur Urol Oncol.* 2021;4:677-96.

3. Draisma G, Boer R, Otto SJ, van der Cruysen IW, Damhuis RA, Schröder FH, et al. Lead times and overdetected due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst.* 2003;95:868-78.
4. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol.* 2016;40:244-52.
5. Hoeks CM, Barentsz JO, Hambrock T, Yakar D, Somford DM, Heijmink SW, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. *Radiology.* 2011;261:46-66.
6. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol.* 2016;69:16-40.
7. Jue JS, Rastinehad AR. MRI Fusion Transperineal Prostate Biopsy Instructions and Troubleshooting. *J Endourol.* 2021;35(S2):S2-S6.
8. Kim MM, Wu S, Lin SX, Crotty RK, Harisinghani M, Feldman AS, et al. Transperineal Multiparametric Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy Combined with Standard Template Improves Prostate Cancer Detection. *J Urol.* 2022;207:86-94.
9. Lee DJ, Recabal P, Sjöberg DD, Thong A, Lee JK, Eastham JA, et al. Comparative Effectiveness of Targeted Prostate Biopsy Using Magnetic Resonance Imaging Ultrasound Fusion Software and Visual Targeting: a Prospective Study. *J Urol.* 2016;196:697-702.
10. Guo LH, Wu R, Xu HX, Xu JM, Wu J, Wang S, Bo XW, Liu BJ. Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial. *Sci Rep.* 2015;5:16089.
11. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol.* 2021;79:243-62.
12. Connor MJ, Gorin MA, Eldred-Evans D, Bass EJ, Desai A, Dudderidge T, et al. Landmarks in the evolution of prostate biopsy. *Nat Rev Urol.* 2023;20:241-58.
13. Williams C, Ahdoot M, Daneshvar MA, Hague C, Wilbur AR, Gomella PT, et al. Why Does Magnetic Resonance Imaging-Targeted Biopsy Miss Clinically Significant Cancer? *J Urol.* 2022;207:95-107.
14. Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev.* 2019;4:CD012663.
15. Hugosson J, Månsson M, Wallström J, Axcróna U, Carlsson SV, Egevad L, et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. *N Engl J Med.* 2022;387:2126-37.
16. Bourgeno HA, Jabbour T, Baudewyns A, Lefebvre Y, Ferriero M, Simone G, et al. The Added Value of Side-specific Systematic Biopsy in Patients Diagnosed by Magnetic Resonance Imaging-targeted Prostate Biopsy. *Eur Urol Oncol.* 2024;S2588-9311(24)00031-2.
17. Lu AJ, Syed JS, Ghabili K, Hsiang WR, Nguyen KA, Leapman MS, et al. Role of Core Number and Location in Targeted Magnetic Resonance Imaging-Ultrasound Fusion Prostate Biopsy. *Eur Urol.* 2019;76:14-7.
18. Bryk DJ, Llukani E, Taneja SS, Rosenkrantz AB, Huang WC, Lepor H. The Role of Ipsilateral and Contralateral Transrectal Ultrasound-guided Systematic Prostate Biopsy in Men With Unilateral Magnetic Resonance Imaging Lesion Undergoing Magnetic Resonance Imaging-ultrasound Fusion-targeted Prostate Biopsy. *Urology.* 2017;102:178-82.
19. Morote J, Borque-Fernando A, Triquell M, Celma A, Regis L, Escobar M, et al. The Barcelona Predictive Model of Clinically Significant Prostate Cancer. *Cancers (Basel).* 2022;14:1589.
20. Morote J, Borque-Fernando Á, Triquell M, Campistol M, Servian P, Abascal JM, et al. Comparison of Rotterdam and Barcelona Magnetic Resonance Imaging Risk Calculators for Predicting Clinically Significant Prostate Cancer. *Eur Urol Open Sci.* 2023;53:46-54.
21. Moore CM, Kasivisvanathan V, Eggener S, Emberton M, Fütterer JJ, Gill IS, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. *Eur Urol.* 2013;64:544-52.

22. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol*. 2019;76:340-51.
23. Roethke MC, Kuru TH, Schultze S, Tichy D, Kopp-Schneider A, Fenchel M, et al. Evaluation of the ESUR PI-RADS scoring system for multiparametric MRI of the prostate with targeted MR/TRUS fusion-guided biopsy at 3.0 Tesla. *Eur Radiol*. 2014;24:344-52. Erratum in: *Eur Radiol*. 2014;24:967.
24. Epstein JI, Zelefsky MJ, Sjöberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur Urol*. 2016;69:428-35.
25. Tewes S, Peters I, Tiemeyer A, Peperhove M, Hartung D, Pertschy S, et al. Evaluation of MRI/Ultrasound Fusion-Guided Prostate Biopsy Using Transrectal and Transperineal Approaches. *Biomed Res Int*. 2017;2017:2176471.
26. Franklin A, Gianduzzo T, Yaxley J, Kua B, Coughlin G, Samarantunga H, et al. Use of a trizonal schema to assess targeting accuracy in prostatic fusion biopsy. *BJU Int*. 2020;126 (Suppl 1):6-11.
27. Mischinger J, Kaufmann S, Russo GI, Harland N, Rausch S, Amend B, et al. Targeted vs systematic robot-assisted transperineal magnetic resonance imaging-transrectal ultrasonography fusion prostate biopsy. *BJU Int*. 2018;121:791-8.
28. Gilberto GM, Arcuri MF, Falsarella PM, Mariotti GC, Lemos PLA Neto, Garcia RG. Complication rates of transrectal and transperineal prostate fusion biopsies - is there a learning curve even in high volume interventional center? *Int Braz J Urol*. 2023;49:334-40.
29. Paesano N, Catalá V, Tcholakian L, Trilla E, Morote J. A Systematic Review of the Current Status of Magnetic Resonance-Ultrasound Images Fusion Software Platforms for Transperineal Prostate Biopsies. *Cancers (Basel)*. 2023;15:3329.
30. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study. *Eur Urol*. 2015;68:927-36.
31. Kachanov M, Leyh-Bannurah SR, Roberts MJ, Sauer M, Beyersdorff D, Boiko S, et al. Optimizing Combined Magnetic Resonance Imaging (MRI)-Targeted and Systematic Biopsy Strategies: Sparing the Multiparametric MRI-Negative Transitional Zone in Presence of Exclusively Peripheral Multiparametric MRI-Suspect Lesions. *J Urol*. 2022;207:333-40.
32. Tschirdewahn S, Wiesenfarth M, Bonekamp D, Püllen L, Reis H, Panic A, et al. Detection of Significant Prostate Cancer Using Target Saturation in Transperineal Magnetic Resonance Imaging/Transrectal Ultrasonography-fusion Biopsy. *Eur Urol Focus*. 2021;7:1300-07.
33. Lv Z, Wang J, Wang M, Hou H, Song L, Li H, et al. Is it necessary for all patients with suspicious lesions undergo systematic biopsy in the era of MRI-TRUS fusion targeted biopsy? *Int Braz J Urol*. 2023;49:359-71.
34. Brisbane WG, Priester AM, Ballon J, Kwan L, Delfin MK, Felker ER, et al. Targeted Prostate Biopsy: Umbra, Penumbra, and Value of Perilesional Sampling. *Eur Urol*. 2022;82:303-10.
35. Porpiglia F, De Luca S, Passera R, De Pascale A, Amparore D, Cattaneo G, et al. Multiparametric Magnetic Resonance/Ultrasound Fusion Prostate Biopsy: Number and Spatial Distribution of Cores for Better Index Tumor Detection and Characterization. *J Urol*. 2017;198:58-64.
36. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med*. 2018;378:1767-77.
37. Rachubinski P, Witt JH, Budäus L, Zinke J, Fangmeyer B, Spieker T, et al. Precision-guidance vs Systematic Sampling: Optimizing Biopsy Assessment of Secondary Prostate Cancer Suspicious Multiparametric Magnetic Resonance Imaging Lesions. *J Urol*. 2022;208:1203-13.
38. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol*. 2019;20:100-9.

39. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *Eur Urol*. 2019;75:570-8.
40. Petov V, Azilgareeva C, Shpikina A, Morozov A, Krupinov G, Kozlov V, et al. Robot-Assisted Magnetic Resonance Imaging-Targeted versus Systematic Prostate Biopsy; Systematic Review and Meta-Analysis. *Cancers (Basel)*. 2023;15:1181.
41. Marra G, Zhuang J, Beltrami M, Callaris G, Zhao X, Marquis A, et al. Transperineal freehand multiparametric MRI fusion targeted biopsies under local anaesthesia for prostate cancer diagnosis: a multicentre prospective study of 1014 cases. *BJU Int*. 2021;127:122-30.
42. Porpiglia F, Checcucci E, DE Cillis S, Piramide F, Amparore D, Piana A, et al. A prospective randomized controlled trial comparing target prostate biopsy alone approach vs. target plus standard in naïve patients with positive mpMRI. *Minerva Urol Nephrol*. 2023;75:31-41.
43. Jaipuria J, Ahmed HU. Clinical and pathologic characteristics to select patients for focal therapy or partial gland ablation of nonmetastatic prostate cancer. *Curr Opin Urol*. 2022;32:224-30.

Correspondence address:**Nahuel Paesano, MD**

Creu Blanca Clinic

Av. Josep Vicenç Foix, 71

Barcelona, 08034, Spain

Telephone: + 34 69 112-7234

E-mail: npaesano@gmail.com

5.5. PUBLICACIÓN 5

Título: Comparing Two Targeted Biopsy Schemes for Detecting Clinically Significant Prostate Cancer in Magnetic Resonance Index Lesions: Two- to Four-Core versus Saturated Transperineal Targeted Biopsy

Revista: Cancers

Año de publicación: 2024

Volumen: 16

Páginas: 2306

DOI: <https://doi.org/10.3390/cancers16132306>

Autores: Juan Morote, Nahuel Paesano, Natàlia Picola, Berta Miró, José M. Abascal, Pol Servian, Enrique Trilla, and Olga Méndez

Factor de impacto (JCR): 4.4

Cuartil (JCR): 2 (Área de Oncología)

Article

Comparing Two Targeted Biopsy Schemes for Detecting Clinically Significant Prostate Cancer in Magnetic Resonance Index Lesions: Two- to Four-Core versus Saturated Transperineal Targeted Biopsy

Juan Morote ^{1,2,3,*}, Nahuel Paesano ^{2,4}, Natàlia Picola ⁵, Berta Miró ⁶, José M. Abascal ^{7,8}, Pol Servian ⁹, Enrique Trilla ^{1,2,3,†} and Olga Méndez ^{3,†}

¹ Department of Urology, Vall d'Hebron University Hospital, 08035 Barcelona, Spain; enrique.trilla@vallhe-bron.cat

² Department of Surgery, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain; npaesa@gmail.com

³ Research Group in Urology, Vall d'Hebron Research Institute, 08035 Barcelona, Spain; olga.mendez@vhir.org

⁴ Clínica Creu Blanca, 08018 Barcelona, Spain

⁵ Department of Urology, Bellvitge University Hospital, Hospitalet de Llobregat, 08907 Barcelona, Spain; npicola.bellvitge@gencat.cat

⁶ Statistics Unit, Vall d'Hebron Research Institute, 08035 Barcelona, Spain; berta.miro@vhir.org

⁷ Department of Urology, Parc de Salut Mar, 08003 Barcelona, Spain; jabascal@psmar.cat

⁸ Department of Health Sciences, Universitat Pompeu Fabra, 08003 Barcelona, Spain

⁹ Department of Urology, Hospital Germans Trias i Pujol, 08916 Badalona, Spain; pservian.germanstrias@gencat.cat

* Correspondence: juan.morote@uab.cat; Tel.: +34-629-011-936

† These authors contributed equally to this work.



Citation: Morote, J.; Paesano, N.; Picola, N.; Miró, B.; Abascal, J.M.; Servian, P.; Trilla, E.; Méndez, O. Comparing Two Targeted Biopsy Schemes for Detecting Clinically Significant Prostate Cancer in Magnetic Resonance Index Lesions: Two- to Four-Core versus Saturated Transperineal Targeted Biopsy. *Cancers* **2024**, *16*, 2306. <https://doi.org/10.3390/cancers16132306>

Academic Editors: Milica Medved and Artrick Chatterjee

Received: 6 June 2024

Revised: 21 June 2024

Accepted: 22 June 2024

Published: 23 June 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Simple Summary: Targeted biopsies of suspicious lesions detected in magnetic resonance imaging are crucial to discover clinically significant prostate cancer, especially those corresponding to index lesions. However, the optimal scheme for targeted biopsies remains unclear, despite the fact that a two- to four-core scheme is usually recommended. Saturated biopsies of the prostate gland have shown high efficiency in detecting significant PCa. In this article, we report a better efficacy for mapping using a 0.5 mm core biopsy scheme than that using the two- to four-core scheme for detecting clinically significant prostate cancer in magnetic resonance index lesions.

Abstract: Since the optimal scheme for targeted biopsies of magnetic resonance imaging (MRI) suspicious lesions remains unclear, we compare the efficacy of two schemes for these index lesions. A prospective trial was conducted in 1161 men with Prostate Imaging Reporting and Data System v 2.1 3–5 undergoing targeted and 12-core systematic biopsy in four centers between 2021 and 2023. Two- to four-core MRI-transrectal ultrasound fusion-targeted biopsies via the transperineal route were conducted in 900 men in three centers, while a mapping per 0.5 mm core method (saturated scheme) was employed in 261 men biopsied in another center. A propensity-matched 261 paired cases were selected for avoiding confounders other than the targeted biopsy scheme. csPCa (grade group ≥ 2) was identified in 125 index lesions (41.1%) when the two- to four-core scheme was employed, while in 187 (71.9%) when the saturated biopsy ($p < 0.001$) was used. Insignificant PCa (iPCa) was detected in 18 and 11.1%, respectively ($p = 0.019$). Rates of csPCa and iPCa remained similar in systematic biopsies. CsPCa detected only in systematic biopsies were 5 and 1.5%, respectively ($p = 0.035$) in each group. The saturated scheme for targeted biopsies detected more csPCa and less iPCa than did the two- to four-core scheme in the index lesions. The rate of csPCa detected only in the systematic biopsies decreased when the saturated scheme was employed.

Keywords: prostate cancer; targeted biopsy; index lesion; number of cores

1. Introduction

Risk-stratified prostate cancer (PCa) screening, based on serum prostate-specific antigen (PSA) testing and magnetic resonance imaging (MRI) scanning as a follow-up measure, is currently recommended by the European Union [1]. This new paradigm of PCa screening is focused on maximizing the early detection of clinically significant PCa (csPCa), while minimizing the number of prostate biopsies and the over-detection of insignificant prostate cancer (iPCa) [2–5].

The Prostate Imaging Reporting and Data System (PI-RADS) predicts the risk of csPCa according to the imaging characteristics of lesions detected in MRI scans [6–8]. Men with PI-RADS < 3 have a very low probability of csPCa, and consequently, in this case, prostate biopsies can usually be avoided [9,10]. MRI can visualize most lesions containing csPCa, reporting them as PI-RADS 3 to 5, with an intermediate, high, and very high-risk of csPCa, respectively [11]. PI-RADS 3 is considered the gray zone of a PI-RADS score, since the csPCa detection rate is 18.5%, with a 95% confidence interval between 16.6 and 20.3%, but a range between 3.4 and 46.5% [12]. A significant contribution of MRI is the possibility of conducting targeted biopsies for suspicious lesions through MRI-transrectal ultrasound (TRUS) fusion images [13]. However, a small percentage of csPCa are not visualized in MRI scans and are detected only in systematic biopsies, which is the reason why these biopsies are still recommended [14].

The recommendation for changing the approach of prostate biopsies from the classic transrectal to the transperineal route has reduced the infrequent but dangerous infectious complications and the inappropriate use of antibiotics [15,16] accompanying this method. It is known that a prostate biopsy scheme for avoiding the upgrading of csPCa in radical prostatectomy specimens requires a mapping biopsy per 0.5 mm, with additional targeted biopsies of suspicious lesions detected by MRI [17]. However, systematic biopsies complementing targeted biopsies for suspicious lesions causes significant over-detection of iPCa [18].

The currently recommended prostate biopsy scheme suggests obtaining a two- to four-core targeted biopsy of suspicious lesions and a 12-core systematic biopsy [14,19–21]. However, the appropriate number of cores obtained from targeted biopsies remains unclear. Two studies have examined the correlation between the PCa grade groups detected in prostate biopsies and those observed in radical prostatectomy specimens, suggesting that obtaining more cores from suspicious lesions reduces the likelihood of upgrading [22,23]. Other studies, conducted in men undergoing transperineal prostate biopsies, suggest the improved detection of csPCa when a saturation scheme for targeted biopsies is employed; however, the results are not uniform [24–27]. The potential of the index lesion, defined from MRI as the largest lesion with the highest PI-RADS score, for defining the aggressiveness of PCa is known [28–30]. However, an appropriate biopsy scheme for the index lesion could minimize unnecessary biopsies from other areas of the prostate gland, as well as systematic biopsies [31]. Mainly, the specifics regarding the differences between the two- to four-core and the saturated scheme for targeted biopsies is the rationale of mapping each 0.5 mm, which has been shown to be the most appropriate scheme for avoiding upgrading in radical prostatectomy specimens [13,22–27].

We hypothesize that the saturated scheme for targeted biopsies detects more csPCa in the index lesions than does the recommended two- to four-core scheme. The objectives of this study are to compare the rates of csPCa and iPCa detection in both targeted biopsy schemes and to assess the rates of csPCa detected only in systematic biopsies.

2. Materials and Methods

2.1. Design, Setting, and Participants

A prospective non-randomized trial including 1161 consecutive men suspected of having PCa, based on a serum PSA > 3.0 ng/mL, was conducted in four centers participating in the csPCa opportunistic early detection program of Catalonia (Spain) between 1 January 2021 and 30 June 2023. All included men exhibited PI-RADS v 2.1 lesions 3 to 5

in pre-biopsy multiparametric MRI (mpMRI), undergoing targeted biopsy of suspicious lesions and 12-core systematic biopsy. Three participant centers, always obtaining two- to four-cores from each suspicious lesion, reported 900 cases, while 261 cases were reported in another center, where a mapping per 0.5 mm core scheme was always employed. Due to the possible influence on csPCa detection, men undergoing treatment with 5-alpha reductase inhibitors and those with prior history of PCa, atypical small acinar proliferation, or multifocal high-grade prostatic intraepithelial neoplasia were not included in this study.

2.2. Diagnostic Approach for csPCa Detection

MpMRI using a 3 Tesla scan was performed in each participant center using a pelvic phased-array surface coil. The acquisition protocol included T2-weighted imaging (T2W), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging, according to the guidelines of the European Society of Urogenital Radiology [6]. MpMRI exams were reported by local expert radiologists using the PI-RADS v 2.1 [8]. Local experienced operators performed prostate biopsies using the Koelis Trinity® hands-free MRI/TUS prostate biopsy system (Koelis Inc., Grenoble, France) in the centers conducting targeted biopsies with the two- to four-core scheme, while the Artemis® hands-free MRI/TUS prostate biopsy system (Eigen Inc., Grass Valley, CA, USA) was used in the center performing the mapping per 0.5 mm core scheme. Experienced local uropathologists examined the biopsy material in each pathology department, reporting PCa using the International Society of Urologic Pathology grade group (GG) classification. CsPCa was considered when the GG was ≥ 2 [32]. Baseline characteristics of the study cohort are summarized in Table 1.

Table 1. Characteristics of cohort study.

Characteristic	Measurement
Number of men	1161
Median age, years (IQR)	67 (61–73)
Median serum PSA, ng/mL (IQR)	6.7 (5.1–9.9)
Abnormal DRE, <i>n</i> (%)	200 (25.8)
Median prostate volume, mL (IQR)	50 (36–70)
Prior negative prostate biopsy, <i>n</i> (%)	403 (34.7)
Family history of PCa, <i>n</i> (%)	96 (8.3%)
Median suspicious lesions, <i>n</i> (IQR)	1 (1–2)
Median length of suspicious lesions, mm (IQR)	11 (5–17)
Localization of the index lesion, <i>n</i> (%)	
Peripheral zone	835 (71.9)
Central-transition zone	278 (23.9)
Anterior zone	48 (4.2)
PI-RADS score of the index lesion, <i>n</i> (%)	
3	260 (22.4)
4	587 (50.4)
5	315 (27.1)
Median cores obtained in targeted biopsy, <i>n</i>	
(IQR) index lesion, <i>n</i> (IQR)	3 (1–7)
Overall PCa detection, <i>n</i> (%)	815 (70.2)
csPCa	601 (51.8)
iPCa	241 (18.4)

IQR = interquartile range; *n* = number; PCa = prostate cancer; csPCa = clinically significant PCa; iPCa = insignificant PCa.

2.3. Variables in the Study and Outcome Variables

Age (years), first degree PCa family history (no vs. yes), type of prostate biopsy (initial vs. repeated), serum PSA (ng/mL), DRE (normal vs. suspicious), MRI-prostate volume (mL), PI-RADS score v 2.1 (3 to 5), size and localization of the index lesion, targeted biopsy scheme (two- to four-core vs. mapping per 0.5-core) were predictive variables in the study. Outcome variables were csPCa and iPCa detection.

2.4. Statistical Analysis

Statistical analysis was conducted after harmonization of the anonymized datasets. Data were prospectively collected and reported according to the Standards of Reporting for MRI-Targeted Biopsy Studies (START) to describe the study population [33]. Quantitative variables are described using medians and interquartile ranges (IQR: 25th–75th percentile), while qualitative variables are described using numbers and percentages. Quantitative variables were compared between groups using the Mann–Whitney U test. Qualitative variables were compared between groups using Pearson’s chi-square test. Relative risk (RR) of csPCa and 95% confidence intervals (CI) were assessed. A logistic regression analysis conducted for detecting independent predictive variables of csPCa, in addition to the targeted biopsy scheme, showed that PI-RADS score, prostate volume, age, serum PSA, location, and size of the index lesion were independent predictors of csPCa and were potential confounders for csPCa detection (Table 2).

Table 2. Multivariate analysis searching confounder variables for csPCa detection in the index lesion, in addition to the targeted biopsy scheme employed.

Predictive Variable	Odds Ratio (95% CI)	p Value
Age, Ref. year	1.061 (1.036–1.086)	<0.001
Serum PSA, Ref. ng/mL	1.062 (1.027–1.099)	<0.001
DRE, Ref. normal	1.154 (0.775–1.718)	=0.481
Type of biopsy, Ref. initial	0.960 (0.695–1.429)	=0.841
PCa family history, Ref. no	1.258 (0.749–2.111)	=0.386
Prostate volume, Ref. mL	0.972 (0.065–0.979)	<0.001
Number of suspicious lesions, Ref. one	1.387 (0.863–2.231)	=0.177
PI-RADS score of the index lesion, Ref. 3	2.718 (2.032–3.365)	<0.001
Size of the index lesion, Ref. mm	1.071 (1.030–1.113)	<0.001
Localization of the index lesion, Ref. peripheral zone	0.611 (0.438–0.852)	=0.004
Targeted prostate biopsy scheme, Ref. 2- to 4-core	2.137 (1.869–3.439)	<0.001

CI = confidence interval; PSA = prostate specific antigen; DRE = digital rectal examination; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System.

A randomized 1:1 matched group from all predictive variables was selected using the R package matching v 4.10, a multivariate and propensity score matching software with automated balance optimization (R Foundation for Statistical Computing, Vienna, Austria). In a subset of 522 men, the two- to four-core scheme was employed, and the mapping per 0.5 mm core scheme was used in the other 261 men. Table 3 shows the suitability of this matched paired group for analysis, since all baseline confounder characteristics for csPCa detection were equally distributed in both study subsets. A *p* value of <0.05 was considered statistically significant. The data were analyzed using the Statistical Package for the Social Sciences (version 29.0; IBM Corp., Armonk, NY, USA).

Table 3. Baseline characteristics of the paired matched study group and a comparative analysis between them, according to biopsy scheme applied for targeted biopsy of the index lesions.

Baseline Characteristic	Biopsy Scheme of the Index Lesion		p Value
	Two- to Four-Core	Mapping × 0.5 mm Core	
Number of men, <i>n</i> (%)	261 (50.0)	261 (50.0)	-
Median age, years (IQR)	67 (61–73)	67 (61–73)	=1.000
Median serum PSA, ng/mL (IQR)	6.7 (5.0–9.6)	6.7 (5.0–9.6)	=1.000
Abnormal DRE, <i>n</i> (%)	65 (24.9)	67 (25.7)	=0.678
Median prostate volume, mL (IQR)	45 (33–62)	45 (33–62)	=1.000
Prior negative prostate biopsy, <i>n</i> (%)	63 (24.1)	68 (26.0)	=0.357
Family history of PCa, <i>n</i> (%)	30 (11.5%)	28 (10.7)	=0.419
Median suspicious lesions, <i>n</i> (IQR)	1 (1–2)	1 (1–2)	=1.000
Median length of the index lesion, mm (IQR)	12 (9–18)	12 (9–18)	=1.000

Table 3. Cont.

Baseline Characteristic	Biopsy Scheme of the Index Lesion		p Value
	Two- to Four-Core	Mapping × 0.5 mm Core	
Index lesion localization, <i>n</i> (%)			
Peripheral zone	179 (68.6)	179 (68.6)	=1.000
Central/transition zone	62 (23.8)	62 (23.8)	=1.000
Anterior zone	20 (7.7)	20 (7.7)	=1.000
PI-RADS score of index lesion, <i>n</i> (%)			
3	71 (27.2)	71 (27.2)	=1.000
4	118 (45.2)	118 (45.2)	=1.000
5	72 (27.6)	72 (27.6)	=1.000
Median number of cores in the index lesion, <i>n</i> (IQR) obtained, <i>n</i> (IQR)	2 (1–3)	9 (5–12)	=0.016
Overall PCa detection, <i>n</i> (%)	328 (63.9)	216 (82.7)	<0.001
csPCa, <i>n</i> (%)	235 (45.8)	187 (71.6)	<0.001
iPCa, <i>n</i> (%)	93 (18.1)	29 (11.1)	=0.012

IQR = interquartile range; *n* = number; PI-RADS = Prostate Imaging Reporting and Data System; PCa = prostate cancer; csPCa = clinically significant PCa; iPCa = insignificant PCa.

3. Results

3.1. Baseline Characteristics of the Study Population

The baseline characteristics of the propensity-matched group comprising 522 men, including 261 men who underwent targeted biopsies employing the two- to four-core scheme and 261 who underwent the mapping per 0.5 mm core scheme, were similar except in regards to the median number of cores utilized in each targeted biopsy scheme, which were 2 (IQR 1–2) and 9 (IQR 5–12), respectively ($p = 0.016$). The detection rate of PCa in the index lesion and the 12-core systematic biopsies, according to the employed scheme, were 63.6 and 82.7%, respectively ($p < 0.001$), with 45.8 and 71.6% csPCa, and 18.1 and 11.1% iPCa, respectively ($p = 0.012$), Table 3.

3.2. CsPCa Detection in the Index Lesions according to the PI-RADS Score and the Biopsy Scheme

Among 142 men with a PI-RADS score of 3, csPCa was identified in 13 of 71 (18.3%) index lesions biopsied using the two- to four-core scheme, while in 26 of 71 (26.8%) when the mapping per 0.5 mm core scheme was employed, with an RR of 1.298 (95% CI 0.824–2.045), $p = 0.158$. Among 236 men with a PI-RADS score of 4, these rates were 47.4% and 87.3%, respectively, with an RR of 2.286 (95% CI 1.802–2.900), $p = 0.001$. Among 144 men with a PI-RADS score of 5, the rates were 77.8% and 90.3%, respectively, with an RR of 1.503 (95% CI 1.079–2.094), $p < 0.001$ (Figure 1).

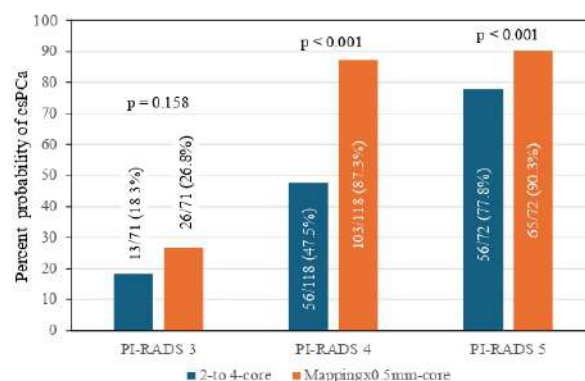


Figure 1. CsPCa detection in the index lesion targeted biopsies, according to the employed two- to four-core and mapping × 0.5 mm core schemes and the PI-RADS score.

3.3. Detection of csPCa and iPCa in the Index Lesions, According to the Employed Biopsy Scheme and Those Detected in Systematic Biopsies

Figure 2 summarizes the csPCa and iPCa detection in the targeted biopsies of the index lesions and systematic biopsies, according to the employed targeted biopsy scheme. CsPCa detection in the index lesions was 47.9% when two- to four-core scheme was applied, while 71.9% when mapping per 0.5 mm core scheme was used, with an RR of 1.616 (95% CI 1.366–1.913), $p < 0.001$. iPCa detected in the index lesions were 18.8 and 11.1%, respectively, with an RR of 0.760 (95% CI 0.624–0.925), $p = 0.006$. The csPCa detection rates in systematic biopsies, according to the biopsy scheme employed in the targeted biopsies, corresponded to 28.0%, when the two- to four-core scheme was used, and 26.8%, when the mapping per 0.5 mm core scheme was employed, with an RR of 0.829 (95% CI 0.789–1.121), $p = 0.228$. The iPCa detection rates in systematic biopsies were 19.2% and 21.5%, respectively, with an RR of 1.191 (95% CI 0.940–1.909), $p = 0.187$.

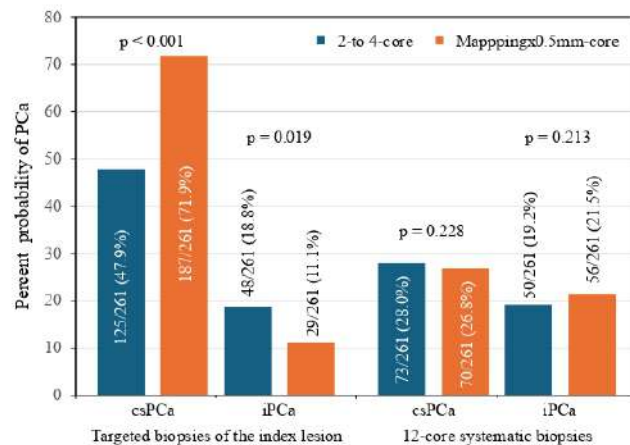


Figure 2. Detection of csPCa and iPCa in the index lesion targeted biopsies and the 12-core systematic biopsies, according to the two- to four-core and mapping $\times$ 0.5 mm core schemes employed in the targeted biopsies.

CsPCa was detected only in 12-core systematic biopsies in 5.0% of cases when the two- to four-core scheme was applied in the targeted biopsies, while it decreased to 1.5% when the mapping per 0.5 mm core scheme was employed, with an RR of 0.642 (95% CI 0.486–0.848), $p = 0.213$ (Figure 3).

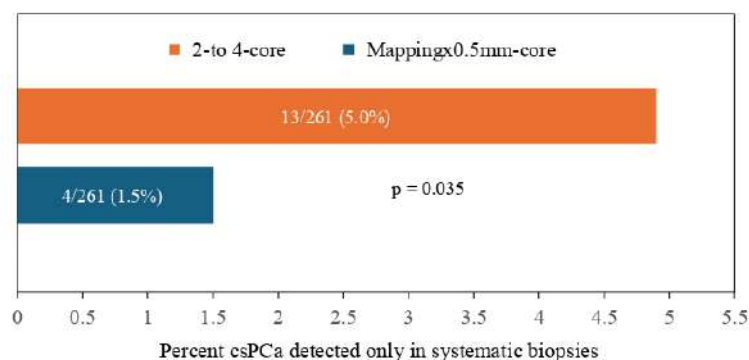


Figure 3. CsPCa detection in only the 12-core systematic biopsies, according to the two- to four-core and mapping $\times$ 0.5 mm core schemes employed in the targeted biopsies.

4. Discussion

The analysis of this prospective and multicenter trial was conducted in a propensity-paired matched group to avoid the influence of existing confounder variables for csPCa detection other than the targeted biopsy scheme. Our main findings were, (i) the csPCa detection in the index lesions improved when the saturated mapping per 0.5 mm core targeted biopsy scheme was employed, compared with the results for the currently recommended two- to four-core scheme; (ii) this improvement was observed in all PI-RADS categories, although it was significant only in categories 4 and 5; (iii) the iPCa detection rates in the index lesions decreased when the saturated scheme was employed, compared with the results for the two- to four-core scheme; (iv) the percentage of csPCa detected only in systematic biopsies decreased when the saturated scheme was employed compared to the results for the two- to four-core scheme.

In 2013, the Ginsburg Study Group first proposed obtaining two to four cores in targeted biopsies of suspicious lesions in MRI-TRUS fusion prostate biopsies conducted via the transperineal route. This group also proposed at least 4-core biopsies of the anterior, mid, posterior, and basal sectors of the right and left prostate lobules, resulting in 24 cores for prostate glands of less than 30 mL, 32 cores for those of 30 to 50 mL, and 38 additional cores for prostate glands of more than 50 mL [17]. In 2016, Radtke et al. observed that the Ginsburg approach was able to identify 97% of csPCa detected in 120 radical prostatectomy specimens, while only 79% of them were identified in systematic biopsies, and 88% were found in targeted biopsies alone [22]. In 2018, Calio et al. examined 122 men who underwent targeted MRI-TRUS index lesion biopsies employing a two-core scheme and 86 men who underwent a mapping per 0.6 mm core scheme. Additionally, all men underwent a 12-core systematic biopsy. The authors observed a surgical specimen upgrading of 40.9% with systematic biopsies, 23.6% with two-core targeted biopsies, and 13.8% with mapping per 0.6 mm core targeted biopsies [23]. Many studies have focused their attention on the findings in the index lesions, due to its high predictive power for defining PCa aggressiveness [28–30].

It is difficult to compare our results with those observed in previous reports due to the variability of study designs. In 2020, Hansen et al. analyzed 487 men who underwent transperineal MRI-TRUS prostate biopsies following the Ginsburg approach. Targeted biopsies of suspicious lesions using the two-core scheme only detected 67% of csPCa. In contrast, extended targeted biopsies obtaining two additional cores from sectors adjacent to the index lesion detected 76% of csPCa, and targeted biopsies using a six-core scheme detected 91% of csPCa [24]. This study suggested that obtaining more cores from targeted biopsies of the index lesion improved csPCa detection. In 2021, Tschirdewahn et al. reported a study conducted in 213 men who underwent targeted biopsies of suspicious MRI lesions, employing the Ginsburg approach, between 2016 and 2018. Targeted biopsies were collected using a four-core scheme. Targeted biopsies involved collecting 4 cores from suspicious lesions and additional cores from adjacent sectors, and systematic biopsies obtained 9 to 10 cores. Targeted saturated biopsies detected 99% of 134 csPCa, while non-saturated targeted biopsies detected 87%, and systematic biopsies detected 82% [25]. This study also confirms that greater core obtention in targeted biopsies increases csPCa detection.

In 2023, Cetin et al. reported an analysis of 167 men in whom targeted biopsies obtained two cores from the center of the suspicious lesions and two additional cores from the periphery. One central core identified 65.6% of csPCa, two central cores identified 92.2%, two central cores and one peripheral core identified 96.9%, and two central cores and two peripheral cores identified 100% of csPCa. These authors concluded that the two central cores scheme was sufficient to detect the vast majority of csPCa because the difference between two and four cores was non-significant [25].

Finally, in 2023, Sanner et al. reported a prospective single-center trial randomizing 170 men who underwent transperineal targeted biopsy of suspicious lesions employing a four-core scheme compared to targeted saturated biopsies using a nine-core scheme. Both schemes were complemented with a 24-core systematic biopsy. Targeted biopsies

detected 91.7% of csPCa, while targeted saturated biopsies detected 100%. Because this difference was non-significant, the authors concluded that csPCa detection did not differ between targeted and saturated targeted biopsies [27]. The results of this prospective and randomized trial contradict the previous retrospective study reported by the same authors [24]. A recently reported study has noted the importance of only biopsying the index lesion with an appropriate scheme for avoiding targeted biopsies of secondary lesions and systematic biopsies [31]. Additionally, our results suggest that saturated targeted biopsies reduce the rate of csPCa detected only in systematic biopsies. This finding requires confirmation in additional studies.

Our study is limited by its non-randomized design, although the propensity-matched paired group selection minimized the effect of confounder variables for csPCa detection. The utilization of different devices for MRI-TRUS biopsies and the level of experience of the surgeon performing the two different types of prostate biopsies can influence the results, as can the inter-variability between pathologists. The csPCa outcome variable detected in prostate biopsies does not represent the true csPCa detected in the radical prostatectomy specimens. Since we decided to conduct this study using the index lesions, a limitation exists in regards to recommending the saturated targeted biopsy scheme for all suspicious lesions. A limitation exists for recommending a prostate biopsy approach based only on a saturated targeted scheme of the index lesion, since the current knowledge suggests the importance of perilesional biopsies for avoiding ipsilateral systematic biopsies [34–37].

One of the strengths of this study is that it is conducted using matched pairs of men suspected of having PCa in order to avoid the influence of confounders for csPCa detection. One of the study's weakness is that it is retrospective, with a non-randomized design. However, new evidence is generated for recommending saturated targeted biopsies, possibly without systematic biopsies, if perilesional biopsies are obtained. Well-designed prospective and multicenter randomized trials identifying the most effective and least aggressive prostate biopsy scheme for transperineal prostate biopsy are needed for maximizing the detection of csPCa, minimizing the over-detection of iPCa, and reducing prostate biopsy site effects.

5. Conclusions

Saturated targeted biopsies, using a mapping per 0.5 mm core scheme, were able to detect more csPCa and less iPCa than the recommended two- to four-core scheme in the index lesions. This advantage was particularly notable in individuals with PI-RADS scores above 3. The rate of csPCa detected only in 12-core systematic biopsies decreased when the mapping per 0.5 mm core scheme for targeted biopsies was employed.

Author Contributions: Conceptualization, J.M. and N.P. (Nahuel Paesano); methodology, J.M.; formal analysis, B.M. and J.M.; resources, J.M.; data curation, N.P. (Nahuel Paesano), N.P. (Natalia Picola), J.M.A. and P.S.; writing—original draft preparation, J.M.; writing—review and editing, N.P., O.M. and E.T.; supervision, E.T. and O.M.; project administration, J.M.; funding acquisition, J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministerio de Asuntos Económicos y Transformación Digital (SP) (MIA.2021.M02.0005) and the Instituto de Salud Carlos III (SP) (PI20/01666).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Vall d'Hebron University Hospital (PRAG21/0002, approved on 12 February 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Datasets from this study are available upon request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Van Poppel, H.; Roobol, M.J.; Chandran, A. Early Detection of Prostate Cancer in the European Union: Combining Forces with PRAISE-U. *Eur. Urol.* **2023**, *84*, 519–522. [CrossRef]
2. Van Poppel, H.; Hogenhout, R.; Albers, P.; van den Bergh, R.C.N.; Barentsz, J.O.; Roobol, M.J. Early Detection of Prostate Cancer in 2020 and Beyond: Facts and recommendations for the European Union and the European Commission. *Eur. Urol.* **2020**, *79*, 327–329. [CrossRef]
3. Van Poppel, H.; Hogenhout, R.; Albers, P.; van den Bergh, R.C.N.; Barentsz, J.O.; Roobol, M.J. A European Model for an Organised Risk-stratified Early Detection Programme for Prostate Cancer. *Eur. Urol. Oncol.* **2021**, *4*, 731–739. [CrossRef] [PubMed]
4. Van Poppel, H.; Roobol, M.J.; Chapple, C.R.; Catto, J.W.F.; N'Dow, J.; Sønksen, J.; Stenzl, A.; Wirth, M. Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021. *Eur. Urol.* **2021**, *80*, 703–711.
5. Van Poppel, H.; Albrecht, T.; Basu, P.; Hogenhout, R.; Collen, S.; Roobol, M. Serum PSA-based early detection of prostate cancer in Europe and globally: Past, present and future. *Nat. Rev. Urol.* **2022**, *19*, 562–572. [CrossRef] [PubMed]
6. Barentsz, J.O.; Richenberg, J.; Clements, R.; Choyke, P.; Verma, S.; Villeirs, G.; Rouviere, O.; Logager, V.; Futterer, J.J. ESUR prostate MR guidelines 2012. *Eur. Radiol.* **2012**, *22*, 746–757. [CrossRef]
7. Weinreb, J.C.; Barentsz, J.O.; Choyke, P.L.; Cornud, F.; Haider, M.A.; Macura, K.J.; Margolis, D.; Schnall, M.D.; Shtern, F.; Tempany, C.M.; et al. PI-RADS Prostate Imaging–Reporting and Data System: 2015, Version 2. *Eur. Urol.* **2016**, *69*, 16–40. [CrossRef]
8. Turkbey, B.; Rosenkrantz, A.B.; Haider, M.A.; Padhani, A.R.; Villeirs, G.; Macura, K.J.; Tempany, C.M.; Choyke, P.L.; Cornud, F.; Margolis, D.; et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur. Urol.* **2019**, *76*, 340–351. [CrossRef]
9. Moldovan, P.C.; Van den Broeck, T.; Sylvester, R.; Marconi, L.; Bellmunt, J.; van den Bergh, R.C.; Bolla, M.; Briers, E.; Cumberbatch, M.G.; Fossati, N.; et al. What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. *Eur. Urol.* **2017**, *71*, 618–629.
10. Wagaskar, V.G.; Levy, M.; Ratnani, P.; Moody, K.; Garcia, M.; Pedraza, A.M.; Parekh, S.; Pandav, K.; Shukla, B.; Prasad, S.; et al. Clinical Utility of Negative Multiparametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer and Clinically Significant Prostate Cancer. *Eur. Urol. Open Sci.* **2021**, *28*, 9–16. [PubMed]
11. Oerther, B.; Engel, H.; Bamberg, F.; Sigle, A.; Gratzke, C.; Benndorf, M. Cancer detection rates of the PI-RADSv2.1 assessment categories: Systematic review and meta-analysis on lesion level and patient level. *Prostate Cancer Prostatic Dis.* **2022**, *25*, 256–263. [CrossRef]
12. Maggi, M.; Panebianco, V.; Mosca, A.; Salciccia, S.; Gentilucci, A.; Di Pierro, G.; Busetto, G.M.; Barchetti, G.; Campa, R.; Sperduti, I.; et al. Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. *Eur. Urol. Focus* **2020**, *6*, 463–478. [CrossRef]
13. Ahmed, H.U.; El-Shater Bosaily, A.; Brown, L.C.; Gabe, R.; Kaplan, R.; Parmar, M.K.; Collaco-Moraes, Y.; Ward, K.; Hindley, R.G.; Freeman, A.; et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. *Lancet* **2017**, *389*, 815–822. [CrossRef]
14. Drost, F.H.; Osses, D.; Nieboer, D.; Bangma, C.H.; Steyerberg, E.W.; Roobol, M.J.; Schoots, I.G. Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. *Eur. Urol.* **2020**, *77*, 78–94. [CrossRef]
15. Hu, J.C.; Assel, M.; Allaf, M.E.; Ehdaie, B.; Vickers, A.J.; Cohen, A.J.; Ristau, B.T.; Green, D.A.; Han, M.; Rezaee, M.E.; et al. Transperineal Versus Transrectal Magnetic Resonance Imaging-targeted and Systematic Prostate Biopsy to Prevent Infectious Complications: The PREVENT Randomized Trial. *Eur. Urol.* **2024**. [CrossRef]
16. Connor, M.J.; Gorin, M.A.; Eldred-Evans, D.; Bass, E.J.; Desai, A.; Dudderidge, T.; Winkler, M.; Ahmed, H.U. Landmarks in the evolution of prostate biopsy. *Nat. Rev. Urol.* **2023**, *20*, 241–258. [CrossRef]
17. Kuru, T.H.; Wadhwa, K.; Chang, R.T.; Echeverria, L.M.; Roethke, M.; Polson, A.; Rottenberg, G.; Koo, B.; Lawrence, E.M.; Seidenader, J.; et al. Definitions of terms, processes and a minimum dataset for transperineal prostate biopsies: A standardization approach of the Ginsburg Study Group for Enhanced Prostate Diagnostics. *BJU Int.* **2013**, *112*, 568–577.
18. Hugosson, J.; Månsson, M.; Wallström, J.; Axcrone, U.; Carlsson, S.V.; Egevad, L.; Geterud, K.; Khatami, A.; Kohestani, K.; Pihl, C.G.; et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. *N. Engl. J. Med.* **2022**, *387*, 2126–2137. [CrossRef]
19. Gandaglia, G.; Pellegrino, A.; Montorsi, F.; Briganti, A. Prostate Cancer: Is There Still a Role for Systematic Biopsies? Yes. *Eur. Urol. Open Sci.* **2022**, *38*, 10–11.
20. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate. Cancer. 2024. Available online: <http://uroweb.org/guidelines/compilations-of-all-guidelines/> (accessed on 5 June 2024).
21. Wei, J.T.; Barocas, D.; Carlsson, S.; Coakley, F.; Eggener, S.; Etzioni, R.; Fine, S.W.; Han, M.; Kim, S.K.; Kirkby, E.; et al. Early Detection of Prostate Cancer: AUA/SUO Guideline Part II: Considerations for a Prostate Biopsy. *J. Urol.* **2023**, *210*, 154–163.
22. Radtke, J.P.; Schwab, C.; Wolf, M.B.; Freitag, M.T.; Alt, C.D.; Kesch, C.; Popenciu, I.V.; Huettnerbrink, C.; Gasch, C.; Klein, T.; et al. Multiparametric Magnetic Resonance Imaging (MRI) and MRI-Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen. *Eur. Urol.* **2016**, *70*, 846–853. [CrossRef]

23. Calio, B.P.; Sidana, A.; Sugano, D.; Gaur, S.; Maruf, M.; Jain, A.L.; Merino, M.J.; Choyke, P.L.; Wood, B.J.; Pinto, P.A.; et al. Risk of Upgrading from Prostate Biopsy to Radical Prostatectomy Pathology-Does Saturation Biopsy of Index Lesion during Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsy Help. *J. Urol.* **2018**, *199*, 976–982. [\[CrossRef\]](#)
24. Hansen, N.L.; Barrett, T.; Lloyd, T.; Warren, A.; Samel, C.; Bratt, O.; Kastner, C. Optimising the number of cores for magnetic resonance imaging-guided targeted and systematic transperineal prostate biopsy. *BJU Int.* **2020**, *125*, 260–269. [\[CrossRef\]](#)
25. Tschirdewahn, S.; Wiesenfarth, M.; Bonekamp, D.; Püllen, L.; Reis, H.; Panic, A.; Kesch, C.; Darr, C.; Heß, J.; Giganti, F.; et al. Detection of Significant Prostate Cancer Using Target Saturation in Transperineal Magnetic Resonance Imaging/Transrectal Ultrasonography-fusion Biopsy. *Eur. Urol. Focus* **2021**, *7*, 1300–1307. [\[CrossRef\]](#)
26. Cetin, S.; Huseyinli, A.; Koparal, M.Y.; Bulut, E.C.; Ucar, M.; Gonul, I.L.; Sozen, S. How many cores should be taken from each region of interest when performing a targeted transrectal prostate biopsy. *Prostate Int.* **2023**, *11*, 122–126. [\[CrossRef\]](#)
27. Saner, Y.M.; Wiesenfarth, M.; Weru, V.; Ladyzhensky, B.; Tschirdewahn, S.; Püllen, L.; Bonekamp, D.; Reis, H.; Krafft, U.; Heß, J.; et al. Detection of Clinically Significant Prostate Cancer Using Targeted Biopsy with Four Cores Versus Target Saturation Biopsy with Nine Cores in Transperineal Prostate Fusion Biopsy: A Prospective Randomized Trial. *Eur. Urol. Oncol.* **2023**, *6*, 49–55. [\[CrossRef\]](#)
28. Ahmed, H.U. The index lesion and the origin of prostate cancer. *N. Engl. J. Med.* **2009**, *361*, 1704–1706. [\[CrossRef\]](#)
29. Valerio, M.; Anele, C.; Freeman, A.; Jameson, C.; Singh, P.B.; Hu, Y.; Emberton, M.; Ahmed, H.U. Identifying the index lesion with template prostate mapping biopsies. *J. Urol.* **2015**, *193*, 1185–1190. [\[CrossRef\]](#)
30. Russo, F.; Regge, D.; Armando, E.; Giannini, V.; Vignati, A.; Mazzetti, S.; Manfredi, M.; Bollito, E.; Correale, L.; Porpiglia, F. Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard. *BJU Int.* **2016**, *118*, 84–94. [\[CrossRef\]](#)
31. Paesano, N.; Catalá, V.; Tcholakian, L.; Alomar, X.; Barranco, M.; Trilla, E.; Morote, J. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. *Int. Braz. J. Urol.* **2024**, *50*, 119–131. [\[CrossRef\]](#)
32. Epstein, J.I.; Egevad, L.; Amin, M.B.; Delahunt, B.; Srigley, J.R.; Humphrey, P.A.; Grading, C. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am. J. Surg. Pathol.* **2016**, *40*, 244–252. [\[CrossRef\]](#)
33. Moore, C.M.; Kasivisvanathan, V.; Eggener, S.; Emberton, M.; Fütterer, J.J.; Gill, I.S.; Grubb Iii, R.L.; Hadaschik, B.; Klotz, L.; Margolis, D.J.; et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: Recommendations from an International Working Group. *Eur. Urol.* **2013**, *64*, 544–552. [\[CrossRef\]](#)
34. Raman, A.G.; Sarma, K.V.; Raman, S.S.; Priester, A.M.; Mirak, S.A.; Riskin-Jones, H.H.; Dhinagar, N.; Speier, W.; Felker, E.; Sisk, A.E.; et al. Optimizing Spatial Biopsy Sampling for the Detection of Prostate Cancer. *J. Urol.* **2021**, *206*, 595–603. [\[CrossRef\]](#)
35. Brisbane, W.G.; Priester, A.M.; Ballon, J.; Kwan, L.; Delfin, M.K.; Felker, E.R.; Sisk, A.E.; Hu, J.C.; Marks, L.S. Targeted Prostate Biopsy: Umbra, Penumbra, and Value of Perilesional Sampling. *Eur. Urol.* **2022**, *82*, 303–310. [\[CrossRef\]](#)
36. Tomioka, M.; Seike, K.; Uno, H.; Asano, N.; Watanabe, H.; Tomioka-Inagawa, R.; Kawase, M.; Kato, D.; Takai, M.; Iinuma, K.; et al. Perilesional Targeted Biopsy Combined with MRI-TRUS Image Fusion-Guided Targeted Prostate Biopsy: An Analysis According to PI-RADS Scores. *Diagnostics* **2023**, *13*, 2608. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Lombardo, R.; Tema, G.; Nacchia, A.; Mancini, E.; Franco, S.; Zammitti, F.; Franco, A.; Cash, H.; Gravina, C.; Guidotti, A.; et al. Role of Perilesional Sampling of Patients Undergoing Fusion Prostate Biopsies. *Life* **2023**, *13*, 1719. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

5.6. PUBLICACIÓN 6

Título: A Systematic Review of the Current Status of Magnetic Resonance–Ultrasound Images Fusion Software Platforms for Transperineal Prostate Biopsies

Revista: Cancers

Año de publicación: 2023

Volumen: 15

Páginas: 3329

DOI: <https://doi.org/10.3390/cancers15133329>

Autores: Nahuel Paesano, Violeta Catalá, Larisa Tcholakian, Enric Trilla, Juan Morote

Factor de impacto (JCR): 4.5

Cuartil (JCR): 1 (Área de Oncología)

Systematic Review

A Systematic Review of the Current Status of Magnetic Resonance–Ultrasound Images Fusion Software Platforms for Transperineal Prostate Biopsies

Nahuel Paesano ^{1,*}, Violeta Catalá ¹, Larisa Tcholakian ¹, Enric Trilla ^{2,3} and Juan Morote ^{2,3}

¹ Clínica Creu Blanca, 08034 Barcelona, Spain; violetacatala@uroima.com (V.C.);

larisa.tcholakian@creublanca.es (L.T.)

² Department of Urology, Vall d'Hebron Hospital, 08035 Barcelona, Spain; enrique.trilla@vallhebron.cat (E.T.);

juan.morote@vallhebron.cat (J.M.)

³ Department of Surgery, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

* Correspondence: nahuel.paesano@creublanca.es

Simple Summary: With the consolidation of multiparametric resonance of the prostate as an effective method in the diagnosis of clinically significant prostate cancer (csPCa), robot-assisted devices have been developed in recent years to use in targeted prostate biopsy. However, their potential advantages over standard biopsy remain unclear. The 2019 European Association of Urology (EAU) prostate cancer (PCa) guidelines recommend transperineal biopsy as the first option over transrectal biopsies. From this systematic review, we confirm that almost with all developed devices, a series of transperineal biopsies have been reported. Those using rigid fusion systems have reported better detection rates of csPCa.

Abstract: Given this new context, our objective is to recognize the suitability of the currently available software for image fusion and the reported series using the transperineal route, as well as to generate new evidence on the complementarity of the directed and systematic biopsies, which has been established through the transrectal approach. Evidence acquisition: This systematic review, registered in Prospero (CRD42022375619), began with a bibliographic search that was carried out in PubMed, Cochrane, and Google Scholar databases. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria and the studied eligibility based on the Participants, Intervention, Comparator, and Outcomes (PICO) strategy were followed. Warp analysis of selected studies was performed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. In addition, a Google search of all currently available fusion platforms was performed. Our Google search found 11 different commercially available robots to perform transperineal image fusion biopsies, of which 10 devices have published articles supporting their diagnostic effectiveness in transperineal prostate biopsies. Results: A total of 30 articles were selected and the characteristics and results of the biopsies of 11,313 patients were analyzed. The pooled mean age was 66.5 years (63–69). The mean pooled PSA level was 7.8 ng/mL (5.7–10.8). The mean pooled prostate volume was 45.4 cc. (34–56). The mean pooled PSA density was 0.17 (0.12–0.27). The overall cancer detection rate for all prostate cancers was 61.4%, while for csPCa it was 47.8%. PCa detection rate was more effective than that demonstrated in the systematic transrectal biopsy. However, the detection of csPCa in the systematic biopsy was only 9.5% in the reported series. To standardize our review, we grouped prostate cancer screening results according to the population studied and the software used. When the same populations were compared between elastic and rigid software, we found that rigid biopsies had a higher csPCa detection rate than biopsies with elastic fusion systems. Conclusion: Platforms performing prostate biopsy using transperineal image fusion have better detection rates of csPCa than systematic transrectal biopsies. Rigid fusion systems have a better csPCa detection rate than elastic ones. We found no diagnostic differences between the different types of robotic systems currently available. The complementarity of systematic biopsy has also been demonstrated in transperineal imaging fusion biopsies.



Citation: Paesano, N.; Catalá, V.; Tcholakian, L.; Trilla, E.; Morote, J. A Systematic Review of the Current Status of Magnetic Resonance–Ultrasound Images Fusion Software Platforms for Transperineal Prostate Biopsies. *Cancers* **2023**, *15*, 3329. <https://doi.org/10.3390/cancers15133329>

Academic Editors: Giorgio Treglia and Ursula Maria Vogl

Received: 14 May 2023

Revised: 19 June 2023

Accepted: 20 June 2023

Published: 24 June 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Keywords: systematic review; robot-assisted prostate biopsy; MR-target transperineal biopsy; software-assisted MRI–TRUS fusion platforms; prostate cancer

1. Introduction

Prostate cancer (PCa) is currently the most common malignancy and the third leading cause of cancer mortality in men in the United States (US) and Europe (EU) [1]. It represents approximately 7.5% of the new cancer cases diagnosed in the EU [2]. Approximately 1.4 million men worldwide were diagnosed with PCa in 2020, representing 15% of all cancers in men [3]. The suspicion of PCa is based on the serum measurement of prostate-specific antigen (PSA) level and the abnormalities detected via the digital rectal examination (DRE), while prostate biopsy is conducted to confirm the diagnosis [4]. Prostate cancer screening continues to be controversial due to the adverse effects of excessive unnecessary prostate biopsies and the over-detection of insignificant tumors (iPCa), estimated to be between 40 and 50% of cases, which has often resulted in over-treatment [5].

The clinically significant PCa (csPCa) in prostate biopsies can be defined in several ways. The most widespread was established from the Gleason pattern 3 + 4 or higher, which is equivalent to the current groups 2 to 5 of the International Society of Urologic Pathology (ISUP-GG) [6]. In recent years, complementary tools have been suggested to avoid unnecessary biopsies and over-detection of iPCa, such as new molecular markers, predictive models, and classic PSA density. However, the greatest contribution has been made by the prostate magnetic resonance imaging (MRI) and the possibility derived from the biopsies of suspicious areas [7]. The development of multiparametric MRI techniques (mpMRI) and the overall improvement in their interpretation through the Prostate Imaging-Report and Data System (PI-RADS) have been essential to identify csPCa suspicious areas and their semi-quantitative risk [8,9]. These innovations and the evolution of the PI-RADS for the categorization of prostate lesions classified from very low to high suspicion of csPCa, have prompted the creation of “softwares” that allows to merge the areas observed in the MRI with the transrectal ultrasound (TRUS) images observed in real time [10]. Image fusion prostate biopsy is an effective tool that allows for increased detection of csPCa and decreased detection of iPCa, regardless of the transrectal or transperineal route used [11]. These fusion software platforms facilitate guided biopsies of the suspicious areas previously identified by mpRMN, called targeted biopsies, and perform systematic biopsies for the rest of the gland.

Differences between devices mainly concern the registration algorithm (rigid versus elastic), the navigation strategy (organ-based versus electromagnetic tracking), post-biopsy needle position documentation and the use of articulating robotic arms. This fusion process is performed by computerized image registration, which consists of an overlay of MRI-detected lesions and real-time TRUS images [12]. In this procedure, separate MRI and ultrasound images for prostate biopsy are spatially aligned using a fusion software. There are several commercially available software-assisted MRI–TRUS fusion platforms that use different recording methods (rigid or elastic) to fuse MRI and ultrasound. Rigid registration allows the surgeon to manually rotate the MRI and TRUS images relative to each other to produce the best alignment between the images, even though the images themselves do not change. In contrast, elastic registration uses a software algorithm to compensate for the changes in the shape of the segmented prostate gland, which can occur between preoperative MRI and intraoperative imaging during prostate biopsy [13].

The 2019 European Association of Urology (EAU) PCa guidelines recommend transperineal biopsy as the first option over transrectal biopsies. This recommendation is based on a meta-analysis of seven studies that have included 1330 biopsied men with suspected PCa and have shown that transperineal biopsies significantly reduce complications from infections compared to transrectal biopsies [14]. Given this new context, it is essential to recognize the suitability of the different “software” used for transperineal biopsy via image

fusion currently available, as well as to generate new evidence on the complementarity of targeted and systematic biopsies, which has been established using the transrectal route in the systematic review of the Cochrane organization [15].

We perform a systematic review of the literature and Google research with the aim of identifying the currently available commercialized software image-fusion systems for performing prostate biopsies via the transperineal route, determining their effectiveness in the diagnosis of csPCa, and revealing the complementarity of the targeted and systematic transperineal biopsies.

2. Evidence Acquisition

2.1. Systematic Review

A literature search was carried out by two independent authors (NEP and JM) on the PubMed, Cochrane and Google Scholar databases for articles published before 28 February 2023. The MeSH (Medical Subject Heading) [16] terms ‘prostate cancer’ AND ‘biopsy’ AND ‘MRI’ as well as the keywords ‘prostate cancer’ AND ‘softwares’ OR ‘robot’ OR ‘elastic fusion systems’ OR ‘rigid fusion systems’ AND ‘transperineal’ OR ‘multiparametric MRI fusion biopsy’ AND ‘systematic prostate biopsy’ AND ‘targeted prostate biopsy’ were used. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [17] were followed. The PICO (Population, Intervention, Comparison, and Outcomes) [18] selection criteria were established as men who underwent prostate biopsy through the transperineal route using software fusion of ultrasound and multiparametric MRI evaluating the results in the detection of csPCa. Studies not published in English, studies that did not report results, systematic reviews, and meta-analyses were excluded. Discrepancies between the two reviewers were resolved by discussion or by consulting a third reviewer. This review was registered in the international prospective registry of systematic reviews (PROSPERO: CRD42022375619).

A total of 321 references were initially identified, however, 83 of them were first excluded due to duplicated titles. After the analysis of abstracts, another 50 were discarded because they were narrative or systematic reviews and meta-analyses, and then 145 studies, analyzed via the transrectal approach or cognitive transperineal technic, were removed as well. Finally, 43 articles were identified, which complied reports on series of biopsies performed using the image fusion software through the transperineal route; 30 out of these 43 met the PICO selection criteria. The PRISMA study selection flowchart is summarized in Figure 1.

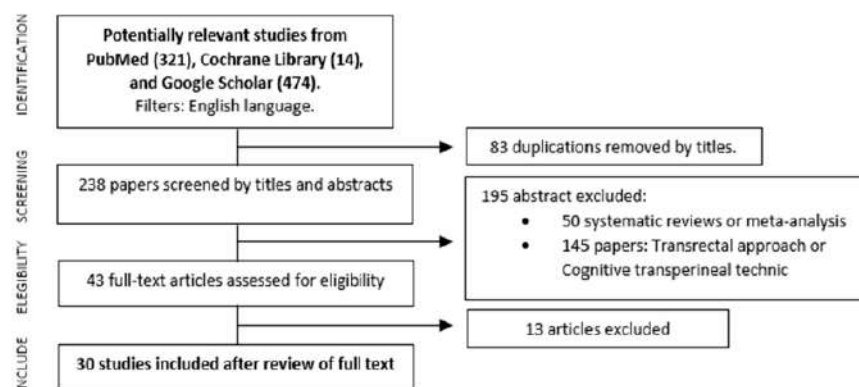


Figure 1. Flowchart of the search strategy.

2.2. Quality Assessment of Selected Studies

The quality of the selected studies and the risk of bias and applicability concern of single studies included were assessed using the tool, Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [19], as shown in Table 1 and Figure 2. We found the heterogeneity of the populations analyzed in the different types of studies selected as a notable reason for the bias of this review. Of the 30 articles, 13 collected data according to the Standards of Reporting for Magnetic Resonance Directed Biopsy (START) Studies of the Prostate working group guidelines [20].

Table 1. Risk of bias assessed using QUADAS-2.

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Jacewicz et al. [21]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Mischinger et al. [22]	⊕	⊕	⊕	⊕	⊕	⊕	?
Lee et al. [23]	?	⊕	?	⊕	?	⊕	⊕
Marra et al. [24]	⊕	⊕	⊕	⊕	⊕	?	⊕
Jacewicz et al. [25]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Miah et al. [26]	?	⊕	⊕	⊕	?	⊕	⊕
Günzel et al. [27]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Mehmood et al. [28]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Hakozaki et al. [29]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Görtz et al. [30]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Hakozaki et al. [31]	?	⊕	⊕	⊕	?	⊕	⊕
Miah et al. [32]	⊕	?	⊕	⊕	⊕	?	⊕
Tschirdewahn et al. [33]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Hansen et al. [34]	⊕	⊕	⊕	⊕	⊕	⊕	?
Lian et al. [35]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Radtke et al. [36]	?	⊕	⊕	⊕	?	⊕	⊕
Kim et al. [37]	?	⊕	⊕	⊕	?	⊕	L
De Vulder et al. [38]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Winoker et al. [39]	⊕	?	⊕	?	⊕	?	⊕
Wajswol et al. [40]	⊕	⊕	⊕	?	?	⊕	?
Hansen et al. [41]	?	⊕	⊕	⊕	⊕	⊕	⊕
Shoji et al. [42]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Kaufmann et al. [43]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Fulco et al. [44]	⊕	⊕	⊕	⊕	?	⊕	⊕
Thaiss et al. [45]	?	⊕	⊕	⊕	?	⊕	⊕
Kozel et al. [46]	⊕	⊕	?	⊕	⊕	⊕	⊕
Dahl et al. [47]	?	⊕	?	⊕	?	⊕	⊕
Pepe et al. [48]	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Fletcher et al. [49]	⊕	⊕	⊕	⊕	?	⊕	⊕
Kaneko et al. [50]	⊕	⊕	⊕	?	?	⊕	⊕

⊕ Low Risk; ⊕ High Risk; ? Unclear Risk.

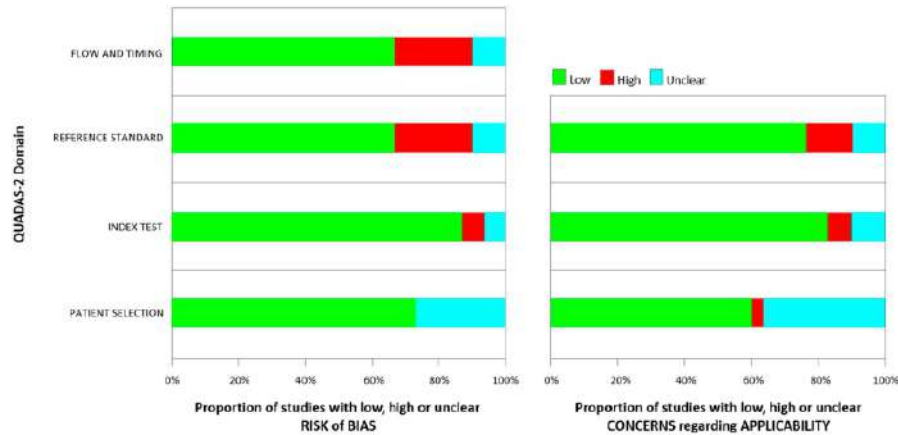


Figure 2. Quality assessment according to QUADAS-2 of the included studies.

2.3. Data Extraction in the Selected Studies

The selected articles were recorded on a standard form, along with information on participants, MRI, and biopsy characteristics. The form included the following details. (1) Article: origin (authors, and year of publication), journal, study design, number of participants, and definition of csPca. (2) Study participants: pre-biopsy population (biopsy naïve and/or prior negative biopsy and/or AS an/or FT control and/or SBRT recurrence), age, mean prostate volume and mean PSA, PSA density and DRE. (3) MRI: type of magnetic resonance, Tesla, type of coil (surface vs. endorectal), time between MRI and biopsy and PI-RADS version. (4) Biopsy: type of anesthesia, approach, patient position, platform used, fusion mode, probe manipulation, prostate segmentation, PCa and csPca detection rates, number of cores and number of lesions, PI-RADS score, positive cores in TB and SB and added value SB. The study time and complications were also analyzed.

2.4. Searching Devices for MRI–TRUS Fusion Prostate Biopsies in Google and Their Characteristics

In addition to the literature review, a Google® search was conducted to identify all robots and software available to perform transperineal fusion prostate biopsies. We found 11 different types of robots. Table 2 describes their characteristics.

Table 2. Types of robots currently available. Google® search.

Fusion Biopsy System (Manufacturer)	Ultrasound Image Acquisition	Ultrasound Tracking Mechanism	Fusion Method	Biopsy Route
Artemis (Eigen, Inc., Grass Valley, CA, USA)	Manual rotation along a fixed axis (ultrasound probe on a tracking arm).	Mechanical arm with encoded joints.	Rigid/Elastic	TP/TR
BioJet (D&K Technologies, Inc., Barum, Germany)	Real-time biplanar TRUS and 3D model of the prostate mounted on a positioning system.	Stepper with 2 built-in encoders.	Rigid/Elastic	TP/TR
Biopsee (MedCom, Inc., Darmstadt, Germany)	Custom-made biplane TRUS probe mounted on a stepper.	Stepper with 2 built-in encoders.	Rigid/Elastic	TP/TR
HI RVS/Real-time Virtual Sonography (Hitachi, Inc., Tokio, Japan)	Real-time biplanar TRUS.	Electromagnetic tracking.	Rigid	TP/TR

Table 2. *Cont.*

Fusion Biopsy System (Manufacturer)	Ultrasound Image Acquisition	Ultrasound Tracking Mechanism	Fusion Method	Biopsy Route
UroNav (In Vivo/Philips, Inc., Cambridge, MA, USA)	Manual ultrasound 2D sweep. Freehand manipulation of ultrasound probe or mounted on a stepper.	Electromagnetic tracking ultrasound.	Rigid/Elastic	TP/TR
Urostation (Koelis, Inc., Meylan, France)	Automatic ultrasound probe rotation, three different volumes elastically registered.	Image-based registration.	Elastic	TP/TR
iSR'obot Mona Lisa (Biobot Surgical, Inc., Singapore)	Motorized translation.	Robotic arm.	Elastic	TP
MIM Symphonyx Bx (BK, Inc., Seoul, South Korea)	Motorized translation.	Encoder.	Rigid	TP/TR
Virtual Navigator (Esaote, Inc., Genova, Italy)	Manual ultrasound sweep. Freehand rotation of ultrasound probe.	Electromagnetic tracking ultrasound and needle.	Rigid	TP/TR
Aplio i800 (Canon Medical Systems, Inc., Crawley, UK)	Freehand sweep.	Fusion Imaging of live US/MRI guidance for targeted biopsy.	Rigid	TP/TR
Logiq (GE, Inc., Boston, MA, USA)	Freehand sweep.	Fusion Imaging of live US/MRI guidance for targeted biopsy.	Rigid	TP/TR

3. Evidence Synthesis

The full texts of the 30 selected articles were analyzed, and their results were structured using demographic data, biopsy and MRI characteristics, definition of csPCa, cancer detection rates, and software used.

Series from all the platforms mentioned in Table 2 have been found, except for the articles about prostate biopsies via transperineal fusion performed with Robot Artemis. It is necessary to clarify that there are currently other intelligent ultrasounds with the capacity to do fusion images with resonance (not only for prostate biopsies), but either the evidence was demonstrated for biopsies by the transrectal route, or no evidence was found for the transperineal route in this review.

Of the 30 articles, 21 studies were conducted prospectively (none randomized) [21,22,24,27–30,32–35,38–43,48–50] and nine retrospectively [23,25,26,31,36,37,44,45,47].

Eight series were multicenter [21,24–26,34,35,40,49] while the remaining 22 were from a single center [22,23,27–33,36–40,42–48,50]. Overall, the characteristics and biopsy results of 11,313 patients were analyzed.

3.1. Demographics

The pooled mean age was 66.5 years (63–69). The mean pooled PSA level was 7.8 ng/mL (5.7–10.8). The combined mean prostate volume was 45.4 cc. (34–56). The mean pooled PSA density was 0.17 (0.12–0.27). A total of 10,457 lesions were analyzed. PI-RADS 1–2: 764 lesions, PI-RADS 3: 2748 lesions, PI-RADS 4: 4126 lesions, and PI-RADS 5: 2339 lesions. Likert 1–2: 12 lesions, Likert 3: 111 lesions, Likert 4: 195 lesions and Likert 5: 162 lesions. Information regarding the result of the DRE has been reported by 10 articles [24,30–32,36,37,40,41,43,50] with an average abnormal DRE of 22% (5–35).

The study population included two articles [42,45] on patients with naïve biopsy, three articles [34,35,48] on patients with previous negative biopsy, twelve articles [22–24,26,28,30,32,33,36,41,43,44] on patients with naïve biopsy and previous negative biopsy, eleven studies [27,29,31,37–40,46,47,49,50] on patients with naïve biopsy and previous negative biopsy and patients in active surveillance (AS) and finally, two articles by Jacewicz et al. [21,25] on patients with no prior biopsy, patients with prior negative biopsy, AS, focal therapy (FT) control, and SBRT recurrence. These data are presented in Table 3.

3.2. Characteristics of the Biopsies and MRI

All resonances performed prior to the biopsies were carried out via 1.5 or 3.0 Tesla resonators scans and interpreted using the PI-RADS score Version 1.0 in 1 article [34], version 2.0 in 26 studies [21–25,27–33,35–44,46–48,50], and version 2.1 in 1 article [45]. In two series [26,49], the reading of the resonance was carried out using the Likert scale.

All biopsies were performed in the lithotomy position. The biopsies were performed using local anesthesia in 11 series [21,24,25,27,37–39,46,47,49,50], 15 with general anesthesia [22,23,26,28,30–36,40,41,43,44], 1 with sedation [48], and 2 with spinal anesthesia [29,42]. One series did not report the type of anesthesia used [45].

Segmentation of the prostate is not a commonly reported step in fusion biopsy series. In our review, 16 series reported who previously segmented the prostate before performing the image fusion. In 11 studies [24,27,32,38,40,42–44,46,47,49], the segmentation was carried out by the urologist, in 3 it was carried out by the radiologists [22,23,33], while in the series by Jacewicz et al. [21,25] the segmentation was carried out by both faculties.

The distribution of the types of robots used in each study can be seen in Table 4. Of the 30 articles analyzed, the biopsies have been carried out using software that performs elastic fusion in 16 studies [21–23,25,27,30,32,37,39,40,42,44–47,50] and in 14, by rigid fusion [24,26,28–31,33–36,38,41,43,48,49]. Görtz et al. [30] made a comparison of both fusion systems using the Biopsee (rigid) and the Uronav (elastic) systems. The number of cores for target biopsy ranged from 2 to 8 and from 12 to 24 for systematic biopsy. The biopsy time, specifically called the probe time by the authors, was reported in only five articles [21,25,42,46,49], and was approximately between 15 and 30 min for each biopsy. The total time between anesthesia, positioning, segmentation, and probe time was mentioned by Jacewicz et al. [21,25] and Kozel et al. [46] and they both coincided in about 60 min; see Table 5.

Table 3. Characteristics of the studies and populations included.

Serie	Author	Country	Study Design	N Centers	N Patients	Pop.	Mean Age (yr)	Mean PSA (ng/mL)	Mean PV (cc)	Mean PSA _d	DRE+ (%)
1	Jacewicz et al., 2021 [21]	Norway	Prospective	2	401	4	69	6.9	40	0.17	NR
2	Mischinger et al., 2018 [22]	Germany	Prospective	1	202	2	66	8	36	0.21	NR
3	Lee et al., 2020 [23]	Singapore	Retrospective	1	433	2	66.1	10.4	43.2	0.27	NR
4	Marra et al., 2021 [24]	Italy	Prospective	4	1014	2	66.8	8.1	51.3	0.2	23.4
5	Jacewicz et al., 2020 [25]	Norway	Retrospective	2	377	4	67	7.2	43	0.17	NR
6	Miah et al., 2019 [26]	UK	Retrospective	11	640	2	63.8	7.8	47.4	0.16	NR
7	Günzel et al., 2022 [27]	Norway	Prospective	1	969	3	68	6.72	45	0.15	NR
8	Mehmood et al., 2021 [28]	KSA	Prospective	1	100	2	64	6.1	50	0.12	NR
9	Hakozaki et al., 2017 [29]	Japan	Prospective	1	177	3	68	7.42	42.9	0.17	28.8
10	Görtz et al., 2022 [30]	Germany	Prospective	1	939	2	65	7.7/7.6 * ¹	44/50 * ¹	0.17/0.15 * ¹	35/28 * ¹
11	Hakozaki et al., 2019 [31]	Japan	Retrospective	1	310	3	68.2	8.6	42.8	0.12	20.9
12	Miah et al., 2019 [32]	UK	Prospective	1	86	2	64.2	10	51.03	0.19	NR
13	Tschirdewahn et al., 2020 [33]	Germany	Prospective	1	213	2	66	7.8	50	0.14	15
14	Hansen et al., 2017 [34]	Germany	Prospective	2	487	5	66	9	56	0.15	NR
15	Lian et al., 2017 [35]	China	Prospective	2	101	5	68.9	10.8	42.1	0.25	NR
16	Radtke et al., 2015 [36]	Germany	Retrospective	1	191	2	66	7.9	44	0.19	20.9
17	Kim et al., 2022 [37]	USA	Retrospective	1	301	3	67	6	45	0.14	5
18	De Vulder et al., 2022 [38]	Belgium	Prospective	1	203	3	69	6.8	49	0.16	NR
19	Winoker et al., 2020 [39]	USA	Prospective	1	168	3	68	7.9	49	0.16	NR
20	Wajswol et al., 2020 [40]	USA	Prospective	1	176	3	67.5	8.25	41	0.2	27.8
21	Hansen et al., 2017 [41]	UK	Prospective	3	807	2	65	6.5	42	0.15	23
22	Shoji et al., 2017 [42]	Japan	Prospective	1	250	1	68	6.7	34	0.19	NR
23	Kaufmann et al., 2021 [43]	Switzerland	Prospective	1	392	2	64	7	43	0.16	16

Table 3. Cont.

Serie	Author	Country	Study Design	N Centers	N Patients	Pop.	Mean Age (yr)	Mean PSA (ng/mL)	Mean PV (cc)	Mean PSA _d	DRE+ (%)
24	Fulco et al., 2020 [44]	Italy	Retrospective	1	272	2	68	7.2	NR	NR	NR
25	Thaiss et al., 2021 [45]	Germany	Retrospective	1	563	1	66	9.8	45	0.21	NR
26	Kozel et al., 2022 [46]	USA	Prospective	1	200	3	67	7.89	52	0.15	NR
27	Dahl et al., 2022 [47]	USA	Retrospective	1	301	3	66	5.7	45	0.15	NR
28	Pepe et al., 2019 [48]	Italy	Prospective	1	875	5	63	9.8	44.6	0.21	NR
29	Fletcher et al., 2023 [49]	UK	Prospective	2	69	3	67	7.9	43	0.16	NR
30	Kaneko et al., 2023 [50]	USA	Prospective	1	96	3	68	7.84	56	0.13	21

Pop: Population. PV: Prostate Volume. PSA_d: Density of PSA (PV/PSA). DRE+: Pathologic Digital Rectal Exam. NR: Not Reported. *1: compared the results between two platforms: Biopsee/Uronav. Population 1: Biopsy Naïve. Population 2: Biopsy Naïve + Prior negative biopsy. Population 3: Biopsy Naïve + Prior negative biopsy + AS. Population 4: Biopsy Naïve + Prior negative biopsy + AS+ FT control + SBRT recurrence. Population 5: Prior negative biopsy.

Table 4. Robots and platforms used.

Serie	MRI Tesla	MRI type	PIRADS Version	Coil Type	Anesthesia	Approach	Patient Position	Platform Used	Fusion Mode	Probe Manipulation	Prostate Segmentation
1	1.5	Biparametric	v2.0	Surface	Local	TP	Lithotomy	Koelis	Elastic	Freehand	Both
2	1.5 or 3.0	Multiparametric	v2.0	Endorectal	General	TP	Lithotomy	iSR'obot Mona Lisa Urofusio	Elastic	Robotic arm	Radiologist
3	3.0	Multiparametric	V2.0	Endorectal	General	TP	Lithotomy	iSR'obot Mona Lisa Urofusio	Elastic	Robotic arm	Radiologist
4	1.5 or 3.0	Both	v2.0	Endorectal	Local	TP	Lithotomy	Esaote	Rigid	Freehand	Urologist
5	1.5 or 3.0	Both	v2.0	Surface	Local	TP	Lithotomy	Koelis	Elastic	Steady pro arm	Both
6	1.5 or 3.0	Multiparametric	Likert	NR	General	TP	Lithotomy	MIM-Symphony-DX	Rigid	Encoders with brachytherapy template	NR
7	1.5 or 3.0	Multiparametric	v2.0	Endorectal	Local	TP	Lithotomy	Koelis	Elastic	Steady Pro arm	Urologist
8	3.0	Multiparametric	v2.0	NR	General	TP	Lithotomy	Biojet	Rigid	Robotic arm	NR
9	3.0	Multiparametric	v2.0	Surface	Spinal	TP	Lithotomy	(RVS) system Hitachi	Rigid	Electromagnetic tracking/Freehand	NR

Table 4. Cont.

Serie	MRI Tesla	MRI type	PIRADS Version	Coil Type	Anesthesia	Approach	Patient Position	Platform Used	Fusion Mode	Probe Manipulation	Prostate Segmentation
10	3.0	Multiparametric	v2.0	Surface	General	TP	Lithotomy	Biopsee/Uronav	Rigid/Elastic	Freehand	NR
11	3.0	Multiparametric	v2.0	Surface	General/Spinal	TP	Lithotomy	(RVS) system Hitachi	Rigid	Electromagnetic tracking	NR
12	3.0	Multiparametric	v2.0	Surface	General	TP	Lithotomy	iSR'obot Mona Lisa Urofusio	Elastic	Robotic arm	Urologist
13	3.0	Multiparametric	v2.0	Endorectal	General	TP	Lithotomy	MM-Symphony-DX	Rigid	Encoders with brachytherapy template	Radiologist
14	1.5 or 3.0	Multiparametric	v1.0	Endorectal	General	TP	Lithotomy	Biopsee	Rigid	Freehand	NR
15	3.0	Multiparametric	v2.0	Endorectal	General	TP	Lithotomy	(RVS) System Hitachi	Rigid	Electromagnetic tracking/Freehand	NR
16	3.0	Multiparametric	v2.0	Endorectal	General	TP	Lithotomy	Biopsee	Rigid	Freehand	NR
17	3.0	Multiparametric	v2.0	Surface	Local	TP	Lithotomy	Uronav	Elastic	Electromagnetic tracking/Freehand	NR
18	3.0	Multiparametric	v2.0	Surface	Local	TP	Lithotomy	Aplio i800	Rigid	Freehand	Urologist
19	1.5 or 3.0	Multiparametric	v2.0	Surface	Local	TP	Lithotomy	Uronav	Elastic	Electromagnetic tracking/Freehand	NR
20	3.0	Multiparametric	v2.0	Surface	General	TP	Lithotomy	Uronav	Elastic	Electromagnetic tracking/Freehand	Urologist
21	3.0	Multiparametric	v2.0	NR	General	TP	Lithotomy	Biopsee	Rigid	Encoders with brachytherapy template	NR
22	3.0	Multiparametric	v2.0	NR	Spinal	TP	Lithotomy	Biojet	Elastic	Robotic arm	Urologist
23	3.0	Multiparametric	v2.0	Surface	General	TP	Lithotomy	Biopsee	Rigid	Encoders with brachytherapy template	Urologist
24	1.5	Multiparametric	v2.0	Endorectal	Local/General	TP	Lithotomy	Koelis	Elastic	Steady pro arm	Urologist
25	3.0	Both	v2.1	Surface	NR	TP	Lithotomy	iSR'obot Mona Lisa Urofusio	Elastic	Robotic arm	NR

Table 4. Cont.

Serie	MRI Tesla	MRI type	PIRADS Version	Coil Type	Anesthesia	Approach	Patient Position	Platform Used	Fusion Mode	Probe Manipulation	Prostate Segmentation
26	3.0	Multiparametric	v2.0	NR	Local	TP	Lithotomy	Uronav	Elastic	Electromagnetic tracking/Freehand	Urologist
27	3.0	Multiparametric	v2.0	Surface	Local	TP	Lithotomy	Uronav	Elastic	Electromagnetic tracking/Freehand	Urologist
28	3.0	Multiparametric	v2.0	NR	Sedation	TP	Lithotomy	GE logic	Rigid	Electromagnetic tracking/Freehand	NR
29	1.5 or 3.0	Multiparametric	Likert	Surface	Local	TP	Lithotomy	Vector Biopsy: Biopsee + VirtuTRAX EM	Rigid	Electromagnetic tracking	Urologist
30	3.0	Multiparametric	v2.0	NR	Local	TP	Lithotomy	Koelis 3D Models	Elastic	The Double-Freehand Technique	NR

Endorectal Coil: whether endorectal coil was used or not when the MRI was performed. NR: Not Reported. Prostate Segmentation: who was the specialist who performed the segmentation and planning of the prostate prior to the biopsy.

Table 5. Characteristics of the biopsies.

Number	N° PIRADS 1–2	N° PIRADS 3	N° PIRADS 4	N° PIRADS 5	N° Cores p/Lesion	N° Cores Systematic	N° Total Cores	Mean Lesion Volume (mL)	Mean MCCL (mm)
1	53	74	137	137	4–5	10–12	NR	NR	8
2	39	39	107	17	5.8 (mean)	NR	NR	NR	NR
3	NR	71	254	108	5	24.5 (mean)	34	NR	NR
4	NR	599	657	144	2–4	10–12	15.3 (mean)	0.5	NR
5	22	97	142	115	1–4	6–10	NR	0.9	9
6	NR	98 (L) *1	173 (L) *1	140 (L) *1	4–6	16.3	NR	NR	7
7	24	45	206	438	4–6	10–12	NR	NR	NR
8	20	17	27	36	2–4	12	NR	NR	NR
9	NR	NR	NR	NR	4–6	12	18	NR	NR
10	NR	367/310 *2	333/332 *2	139/124 *2	4/5 *2	24/25 *2	29/34 *2	NR	NR

Table 5. *Cont.*

Number	N° PIRADS 1–2	N° PIRADS 3	N° PIRADS 4	N° PIRADS 5	N° Cores p/Lesion	N° Cores Systematic	N° Total Cores	Mean Lesion Volume (mL)	Mean MCCL (mm)
11	NR	NR	NR	NR	4	15	20	NR	NR
12	NR	22	55	30	8.1 (mean)	20.2 (mean)	NR	NR	8
13	NR	99	78	25	9	24	33	NR	NR
14	144	128	100	115	3	24	27	NR	NR
15	13	31	36	21	4.2	12	16–18	NR	NR
16	13	50	81	50	3	24	27	NR	NR
17	NR	62	151	88	3–4	20	24	NR	NR
18	NR	56	121	46	5	10	15	NR	NR
19	NR	26	76	66	3–4	12	16–18	NR	NR
20	14	53	128	73	4–5	12	16–18	NR	NR
21	236	153		418 ^{*3}	4	20	24	NR	NR
22	NR	NR	NR	NR	2–4	12	16–18	NR	NR
23	124	87	123	58	5	35	42	NR	NR
24	NR	115	129	28	3–5	10	15	NR	NR
25	29	95	324	115	4	14	18	3.2	NR
26	6	73	135	51	2–3	12	15	NR	NR
27	NR	62	151	88	3	20	23	NR	NR
28	NR	NR	NR	NR	4	20	30	NR	NR
29	12 (L) ^{*1}	13 (L) ^{*1}	22 (L) ^{*1}	22 (L) ^{*1}	2–4	12	NR	NR	NR
30	27	17	25	27	2–4	12–14	NR	NR	NR

(L)^{*1}: Likert score. ^{*2}: Gortz et al. [30] compared the results between two platforms: Biopsee/Uronav. ^{*3}: The authors pooled the results obtained from PIRADS 4 and 5 lesions. NR: Not Reported. MCCL: Maximum cancer core length.

3.3. Significant Clinically Prostate Cancer Definition

CsPCa was defined in different ways by the authors: (i) ISUP-GG ≥ 2 [21–23,25,27,28,30–34,36,37,39–50], (ii) ISUP-GG ≥ 2 or ≥ 3 positive cores with $\geq 50\%$ of extension [24], (iii) using the Epstein criteria [29], (iv) ISUP-GG ≥ 2 or Gleason 6 with MCCL (Maximum cancer core length) ≥ 4 mm [35,38], (v) Gleason $\geq 4 + 3$ or any grade with MCCL ≥ 6 mm, and (vi) Gleason $\geq 3 + 4$ or any ISUP-GG with MCCL ≥ 4 mm [26]. Table 6 presents the definition details.

Table 6. Results.

Number	csPCa Definition	PCa (%)	csPCa (%)	csPCa (%) SB	csPCa (%) PIRADS 1–2	csPCa (%) PIRADS 3	csPCa (%) PIRADS 4	csPCa (%) PIRADS 5
1	ISUP ≥ 2	65	48	2	17	20	39	77
2	ISUP ≥ 2	61	52	NR	7.6	25.6	72	88
3	ISUP ≥ 2	57	46	17	NR	16	38	85
4	ISUP ≥ 2 / ≥ 3 positive cores / $\geq 50\%$ of extension	43.9	39.4	15.9	NR	15.4	46.2	73.9
5	ISUP ≥ 2	64	51	NR	18	20	60	84
6	Ahmed D1. Gleason $\geq 4 + 3$ or any grade ≥ 6 mm. Ahmed D2. Gleason $\geq 3 + 4$ or any grade ≥ 4 mm.	65	49.8	0.8	NR	21.6 (L) ^{a1}	47.1 (L) ^{a1}	84.2 (L) ^{a1}
7	ISUP ≥ 2	66	49	1.5	9	15	50	73
8	ISUP ≥ 2	45	33.3	NR	NR	NR	NR	NR
9	Epstein criteria	65.5	63.3	14	NR	NR	NR	NR
10	ISUP ≥ 2	62.5/59.5 ^{a2}	46/46 ^{a2}	9	NR	NR	NR	NR
11	ISUP ≥ 2	47	43.9	NR	NR	3.1	50.2	80.8
12	ISUP ≥ 2	51.2	40.7	10.5	NR	0	40	53.3
13	ISUP ≥ 2	59	40	NR	NR	NR	NR	NR
14	ISUP ≥ 2	51	39	11	NR	19.5	32	70.4
15	ISUP ≥ 2 or Gleason 6 with MCCL ≥ 4 mm.	40.6	24.8	NR	NR	NR	NR	NR
16	ISUP ≥ 2	72.7	53.9	NR	NR	NR	NR	NR
17	ISUP ≥ 2	79.1	62.2	10.9	NR	33	62	72
18	ISUP ≥ 2 or Gleason 6 with MCCL ≥ 4 mm.	73.5	60.1	NR	NR	23.2	66.1	89.1
19	ISUP ≥ 2	79	59	NR	NR	42.3	76.3	95.5
20	ISUP ≥ 2	76.7	58.5	9.6	28.6	42.3	76.3	95.5
21	ISUP ≥ 2	68	49	NR	NR	30.7		71 ^{a3}
22	ISUP ≥ 2	58	55	NR	0	6.8	49	80
23	ISUP ≥ 2	51	40	NR	NR	57	83	98
24	ISUP ≥ 2	43	27.2	NR	NR	6.09	34.1	82.1
25	ISUP ≥ 2	59.9	51.1	2.9	NR	6.6	64.7	74.8
26	ISUP ≥ 2	71	58.5	6	NR	NR	NR	NR
27	ISUP ≥ 2	79	49.1	22.1	NR	NR	NR	NR
28	ISUP ≥ 2	34.5	22.5	NR	NR	NR	NR	NR
29	ISUP ≥ 2	92.9	77.1	NR	NR	62	68	95
30	ISUP ≥ 2	62	48	NR	3.7	47		71 ^{a3}

csPCa definition: Definition of clinically significant prostate cancer. PCa (%): Overall prostate cancer detection rate. csPCa (%): Clinically significant prostate cancer detection rate. csPCa (%) SB: Detection of clinically significant prostate cancer only in systematic biopsy. csPCa (%) PIRADS: Detection of clinically significant cancer according to the PIRADS score. (L)^{a1}: Likert score. ^{a2}: Gortz et al. [30] compared the results between two platforms: Biopsee/UroNav. ^{a3}: The authors pooled the results obtained from PIRADS 4 and 5 lesions. NR: Not Reported. MCCL: Maximum cancer core length.

3.4. Cancer Detection Rates (CDR)

Although the sample is heterogeneous due to the mentioned characteristics, the overall CDR for all prostate cancers was 61.4%, while for csPCa it was 47.8%.

The CDR of csPCa according to the PI-RADS category of lesions was 24.5% for PI-RADS 3 lesions, 55.9% for PI-RADS 4, and 81.5% for PI-RADS 5.

The added value of systematic biopsy, defined as the diagnosis of csPCa only in systematic biopsy, was reported in only 14 articles [21,23,24,26,27,29,30,32,34,37,40,45–47], with a mean of 9.5%.

3.5. Cancer Detection according to Population and Software

To standardize our review, we grouped the prostate cancer detection results according to the population studied and the software used. Table 7 (elastic) and Table 8 (rigid) present the results.

Table 7. Population and elastic fusion.

N° of Patients	Population	Mean Age (yr)	Mean PSA (ng/mL)	Mean PV (cc)	Mean PSA _d	PCa (%)	csPCa (%)
813	Biopsy Naïve	67	8.25	39.5	0.2	58.9	53
993	Biopsy-Naïve + Prior negative biopsy	66	8.9	43.4	0.2	53	41.4
2211	Biopsy-Naïve + Prior negative biopsy + AS	67.3	7.1	47.5	0.15	73.2	54.9
778	Biopsy-Naïve + Prior negative biopsy + AS+ FT control + SBRT recurrence.	68	7	41.5	0.17	64.5	49.5

PV: Prostate volume. PSA_d: Density of PSA (PV/PSA).

Table 8. Population and rigid fusion.

N° of Patients	Population	Mean Age (yr)	Mean PSA (ng/mL)	Mean PV (cc)	Mean PSA _d	PCa (%)	csPCa (%)
1463	Prior negative biopsy	65.9	9.86	47.5	0.2	42	28.7
3357	Biopsy-Naïve + Prior negative biopsy	65	7.3	46.8	0.16	57.8	43.6
759	Biopsy-Naïve + Prior negative biopsy + AS	68	7.6	44.4	0.15	69.7	61.1

PV: Prostate volume. PSA_d: Density of PSA (PV/PSA).

When we analyze our series according to the type of software used to perform the biopsy, we observe that with elastic fusion robots a CDR of 64.8% is obtained for all prostate cancers and for csPCa, it is 50.3%. In contrast, with rigid fusion robots, the CDR for PCa was 57.9% and for csPCa, it was 45.4%. Comparing the same populations between elastic and rigid software, we found that in the biopsy-naïve and prior negative biopsy population, the detection rate of global prostate cancer and csPCa with the elastic fusion biopsy was 53% and 41.4%, respectively, and with the rigid biopsy it was 57.8% and 43.6% respectively. On the other hand, when comparing the biopsy-naïve and prior negative biopsy and the AS populations, the global CDRs and csPCa in the elastic biopsies were 73.2% and 54.9%, respectively, and in the rigid biopsies, they were 69.7% and 61.1%, respectively.

4. Discussion

In 2009, Ahmed et al. argued that patients undergoing a TRUS guided biopsy were at risk for a sub-diagnosis of clinical csPCa and an over-diagnosis of iPCa [51]. In 2017, the PROMIS trial finally provided level 1 evidence to support the use of mpMRI before prostate biopsy. This study showed that mpMRI had a reported sensitivity, specificity, positive predictive value, and negative predictive value of 93% (95% CI 88–96), 41% (95% CI 36–46), 51% (95% CI 46–56) and 89% (95% CI 83–94), respectively. The comparison of this data showed that the sensitivity of mpMRI was significantly better than transrectal systematic biopsy: 93% (95% CI 88–96%) versus 48% (95% IC 42–55). The PROMIS trial also showed that mpMRI could avoid 27% of unnecessary biopsies [52]. Following the PROMIS

trial results, the PRECISION trial was conducted, which evaluated the role of MRI-guided prostate biopsy in improving the detection of clinically significant prostate cancer. This study showed a higher rate of detection of csPCa in the targeted biopsy group over the systematic biopsy group (38% vs. 26%, respectively) [53].

Despite the findings of the PRECISION trial, the additional diagnostic yield of retaining routine systematic prostate biopsy performed in conjunction with mpMRI-targeted strategies remains a matter of debate [54]. Multicenter studies, such as MRI-FIRST trial, 4 M trial and PAIREDCAP trial, in which the role of systematic 12-core transrectal biopsy and the MRI-targeted biopsies was evaluated, showed similar results in that the greatest yield from biopsy is obtained when both types of biopsies are performed [54–57].

Petov et al. have recently published a meta-analysis which concluded that robotic biopsy on targeted and systematic biopsy have comparable csPCa and overall detection rates [58]. In line with the results of these studies, the Cochrane systematic review makes clear its position regarding the complementarity of systematic biopsies with targeted biopsies via the transrectal route [15]. However, the complementarity of both types of biopsies via the transperineal route is not yet established. Recently, Porpiglia et al. [59] compared the detection rate of csPCa between targeted biopsy alone and targeted biopsy complemented with systematic biopsy. The fusion biopsy was performed with an unusual scheme in naïve biopsy men with positive mpMRI. If the PIRADS 4–5 lesion was anterior, a transperineal approach was used. If the PIRADS 4–5 lesion was posterior, a transrectal approach was used. This trial was designed as a non-inferiority study and concluded that fusion-targeted biopsy alone was not inferior than the fusion biopsy complemented with systematic biopsy for the detection of csPCa.

The value of targeted fusion-biopsy is widely acknowledged as MRI-TRUS fusion-biopsies detect more csPCa than the conventional 12-core TRUS systematic biopsies [51]. Among patients with MRI-visible prostate lesions, the addition of MRI-targeted biopsy to systematic biopsy increased the detection of csPCa and led to a net decrease in the detection of iPCa. Although many of these benefits resulted from MRI-targeted biopsy alone, omission of systematic biopsy would have led to missing the diagnosis of 8.8% of csPCa [52]. In our review, the detection of csPCa only in systematic biopsy was reported in 14 articles, which is an average of 9.5%, ranging from 0.8% to 22.1%. This significant difference may be due to multiple factors typical of the correct characterization of mpMRI, but also due to the inexperience of the surgeon, generating imprecision when establishing suspicious lesions [60].

Regarding the biopsy approach route, since 2019, the European Association of Urology (EAU) PCa guidelines recommend transperineal biopsy as the first option over transrectal biopsies. Tewes et al. compared fusion-guided transrectal biopsies with the transperineal route and found that the rate of targeted biopsy PCa detection rate was 39% via the transrectal route and 75% via the transperineal route [61]. Pepe et al. reported that the transperineal cognitive targeted biopsy detected a significantly higher percentage of csPCa from the anterior area compared to the transrectal directed biopsy [62]. The recent publication by Zattoni et al., reporting a multicenter study of 5241 fusion biopsies from both access routes, concluded that target biopsies via the transperineal route improve the detection of csPCa compared to targeted biopsies via the transrectal route, especially in the apex, transition/central zone, and anterior zones [63].

In this context of precision medicine, for the most sophisticated and accurate detection of csPCa, we have carried out, to our knowledge, the first systematic review that analyzes the diagnostic effectiveness of the currently available software and robots for MRI-TRUS fusion targeted biopsies through the transperineal route. This review showed that prostate biopsies performed guided by the image fusion robots through the transperineal route exhibits a higher detection rate of csPCa compared with the traditional systematic transrectal prostate biopsy. All the devices analyzed in this systematic review are approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Of all the robots reported in this article, Artemis (Eigen, Inc.) is the only one that, to date, has no articles evaluating its results via the transperineal approach. In this review, we found

no differences between the robots used and the PCa detection rate. Differences between devices mainly concern the registration algorithm (rigid vs. elastic), navigation strategy (organ-based versus electromagnetic tracking), post biopsy needle position documentation and use of articulating robotic arms. Venderink et al. [64] did not identify a significant difference between rigid and elastic images for MRI–TRUS fusion-guided biopsy in csPCa detection. However, the review was carried out through series in which, for the most part, the approach was transrectal. Gortz et al. [30] carried out the first comparative and randomized study between two series of transperineal fusion biopsy performed with rigid biopsy software and another with elastic biopsy. Their results concluded that transperineal MRI/TRUS targeted biopsies directed with a rigid image registration system showed a significantly higher PCa detection rate than elastic TB. We also observed this trend in our analysis of the data, which was sorted based on the types of populations biopsied and the type of biopsy used (rigid vs. elastic). Our findings revealed that transperineal rigid biopsy led to a higher detection rate of clinically significant prostate cancer.

In the latest studies that have been reviewed in this article, there is evidence of a tendency in most recent publications on prostate biopsies via image fusion to be not only mainly transperineal but also to be conducted under local anesthesia, demonstrating the feasibility of this technique with very good results. In addition, novel transperineal biopsy techniques are being developed with existing software platforms to further improve detection rates of csPca using local anesthesia via the transperineal route. Such is the case of the recent publications by Fletcher et al. [49] with Vector Biopsy and by Kaneco et al. [50] with the Double-Freehand Technique.

This review has some limitations. The populations analyzed are very heterogeneous. To somewhat lessen the impact of this breadth of populations analyzed, a homogenization was performed based on the population characteristics and through the rigid vs. elastic software used. Additionally, the series analyzed are not free of bias. The collection of the sample is not uniform, and the criteria for the interpretation of clinically significant prostate cancer vary from one series to another. Not all series used the START criteria for their structure. The experience of surgeons when performing biopsies was reported in a very few series and has a notable impact on the interpretation of the images to be segmented, on the manipulation of the robot, and on the degree of cognition for interpretation. Moreover, the segmentation of the prostate is a step rarely reported in the series and we believe that its correct performance is fundamental for the correct result of the biopsy.

5. Conclusions

This systematic review shows that the software analyzed for performing prostate biopsies directed via transperineal image fusion constitutes an effective method for the detection of csPCa. Targeted transperineal MRI–TRUS fusion prostate biopsies using a rigid image registration system showed a higher csPCa detection rate than those using elastic image registration. No diagnostic differences between the different types of robotic systems currently available were observed. However, one spread robotic system has not been analyzed. The complementarity of systematic biopsy has also been demonstrated in the transperineal MRI–TRUS image fusion biopsies, regardless of the fusion prototype used.

Author Contributions: Conceptualization, N.P. and J.M.; formal analysis, N.P., V.C., L.T., E.T. and J.M.; data curation, N.P. and J.M.; writing—original draft preparation, N.P. and J.M.; writing—review and editing, N.P., V.C., L.T., E.T. and J.M.; supervision, V.C., E.T. and J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are available in PubMed, Cochrane, and Google Scholar databases.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics. *CA Cancer J. Clin.* **2022**, *72*, 7–33. [\[CrossRef\]](#)
2. Bertuccio, P.; Santucci, C.; Carioli, G.; Malvezzi, M.; La Vecchia, C.; Negri, E. Mortality Trends from Urologic Cancers in Europe over the Period 1980–2017, and a Projection to 2025. *Eur. Urol. Oncol.* **2021**, *4*, 677–696. [\[CrossRef\]](#)
3. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Morote, J.; Borque-Fernando, Á.; Triquell, M.; Campistol, M.; Celma, A.; Regis, L.; Abascal, J.M.; Servian, P.; Planas, J.; Mendez, O.; et al. A Clinically Significant Prostate Cancer Predictive Model Using Digital Rectal Examination Prostate Volume Category to Stratify Initial Prostate Cancer Suspicion and Reduce Magnetic Resonance Imaging Demand. *Cancers* **2022**, *14*, 5100. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Draisma, G.; Boer, R.; Otto, S.J.; van de Cruijsen, I.W.; Damhuis, R.A.; Schröder, F.H.; de Koning, H.J. Lead times and overdiagnosis due to prostate specific antigen screening: Estimates from the European Randomized study of Screening for Prostate Cancer. *J. Natl. Cancer Inst.* **2003**, *95*, 868–878. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Epstein, J.I.; Egevad, L.; Amin, M.B.; Delahunt, B.; Srigley, J.R.; Humphrey, P.A. Grading Committee The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am. J. Surg. Pathol.* **2016**, *40*, 244–252. [\[CrossRef\]](#)
7. Stabile, A.; Giganti, F.; Rosenkrantz, A.B.; Villeirs, G.; Emberton, M.; Moore, C.M.; Kasivisvanathan, V. Multiparametric MRI for prostate cancer diagnosis: Current status and future directions. *Nat. Rev. Urol.* **2020**, *17*, 41–61. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Hoeks, C.M.; Barentsz, J.O.; Hambrock, T.; Yakar, D.; Somford, D.M.; Heijmink, S.W.; Scheenen, T.W.; Vos, P.C.; Huisman, H.; van Oort, I.M.; et al. Prostate cancer: Multiparametric MR imaging for detection, localization, and staging. *Radiology* **2011**, *261*, 46–66. [\[CrossRef\]](#)
9. Weinreb, J.C.; Barentsz, J.O.; Choyke, P.L.; Cornud, F.; Haider, M.A.; Macura, K.J. PI-RADS Prostate Imaging—Reporting and Data System: 2015, Version 2. *Eur. Urol.* **2016**, *69*, 16–40. [\[CrossRef\]](#)
10. Jue, J.S.; Rastinehad, A.R. MRI Fusion Transperineal Prostate Biopsy Instructions and Troubleshooting. *J. Endourol.* **2021**, *35*, S2–S6. [\[CrossRef\]](#)
11. Di Franco, C.; Jallous, H.; Porru, D.; Gilberto, G.L.; Cebrelli, T.; Tinelli, C.; Rovereto, B. A retrospective comparison between transrectal and transperineal prostate biopsy in the detection of PCa. *Arch. Ital. Urol. Androl.* **2017**, *89*, 55–59. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Westhoff, N.; Siegel, F.P.; Hausmann, D.; Polednik, M.; von Hardenberg, J.; Michel, M.S.; Ritter, M. Precision of MRI/ultrasound-fusion biopsy in prostate cancer diagnosis: An ex vivo comparison of alternative biopsy techniques on prostate phantoms. *World J. Urol.* **2017**, *35*, 1015–1022. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Ippoliti, S.; Fletcher, P.; Orecchia, L.; Miano, R.; Kastner, C.; Barrett, T. Optimal biopsy approach for detection of clinically significant prostate cancer. *Br. J. Radiol.* **2022**, *95*, 20210413. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Mottet, N.; Cornford, P.; van den Bergh, R.C.N.; Briers, E.; De Santis, M.; Gillessen, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; et al. EAU EANM ESTRO ESUR ISUP SIOG Guidelines on Prostate Cancer 2022 Update. Part 1: Screening Diagnosis, and Local Treatment with Curative Intent. *Eur. Urol.* **2021**, *79*, 243–262. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Drost, F.H.; Osses, D.F.; Nieboer, D.; Steyerberg, E.W.; Roobol, M.J.; Schoots, I.G. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst. Rev.* **2019**, *4*, CD012663. [\[CrossRef\]](#)
16. Lu, Z.; Kim, W.; Wilbur, W.J. Evaluation of query expansion using MeSH in PubMed. *Inf. Retrieval.* **2009**, *12*, 69–80. [\[CrossRef\]](#)
17. Shamseer, L.; Moher, D.; Clarke, M.; Ghersi, G.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ* **2015**, *350*, g747. [\[CrossRef\]](#)
18. Huang, X.; Lin, J.; Demner-Fushman, D. Evaluation of PICO as a knowledge representation for clinical questions. In *AMIA Annual Symposium Proceedings*; American Medical Informatics Association: Bethesda, MD, USA, 2006; Volume 2006, pp. 359–363.
19. Whiting, P.F.; Rutjes, A.W.; Westwood, M.E.; Mallett, S.; Deeks, J.J.; Reitsma, J.B.; Leeflang, M.M.; Sterne, J.A.; Bossuyt, P.M.; QUADAS-2 Group. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* **2011**, *155*, 529–536. [\[CrossRef\]](#)
20. Moore, C.M.; Kasivisvanathan, V.; Eggener, S.; Emberton, M.; Fütterer, J.J.; Gill, I.S.; Grubb III, R.L.; Hadaschik, B.; Klotz, L.; Margolis, D.J.; et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: Recommendations from an International Working Group. *Eur. Urol.* **2013**, *64*, 544–552. [\[CrossRef\]](#)
21. Jacewicz, M.; Rud, E.; Galtung, K.E.; Noor, D.; Baco, E. Cancer Detection Rates in Targeted Transperineal MRI-TRUS Elastic Fusion-guided Prostate Biopsies Performed Under Local Anesthesia. *Anticancer Res.* **2021**, *41*, 4395–4400. [\[CrossRef\]](#)
22. Mischinger, J.; Kaufmann, S.; Russo, G.I.; Harland, N.; Rausch, S.; Amend, B.; Scharpf, M.; Loewe, L.; Todenhoefer, T.; Notohamiprodjo, M.; et al. Targeted vs systematic robot-assisted transperineal magnetic resonance imaging-transrectal ultrasonography fusion prostate biopsy. *BJU Int.* **2018**, *121*, 791–798. [\[CrossRef\]](#)
23. Lee, A.Y.; Chen, K.; Law, Y.M.; Ho, H.S.; Cheng, C.W.; Yuen, J.S.; Tay, K.J. Robot-assisted Magnetic Resonance Imaging-ultrasound Fusion Transperineal Targeted Biopsy. *Urology* **2021**, *155*, 46. [\[CrossRef\]](#)

24. Marra, G.; Zhuang, J.; Beltrami, M.; Callaris, G.; Zhao, X.; Marquis, A.; Kan, Y.; Oderda, M.; Huang, H.; Faletti, R.; et al. Transperineal freehand multiparametric MRI fusion targeted biopsies under local anaesthesia for prostate cancer diagnosis: A multicentre prospective study of 1014 cases. *BJU Int.* **2021**, *127*, 22–130. [\[CrossRef\]](#)
25. Jacewicz, M.; Günzel, K.; Rud, E.; Lauritzen, P.M.; Galtung, K.F.; Hinz, S.; Magheli, A.; Baco, E. Multicenter transperineal MRI-TRUS fusion guided outpatient clinic prostate biopsies under local anesthesia. *Urol. Oncol.* **2021**, *39*, e1–e432. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Miah, S.; Hosking-Jervis, F.; Connor, M.J.; Eldred-Evans, D.; Shah, T.T.; Arya, M.; Barber, N.; Bhardwa, J.; Bott, S.; Burke, D.; et al. A Multicentre Analysis of the Detection of Clinically Significant Prostate Cancer Following Transperineal Image-fusion Targeted and Nontargeted Systematic Prostate Biopsy in Men at Risk. *Eur. Urol. Oncol.* **2020**, *3*, 262–269. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Günzel, K.; Magheli, A.; Busch, J.; Baco, E.; Cash, H.; Heinrich, S.; Edler, D.; Schostak, M.; Borgmann, H.; Schlegel, J.; et al. Evaluation of systematic prostate biopsies when performing transperineal MRI/TRUS fusion biopsy with needle tracking—what is the additional value? *Int. Urol. Nephrol.* **2022**, *54*, 2477–2483. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Mehmood, S.; Alothman, K.L.; Alwehaibi, A.; Alhashim, S.M. Diagnostic efficacy and safety of transperineal prostate targeted and systematic biopsy: The preliminary experience of first 100 cases. *Arch. Ital. Urol. Androl.* **2021**, *28*, 127–131. [\[CrossRef\]](#)
29. Hakozi, Y.; Matsushima, H.; Kumagai, J.; Murata, T.; Masuda, T.; Hirai, Y.; Oda, M.; Kawauchi, N.; Yokoyama, M.; Homma, Y. A prospective study of magnetic resonance imaging and ultrasonography (MRI/US)-fusion targeted biopsy and concurrent systematic transperineal biopsy with the average of 18-cores to detect clinically significant prostate cancer. *BMC Urol.* **2017**, *17*, 117. [\[CrossRef\]](#)
30. Görtz, M.; Nyarangi-Dix, J.N.; Pursche, L.; Schütz, V.; Reimold, P.; Schwab, C.; Stenzinger, A.; Sültmann, H.; Duensing, S.; Schlemmer, H.P.; et al. Impact of Surgeon's Experience in Rigid versus Elastic MRI/TRUS-Fusion Biopsy to Detect Significant Prostate Cancer Using Targeted and Systematic Cores. *Cancers* **2022**, *14*, 886. [\[CrossRef\]](#)
31. Hakozi, Y.; Matsushima, H.; Murata, T.; Masuda, T.; Hirai, Y.; Oda, M.; Kawauchi, N.; Yokoyama, M.; Kume, H. Detection rate of clinically significant prostate cancer in magnetic resonance imaging and ultrasonography-fusion transperineal targeted biopsy for lesions with a prostate imaging reporting and data system version 2 score of 3–5. *Int. J. Urol.* **2019**, *26*, 217–222. [\[CrossRef\]](#)
32. Miah, S.; Servian, P.; Patel, A.; Lovegrove, C.; Skelton, L.; Shah, T.T.; Eldred-Evans, D.; Arya, M.; Tam, H.; Ahmed, H.U.; et al. A prospective analysis of robotic targeted MRI-US fusion prostate biopsy using the centroid targeting approach. *J. Robot. Surg.* **2020**, *14*, 69–74. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Tschirdewahn, S.; Wiesenfarth, M.; Bonekamp, D.; Püllen, L.; Reis, H.; Panic, A.; Kesch, C.; Darr, C.; Heß, J.; Giganti, F.; et al. Detection of Significant Prostate Cancer Using Target Saturation in Transperineal Magnetic Resonance Imaging/Transrectal Ultrasonography-fusion Biopsy. *Eur. Urol. Focus.* **2021**, *7*, 1300–1307. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Hansen, N.L.; Kesch, C.; Barrett, T.; Koo, B.; Radtke, J.P.; Bonekamp, D.; Schlemmer, H.P.; Warren, A.Y.; Wicczorek, K.; Hohenfellner, M.; et al. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy. *BJU Int.* **2017**, *120*, 631–638. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Lian, H.; Zhuang, J.; Wang, W.; Zhang, B.; Shi, J.; Li, D.; Fu, Y.; Jiang, X.; Zhou, W.; Guo, H. Assessment of free-hand transperineal targeted prostate biopsy using multiparametric magnetic resonance imaging-transrectal ultrasound fusion in Chinese men with prior negative biopsy and elevated prostate-specific antigen. *BMC Urol.* **2017**, *17*, 52. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Radtke, J.P.; Boxler, S.; Kuru, T.H.; Wolf, M.B.; Alt, C.D.; Popeneciu, I.V.; Steinemann, S.; Huettenbrink, C.; Bergstraesser-Gasch, C.; Klein, T.; et al. Improved detection of anterior fibromuscular stroma and transition zone prostate cancer using biparametric and multiparametric MRI with MRI-targeted biopsy and MRI-US fusion guidance. *Prostate Cancer Prostatic Dis.* **2015**, *18*, 288–296. [\[CrossRef\]](#)
37. Kim, M.M.; Wu, S.; Lin, S.X.; Crotty, R.K.; Harisinghani, M.; Feldman, A.S.; Wu, C.L.; Dahl, D.M. Transperineal Multiparametric Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy Combined with Standard Template Improves Prostate Cancer Detection. *J. Urol.* **2022**, *207*, 86–94. [\[CrossRef\]](#)
38. De Vulder, N.; Slots, C.; Geldof, K.; Ramboer, K.; Dekimpe, P.; Uvin, P.; Walgraeve, M.S.; Van Holsbeeck, A.; Gieraerts, K. Safety and efficacy of software-assisted MRI-TRUS fusion-guided transperineal prostate biopsy in an outpatient setting using local anaesthesia. *Abdom. Radiol. (N. Y.)* **2023**, *48*, 694–703. [\[CrossRef\]](#)
39. Winoker, J.S.; Wajswol, E.; Falagario, U.; Maritini, A.; Moshier, E.; Voutsinas, N.; Knauer, C.J.; Sfakianos, J.P.; Lewis, S.C.; Taouli, B.A.; et al. Transperineal Versus Transrectal Targeted Biopsy with Use of Electromagnetically tracked MR/US Fusion Guidance Platform for the Detection of Clinically Significant Prostate Cancer. *Urology* **2020**, *146*, 278–286. [\[CrossRef\]](#)
40. Wajswol, E.; Winoker, J.S.; Anastos, H.; Falagario, U.; Okhawere, K.; Martini, A.; Treacy, P.J.; Voutsinas, N.; Knauer, C.J.; Sfakianos, J.P.; et al. A cohort of transperineal electromagnetically tracked magnetic resonance imaging/ultrasonography fusion-guided biopsy: Assessing the impact of inter-reader variability on cancer detection. *BJU Int.* **2020**, *125*, 531–540. [\[CrossRef\]](#)
41. Hansen, N.L.; Barrett, T.; Kesch, C.; Pepdjonovic, L.; Bonekamp, D.; O'Sullivan, R.; Distler, F.; Warren, A.; Samel, C.; Hadaschik, B.; et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. *BJU Int.* **2018**, *122*, 40–49. [\[CrossRef\]](#)

42. Shoji, S.; Hiraiwa, S.; Ogawa, T.; Kawakami, M.; Nakano, M.; Hashida, K.; Sato, Y.; Hasebe, T.; Uchida, T.; Tajiri, T. Accuracy of real-time magnetic resonance imaging-transrectal ultrasound fusion image-guided transperineal target biopsy with needle tracking with a mechanical position-encoded stepper in detecting significant prostate cancer in biopsy-naïve men. *Int. J. Urol.* **2017**, *24*, 288–294. [\[CrossRef\]](#)
43. Kaufmann, B.; Saba, K.; Schmidli, T.S.; Stutz, S.; Bissig, L.; Britschgi, A.J.; Schaeren, E.; Gu, A.; Langenegger, N.; Sulser, T.; et al. Prostate cancer detection rate in men undergoing transperineal template-guided saturation and targeted prostate biopsy. *Prostate* **2022**, *82*, 388–396. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Fulco, A.; Chiaradia, F.; Ascalone, L.; Andracchio, V.; Greco, A.; Cappa, M.; Scarcia, M.; Ludovico, G.M.; Pagliarulo, V.; Palmieri, C.; et al. Multiparametric Magnetic Resonance Imaging-Ultrasound Fusion Transperineal Prostate Biopsy: Diagnostic Accuracy from a Single Center Retrospective Study. *Cancers* **2021**, *3*, 4833. [\[CrossRef\]](#)
45. Thaiss, W.M.; Moser, S.; Hepp, T.; Kruck, S.; Rausch, S.; Scharpf, M.; Nikolaou, K.; Stenzl, A.; Bedke, J.; Kaufmann, S. Head-to-head comparison of biparametric versus multiparametric MRI of the prostate before robot-assisted transperineal fusion prostate biopsy. *World J. Urol.* **2022**, *40*, 2431–2438. [\[CrossRef\]](#)
46. Kozel, Z.; Martin, C.; Mikhail, D.; Smith, A.; Griffiths, L.; Nethala, D.; Vira, M.; Schwartz, M. Initial experience and cancer detection rates of office-based transperineal magnetic resonance imaging-ultrasound fusion prostate biopsy under local anesthesia. *Can. Urol. Assoc. J.* **2022**, *16*, E350–E356. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Dahl, D.M.; Kim, M.M.; Wu, S.; Lin, S.X.; Crotty, R.K.; Cornejo, K.M.; Harisinghani, M.G.; Feldman, A.S.; Wu, C.L. Detection of clinically significant prostate cancer by transperineal multiparametric magnetic resonance imaging-ultrasound fusion targeted prostate biopsy in smaller prostates. *Urol. Oncol.* **2022**, *40*, e9–e451. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Pepe, P.; Pennisi, M.; Fraggetta, F. How Many Cores Should be Obtained During Saturation Biopsy in the Era of Multiparametric Magnetic Resonance? Experience in 875 Patients Submitted to Repeat Prostate Biopsy. *Urology* **2020**, *137*, 133–137. [\[CrossRef\]](#)
49. Fletcher, P.; De Santis, M.; Ippoliti, S.; Orecchia, L.; Charlesworth, P.; Barrett, T.; Kastner, C. Vector Prostate Biopsy: A Novel Magnetic Resonance Imaging/Ultrasound Image Fusion Transperineal Biopsy Technique Using Electromagnetic Needle Tracking Under Local Anaesthesia. *Eur. Urol.* **2023**, *83*, 249–256. [\[CrossRef\]](#)
50. Kaneko, M.; Medina, L.G.; Lenon, M.S.L.; Sayegh, A.S.; Lebastchi, A.H.; Cacciamani, G.E.; Aron, M.; Duddalwar, V.; Palmer, S.L.; Gill, I.S.; et al. Transperineal magnetic resonance imaging/transrectal ultrasonography fusion prostate biopsy under local anaesthesia: The ‘double-freehand’ technique. *BJU Int.* **2023**, *131*, 770–774. [\[CrossRef\]](#)
51. Ahmed, H.U.; Kirkham, A.; Arya, M.; Illing, R.; Freeman, A.; Allen, C.; Emberton, M. Is it time to consider a role for MRI before prostate biopsy? *Nat. Rev. Clin. Oncol.* **2009**, *6*, 197–206. [\[CrossRef\]](#)
52. Ahmed, H.U.; El-Shater Bosaily, A.; Brown, L.C.; Gabe, R.; Kaplan, R.; Parmar, M.K.; Collaco-Moraes, Y.; Ward, K.; Hindley, R.G.; Freeman, A.; et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. *Lancet* **2017**, *389*, 815–822. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Kasivisvanathan, V.; Rannikko, A.S.; Borghi, M.; Panebianco, V.; Mynderse, L.A.; Vaarala, M.H.; Briganti, A.; Budäus, L.; Hellawell, G.; Hindley, R.G.; et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N. Engl. J. Med.* **2018**, *378*, 1767–1777. [\[CrossRef\]](#)
54. Connor, M.J.; Gorin, M.A.; Eldred-Evans, D.; Bass, E.J.; Desai, A.; Dudderidge, T.; Winkler, M.; Ahmed, H.U. Landmarks in the evolution of prostate biopsy. *Nat Rev Urol.* **2023**, *20*, 241–258. [\[CrossRef\]](#)
55. Rouvière, O.; Puech, P.; Renard-Penna, R.; Claudon, M.; Roy, C.; Mège-Lechevallier, F.; Decaussin-Petrucci, M.; Dubreuil-Chambardel, M.; Magaud, L.; Remontet, L.; et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): A prospective, multicentre, paired diagnostic study. *Lancet Oncol.* **2019**, *20*, 100–109. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Van der Leest, M.; Cornel, E.; Israël, B.; Hendriks, R.; Padhani, A.R.; Hoogenboom, M.; Zamecnik, P.; Bakker, D.; Yanti Setiasti, A.; Veltman, J.; et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Mu. *Eur. Urol.* **2019**, *75*, 570–578. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Elkhoury, F.F.; Felker, E.R.; Kwan, L.; Sisk, A.E.; Delfin, M.; Natarajan, S.; Marks, L.S. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naïve: The prospective assessment of image registration in the diagnosis of prostate cancer (PAIREDCAP) study. *JAMA Surg.* **2019**, *154*, 811–818. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Petov, V.; Azilgareeva, C.; Shpikina, A.; Morozov, A.; Krupinov, G.; Kozlov, V.; Singla, N.; Gómez Rivas, J.; Jesús, M.S.; Puliaatti, S.; et al. Robot-Assisted Magnetic Resonance Imaging-Targeted versus Systematic Prostate Biopsy: Systematic Review and Meta-Analysis. *Cancers* **2023**, *15*, 1181. [\[CrossRef\]](#)
59. Porpiglia, F.; Checucci, E.; De Cillis, S.; Piramide, F.; Amparore, D.; Piana, A.; Volpi, G.; Granato, S.; Zamengo, D.; Stura, I.; et al. A prospective randomized controlled trial comparing target prostate biopsy alone approach vs. target plus standard in naïve patients with positive mpMRI. *Minerva Urol. Nephrol.* **2023**, *75*, 31–41. [\[CrossRef\]](#)
60. Calio, B.; Sidana, A.; Sugano, D.; Gaur, S.; Jain, A.; Maruf, M.; Xu, S.; Yan, P.; Kruecker, J.; Pinto, P.; et al. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: Evidence of a learning curve. *Prostate Cancer Prostatic Dis.* **2017**, 436–441. [\[CrossRef\]](#)

61. Tewes, S.; Peters, I.; Tiemeyer, A.; Peperhove, M.; Hartung, D.; Pertschy, S.; Kuczyk, M.A.; Wacker, F.; Hueper, K. Evaluation of MRI/Ultrasound Fusion-Guided Prostate Biopsy Using Transrectal and Transperineal Approaches. *Biomed. Res. Int.* **2017**, *2017*, 217647. [[CrossRef](#)]
62. Pepe, P.; Garufi, A.; Priolo, G.; Pennisi, M. Transperineal versus Transrectal MRI/TRUS Fusion Targeted Biopsy: Detection Rate of Clinically Significant Prostate Cancer. *Clin. Genitourin. Cancer* **2017**, *15*, e33–e36. [[CrossRef](#)] [[PubMed](#)]
63. Zattoni, F.; Marra, G.; Kasivisvanathan, V.; Grummet, J.; Nandurkar, R.; Ploussard, G.; Olivier, J.; Chiu, P.K.; Valerio, M.; Gontero, P.; et al. The Detection of Prostate Cancer with Magnetic Resonance Imaging-Targeted Prostate Biopsies is Superior with the Transperineal vs the Transrectal Approach. A European Association of Urology-Young Academic Urologists Prostate Cancer Working Group Multi-Institutional Study. *J. Urol.* **2022**, *208*, 830–837. [[PubMed](#)]
64. Venderink, W.; De Rooij, M.; Sedelaar, J.P.M.; Huisman, H.J.; Fütterer, J.J. Elastic Versus Rigid Image Registration in Magnetic Resonance Imaging–transrectal Ultrasound Fusion Prostate Biopsy: A Systematic Review and Meta-analysis. *Eur. Urol. Focus.* **2018**, *4*, 219–227. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

5.7. PUBLICACIÓN 7

Título: External validation of the Barcelona magnetic resonance imaging predictive model for detecting significant prostate cancer including men receiving 5-alpha reductase inhibitors

Revista: World Journal of Urology

Año de publicación: 2024

Volumen: 42

Páginas: 393

DOI: <https://doi.org/10.1007/s00345-024-05092-0>

Autores: Juan Morote, Ángel Borque-Fernando, Luis M. Esteban, Natàlia Picola, Jesús Muñoz-Rodríguez, Nahuel Paesano, Xavier Ruiz-Plazas, Marta V. Muñoz-Rivero, Ana Celma, Gemma García-de Manuel, Berta Miró, José M. Abascal and Pol Servian

Factor de impacto (JCR): 2.9

Cuartil (JCR): 2 (Área de Urología y Nefrología)



External validation of the barcelona magnetic resonance imaging predictive model for detecting significant prostate cancer including men receiving 5-alpha reductase inhibitors

Juan Morote^{1,2} · Ángel Borque-Fernando³ · Luis M. Esteban⁴ · Natàlia Picola⁵ · Jesús Muñoz-Rodríguez⁶ · Nahuel Paesano^{2,7} · Xavier Ruiz-Plazas⁸ · Marta V. Muñoz-Rivero⁹ · Ana Celma¹ · Gemma García-de Manuel¹⁰ · Berta Miró¹¹ · José M. Abascal¹² · Pol Servian¹³

Received: 1 December 2023 / Accepted: 25 May 2024
 © The Author(s) 2024

Abstract

Purpose To validate the Barcelona-magnetic resonance imaging predictive model (BCN-MRI PM) for clinically significant prostate cancer (csPCa) in Catalonia, a Spanish region with 7.9 million inhabitants. Additionally, the BCN-MRI PM is validated in men receiving 5-alpha reductase inhibitors (5-ARI).

Materials and methods A population of 2,212 men with prostate-specific antigen serum level > 3.0 ng/ml and/or a suspicious digital rectal examination who underwent multiparametric MRI and targeted and/or systematic biopsies in the year 2022, at ten participant centers of the Catalanian csPCa early detection program, were selected. 120 individuals (5.7%) were identified as receiving 5-ARI treatment for longer than a year. The risk of csPCa was retrospectively assessed with the Barcelona-risk calculator 2 (BCN-RC 2). Men undergoing 5-ARI treatment for less than a year were excluded. CsPCa was defined when the grade group was ≥ 2 .

Results The area under the curve of the BCN-MRI PM in 5-ARI naïve men was 0.824 (95% CI 0.783–0.842) and 0.849 (0.806–0.916) in those receiving 5-ARI treatment, p 0.475. Specificities at 100, 97.5, and 95% sensitivity thresholds were to 2.7, 29.3, and 39% in 5-ARI naïve men, while 43.5, 46.4, and 47.8%, respectively in 5-ARI users. The application of BCN-MRI PM would result in a reduction of 23.8% of prostate biopsies missing 5% of csPCa in 5-ARI naïve men, while reducing 25% of prostate biopsies without missing csPCa in 5-ARI users.

Conclusions The BCN-MRI PM has achieved successful validation in Catalonia and, notably, for the first time, in men undergoing 5-ARI treatment.

Keywords Risk calculator · Predictive model · Significant prostate cancer · 5-alpha reductase inhibitor · Validation

Introduction

Prostate cancer (PCa) is the most common malignant neoplasm and the third leading cause of cancer death in men worldwide [1]. In 2009, the European Randomised Screening Prostate Cancer (ERSPC) trial reported a decrease in PCa-specific mortality in men subjected to screening compared to those of the control arm after seven years of

follow-up [2]. Fifteen years later a higher than 20% decrease in specific PCa mortality remains based on the early detection and treatment of clinically significant PCa (csPCa) [3]. As consequence, the focus of early detection of PCa has evolved to csPCa. This paradigm shift has been made possible through the widespread use of prostatic magnetic resonance imaging (MRI), which is employed to select candidates for prostate biopsy and perform targeted biopsies of

Juan Morote and Ángel Borque-Fernando Co-first authors.

José M. Abascal and Pol Servian Co-last authors.

Extended author information available on the last page of the article

Published online: 10 July 2024

Springer

suspicious lesions identified as having csPCa through MRI pinpointing [4]. Despite these advancements, uncertain scenarios with excessive unnecessary prostate biopsies and over-detection of insignificant tumors (iPCa) remain. Current predictive models, based on the prostate imaging report and data system (PI-RADS) and clinical data, have emerged as leading tools to improve the efficacy of csPCa diagnostic approaches [5]. The European Association of Urology currently advocates risk-stratified pathways for csPCa screening, based on predictive models [6].

The Barcelona MRI-predictive model (BCN-MRI PM) was developed to predict individual probabilities of csPCa in 1,486 men with suspected PCa who underwent pre-biopsy multiparametric MRI (mpMRI) followed by targeted and/or systematic biopsies, and the web app BCN-risk calculator 2 (BCN-RC 2) was designed. This development was conducted at a single institution and subsequently externally validated in a cohort of 946 men from two other institutions in the metropolitan area of Barcelona. Men treated with 5- α reductase inhibitors (5-ARI) were excluded from the development and external validation cohorts due to their known impact on serum PSA levels and prostate volume [7]. The performance of the BCN-RC 2 was superior to that of the Rotterdam MRI-RC in the external validation cohort [8].

Symptomatic benign prostatic hyperplasia (BPH) is a highly prevalent condition at the age when PCa screening is recommended. This results in many men with suspected PCa receiving medical treatment, being 5-ARIs used for alleviating voiding symptoms and preventing disease progression [9]. It is known the effect of 5-ARIs in PCa prevention, especially in low-grade tumors [10, 11], which resulted in a relative increase in high-grade PCa detection without consequences on PCa mortality [12]. The role of 5-ARIs in preventing the progression of low-grade PCa on active surveillance is currently under discussion [13].

Our main objective is to validate the BCN-MRI PM in Catalonia, a Spanish region with 7.9 million inhabitants. Additionally, considering that some men suspected of having PCa undergo 5-ARI treatment, a secondary objective is to validate the BCN-MRI PM in this specific cohort.

Methods

Design, participants, and setting

This is a retrospective study for the validation of the BCN-MRI-PM in 2,212 suspected PCa men who underwent mpMRI and prostate biopsy between January 1, and December 31, 2022, in ten participant centres of the Catalanian sPCa early detection programme. Among them, 120 (5.4%) were found to be receiving 5-ARI treatment for longer than

one year. Twelve men undergoing 5-ARI treatment less than one year were previously excluded for the study.

Diagnostic pathway of csPCa

sPCa early detection program of Catalonia is an opportunistic program existing from the year 2010. Serum PSA testing is offered or demanded by men to general practitioners or urologist at the primary health system, as DRE unfrequently. When serum PSA is higher than 3.0 ng/mL or an abnormal DRE is detected, men are referred to the sPCa early detection office, usually attended by the urologists who perform prostate biopsies, in hospital centers. PCa suspicion is verified by repeating serum PSA measurement, an specialized DRE performed, specific anamnesis of PCa family history and previous negative prostate biopsy and MRI requested. Finally, PCa will be detected and treatment strategy or appropriate follow up suggested. Men under special conditions, as BCRA mutations, are accepted in the sPCa early detection office, following a structured pathway.

Men suspected of having PCa are subjected to 1.5 or 3.0 Tesla mpMRI, currently reported with the PI-RADS v2.1 by experienced radiologists in each participant center. Prostate biopsy was carried out in men with suspicious lesions detected in mpMRI (PI-RADS score ≥ 3) and those with PI-RADS score ≤ 2 but having any data suggesting at high risk of PCa as PSA density > 0.15 , previous negative biopsy with increased PSA, and others considered.

Two to 4-core transrectal ultrasound (TRUS)-MRI image fusion-targeted biopsies of suspicious lesions and 12-core systematic biopsies were always performed in men with PI-RADS ≥ 3 . Only 12-core systematic biopsies were performed in those men with PI-RADS score ≤ 2 who were considered for a prostate biopsy. Fusion MRI-TRUS image was achieved using cognitive or commercial software techniques. Prostate biopsy procedures were performed through the transrectal or transperineal route by experienced urologists without specific criteria, besides the recommendation of transperineal route from 2019. Biopsy material was referred to each local pathology department where experienced uropathologists diagnosed csPCa when the International Society of Urologic Pathology (ISUP) grade group was two or higher [14].

Intervention

The probability of csPCa was assessed through the BCN-RC 2, available at the web application link <https://mrpca-prediction.shinyapps.io/MRIPCaPrediction/>. The predictive variables utilized by the BCN-RC 2 are, age (years), first degree PCa family history (no vs. yes), type of biopsy (initial vs. repeated), serum PSA level (ng/ml), DRE (normal

vs. suspicious), MRI prostate volume (cc), and PI-RADS v.2.1 (1–5). The probability of sPCa was the endpoint variable of the study.

Ethical considerations

This study received the approval from the ethical committee of the coordinating center (PRAG-02/2020), and it was supported by the Instituto de Salud Carlos III and the European Union (PI2020/01666). All participants signed informed consent.

Statistical analysis

Quantitative variables were described as median and interquartile range (25–75 percentiles), and qualitative variables as percentages. Descriptive variables were compared with the Mann-Whitney U test and the Chi-square test. Calibration of the predictive model was assessed in non-5ARI naïve men and 5-ARI users. Discrimination power was determined using the receiver operating characteristic (ROC) curves and the area under the curve (AUC) which were compared with the DeLong test. The clinical utility of the models was determined using the clinical utility curve (CUC) that explored the potential rates of missed csPCa detection and the avoidable prostate biopsies. Specificities of 100, 97.5, and 95% sensitivity thresholds were analysed. The net benefit of using the BCN-RC 2 for prostate biopsy candidate's over biopsying men with positive mpMRI was analyzed with decision curve analysis (DCA). Significant

differences were considered when the p value was <0.05 . Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statements were followed. Statistical analyses were computed using R programming language v.4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS v.24 (IBM, statistical package for social sciences, San Francisco, US).

Results

Characteristics of the study population

The characteristics of 2,212 suspected PCa men included in this study, and those corresponding to 2,092 5-ARI naïve men and 120 who were undergoing 5-ARI treatment are summarized and compared in Table 1. The median age ranged from 68 years in 5-ARI naïve to 72 in 5-ARI users, $p < 0.001$. The median serum PSA levels were 7.3 and 8.0 ng/ml, respectively, $p = 0.107$. The median prostate volumes were 53 and 69 cc, respectively, $p < 0.001$. The rates of abnormal DRE were 26.8 and 35.0%, respectively, $p = 0.057$. The rates of PCa family history were 8.1 and 4.2%, respectively, $p = 0.160$. The rates of repeated biopsies were 31.4 and 36.7%, respectively, $p = 0.228$.

MpMRI was performed in a 3.0 Tesla scanner in 70.3% of 5-ARI naïve men and 65.0% of 5-ARI users, $p = 0.216$. The distribution of PI-RADS categories in 5-ARI naïve men corresponded to PI-RADS < 3 in 15.3%, to 3 in 20.5%, to 4 in 43.2%, and to 5 in 21.0%, compared to 12.5%, 16.7%,

Table 1 Descriptive characteristics of the overall study population and comparison according to the 5-ARI exposure

Characteristic	Overall population	5-ARI naïve	5-ARI users	p Value
Number of men, (%)	2,212	2,092 (94.6)	120 (5.7)	-
Median age (IQR), years	68 (62–73)	68 (62–73)	72 (68–76)	<0.001
Median PSA (IQR), ng/ml	7.3 (5.3–11.0)	7.3 (5.3–11.0)	8.0 (5.0–13.0)	0.107
Suspicious DRE, n (%)	603 (27.3)	561 (26.8)	42 (35.0)	0.057
Repeated biopsy, n (%)	701 (31.7)	657 (31.4)	44 (36.7)	0.228
PCa family history, (%)	174 (7.9)	169 (8.1)	5 (4.2)	0.160
Median Prostate volume (IQR), cc	53 (39–75)	53 (38–74)	69 (49–97)	<0.001
PSA density, ng/ml/cc	0.14 (0.09–0.13)	0.14 (0.09–0.22)	0.12 (0.08–0.21)	0.025
3.0 Tesla mpMRI, n (%)	1,549 (70.0)	1,471 (70.3)	78 (65.0)	0.216
PI-RADS score, n (%)				
≤ 2	335 (15.1)	320 (15.3)	15 (12.5)	0.328
3	449 (20.3)	429 (20.5)	20 (16.7)	
4	960 (43.4)	903 (43.2)	57 (47.5)	
5	468 (21.2)	440 (21.0)	28 (23.3)	
Software fusion MRI-TRUS image technique, n (%)	1,375 (62.2)	1,303 (62.3)	72 (60.0)	0.384
Transperineal prostate biopsy route, n (%)	988 (44.7)	943 (45.1)	45 (37.5)	0.104
Overall PCa, n (%)	1,402 (63.4)	1,336 (63.9)	66 (55.0)	0.052
csPCa, n (%)	986 (44.6)	935 (44.7)	51 (42.5)	0.706
iPCa, n (%)	416 (18.8)	401 (19.2)	15 (12.5)	0.072

5-ARI: 5-alpha reductase inhibitor; IQR: interquartile range; PSA: prostate-specific antigen; DRE: digital rectal examination; PCa: prostate cancer; PI-RADS: Prostate imaging-report and data system; csPCa: clinically significant PCa; iPCa: insignificant PCa

47.5% and 23.3%, respectively, p 0.328. The MRI-TRUS fusion image technique was cognitive in 45.1% of 5-ARI naïve men and 37.5% of 5-ARI users, p 0.384. Prostate biopsy was made through transperineal route in 62.3% of 5-ARI naïve men, and 60.0% of 5-ARI users, p 0.104.

Overall PCa was detected in 1,402 men (63.4%), being 986 with csPCa (44.6) and 416 (18.8%) with iPCa. Overall PCa was detected in 1,336 (63.9%) 5-ARI naïve men, and 66 (55%) 5-ARI users, p 0.052. CsPCa was detected in 935 (44.7%) 5-ARI naïve men and 51 (42.5%) 5ARI users, p 0.706. IPCa were detected in 401 (19.2%) 5-ARI men and 15 (12.5%) 5-ARI users, p 0.072.

Calibration of the BCN-MRI predictive model in 5-ARI naïve men and 5-ARI users

Calibration curves of the BCN-MRI PM in 5-ARI naïve men and 5-ARI users are presented in Supplementary Fig. 1A and 1B respectively. A small overdetection of csPCa at low predicted probability of csPCa and a small down detection in predicted probabilities over 50% in 5-ARI naïve men is observed, being the adjustment of the calibration curve to the ideal curve slowly better in 5-ARI users.

Discrimination ability, clinical efficacy, and net benefit of the BCN-MRI predictive model for csPCa detection in 5-ARI naïve men and 5-ARI users

ROC curves of predicted probabilities of csPCa from the BCN-MRI PM are presented in Fig. 1A and B. The AUC in 5-ARI naïve men was 0.824 (95% CI 0.783–0.842), while 0.848 (0.806–0.916) in 5-ARI users, p 0.157.

Specificities corresponding to 100, 97.5, and 95% thresholds sensitivity in 5-ARI naïve men and 5-ARI users are presented in Table 1B and 1E. We note that 17.3% of prostate biopsies would be avoided using the BCN-MRI PM, missing 2.5% of sPCa in 5-ARI naïve men, while in 5-ARI users 25% of prostate biopsies would be avoided without missing sPCa. The rates of avoided prostate biopsies and its corresponding missing rate of csPCa in continuous threshold (0 to 100%) are presented in CUCs in both 5-ARI naïve men and 5-ARI users, Supplementary Fig. 2A and 3B respectively.

The net benefit of applying the BCN-MRI PM instead of biopsy all men, analyzed from DCAs performed in both 5-ARI naïve men and 5-ARI users are presented in Fig. 1C and E respectively.

The discrimination ability of the BCN-MRI PM for csPCa observed in the present validation cohort of 5-ARI naïve men and 5-ARI users is aligned with that observed previously in 5-ARI naïve men in the BCN-MRI PM

development cohort and the external validation in the metropolitan area of Barcelona [7], Supplementary Table 1.

Discussion

External validation of predictive models is mandatory in populations where they are going to be implemented [15]. The BCN-RC 2 is a user-friendly web app risk calculator designed from the BCN-MRI PM for the individual assessment of csPCa risk in men suspected of having PCa after mpMRI. This tool also has the option to select the threshold for the appropriate selection of candidates for prostate biopsy [7]. The BCN-MRI PM has been successfully validated in Catalonia, a region with 7.9 million inhabitants. Additionally, the BCN-MRI PM has been validated in men with suspected PCa receiving 5-ARI treatment for symptomatic BPH. This marks the first instance of validation for an MRI predictive model for csPCa detection in men undergoing 5-ARI treatment.

The validation of BCN-MRI PM in 5-ARI naïve men aligns with the previous validation conducted in the Barcelona metropolitan area [7]. The exclusion of twelve men with 5-ARI treatment less than a year was based on the progressive effect on serum PSA between six and twelve months, and the small number of cases [16–18]. Regarding the performance of BCN-MRI PM in men with symptomatic BPH treated with 5-ARI, we observed a calibration slightly better than that in 5-ARI naïve men. The discrimination ability of BCN-MRI PM for csPCa in 5-ARI treated men was slightly superior to that observed in 5-ARI naïve men. Using the 100% sensitivity threshold, the BCN-MRI PM was able to avoid 25% of prostate biopsies. In contrast the BCN-MRI PM could avoid 17.3% using the 97.5% sensitivity threshold and 23.8% using the 95% sensitivity threshold.

We were surprised to observe similar median serum PSA level in 5-ARI naïve men compared to those of men undergoing 5-ARI treatment. This is a shared concern aligned with the findings other studies reporting comparable serum PSA levels in 5-ARI users and 5-ARI naïve individuals at the time of prostate biopsy [16, 17]. In the recently reported PROstate Mri Outcome Database (PROMOD) study, which includes 705 men receiving 5-ARI treatment and 6,913 5-ARI naïve men, the median serum PSA levels were respectively 6.0 and 6.5 ng/ml respectively. Although a significant difference between both median values was found, the PSA serum level in 5-ARI users was notably distant from the expected half of the serum PSA level observed in 5-ARI naïve men [18]. This contrast with the recommendation for closely monitoring serum PSA level after the nadir following one year of 5-ARI treatment, and establishing PCa suspicion based on a confirmed increase of serum PSA

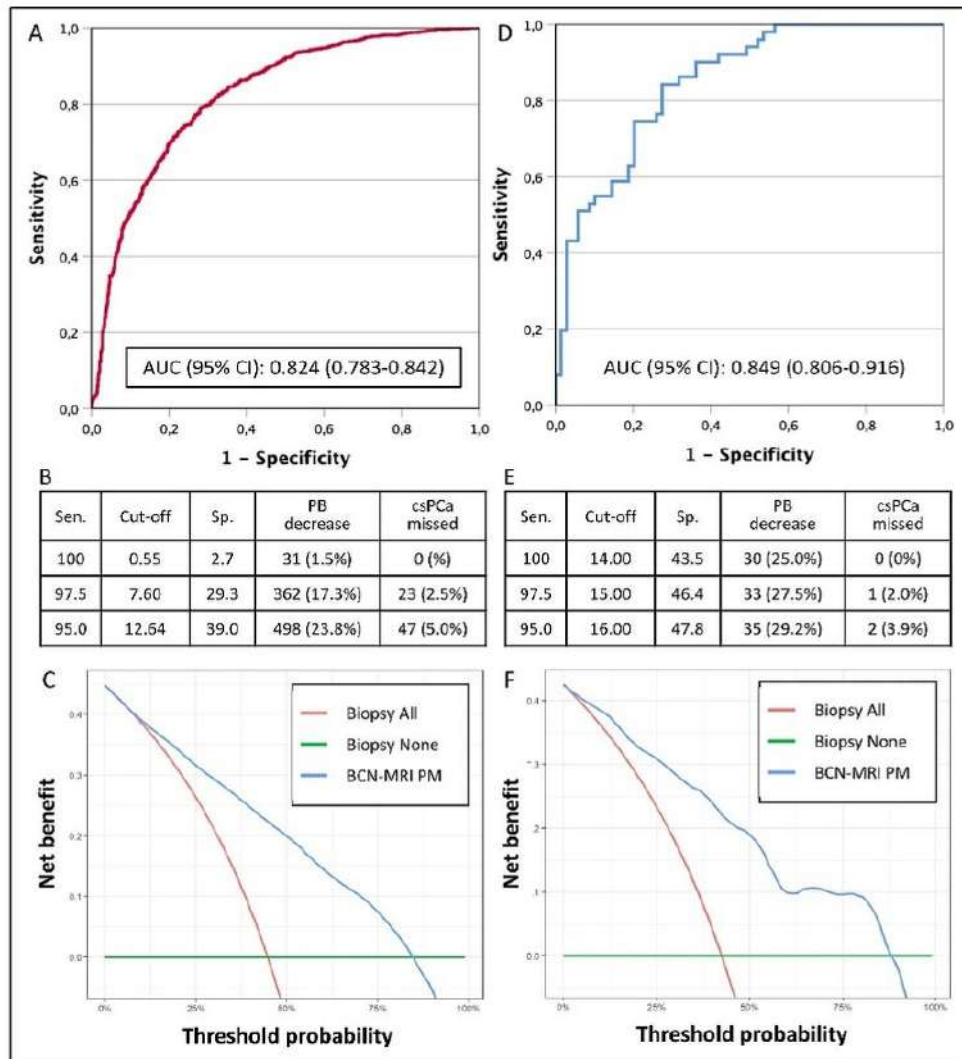


Fig. 1 Discrimination ability, clinical efficacy, and net benefit of the BCN-MRI PM for the detection of csPCa in 5-ARI naïve suspected PCa men (A-C) and in those receiving 5-ARI treatment (D-F)

levels higher than 0.3 ng/ml [19]. An awareness for patients exposed to 5-ARI treatment requires a close monitoring of serum PSA level to prevent the delay in diagnosing high-grade PCa which still appears necessary [20].

The MRI in Primary Prostate Cancer after Exposure to Dutasteride (MAPPED) study was designed to investigate the radiological effects of six month's exposure to dutasteride on low-grade PCa volume [21]. Preliminary data suggested that dutasteride is associated with an increase in the tumour apparent diffusion coefficient (ADC) and reduced visibility of the tumour on diffusion weighted imaging

(DWI), without affecting T2 sequences of mpMRI [21–23]. Starobinets et al. have suggested an enhanced discrimination of mpMRI between the areas with tumours and those with benign tissue located in the peripheral zone [24]. The effect of 5-ARI exposure on the PI-RADS category and its corresponding detection of csPCa and iPCa in men with suspected PCa has been poorly analyzed [16, 17, 25]. Recently, Falagio et al. observed that exposure to 5-ARIs does not affect the association of PI-RADS score with csPCa, although a higher rate of high-grade PCa was detected in 5-ARI users with PI-RADS 5 [18].

Limitations of our study can be attributed to its retrospective design and the used criteria for defining csPCa, which may not fully reflect the final pathology through the entire prostate gland. The successful validation in the early sPCa in Catalonia, does not mean a validation in a conventional screening program. Regarding 5-ARI users it would be necessary to consider a follow up of negative biopsies. However, it's important to acknowledge inherent constraints associated with predictive models exists. These models evaluate individual probabilities of a condition based on the characteristics of development cohort. Given that MRI is reported according to the PI-RADS score, the effectiveness of MRI predictive models should be analyzed regarding these scores to identify scenarios in which they are most useful [26]. Predictive models face challenges due to ongoing changes in the characteristics of populations where they are implemented, often necessitating recalibrations and readjustments to maintain accuracy [27]. Achieving real-time updates of predictive models poses a challenge for the future risk calculators [28]. Establishing a continuous feedback loop that involves new cases, employs appropriate machine learning algorithms, and utilizes federated networks can pave the way for risk calculators that undergo continuous updates at each participant site, ensuring their ongoing accuracy [29].

Conclusions

The BCN-MRI PM, developed for the individual assessment of csPCa probability in prostate biopsy of suspected PCa men has undergone successful validation in the population of Catalonia. Moreover, this model has also been validated in men suspected of having PCa who undergo 5-ARI treatment due to symptomatic BPH. The BCN-MRI PM is deemed ready for use in all men with suspected PCa in Catalonia.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00345-024-05092-0>.

Author contributions Conceptualization: JM, AB-F, LME. Methodology: NP, JM-R, NP, XR-P, MVM-R, AC, GG-deM, PS, JMA. Formal analysis and investigation: JM, AB-F, LME, BM. Writing - original draft preparation: JM. Writing - review and editing: AB-F, LME. Funding acquisition: JM. All authors read and approved the final manuscript.

Funding This research was supported by the Instituto de Salut Carlos III (SP) and the European Union (PI20/01666). Open Access Funding provided by Universitat Autònoma de Barcelona.

Data availability The data presented in this study are available on request from the corresponding author.

Code Availability Not applicable.

Declarations

Ethics approval and consent to participate This study received the approval from the ethical committee of Vall d'Hebron Hospital (PRAG-02/2020). Written informed consent was obtained from all subjects involved in the study.

Consent to participate Not applicable.

Conflict of interest The authors (JM, AB-F, LME, NP, JM-R, NP, XR-P, MVM-R, AC, GG-deM, BM, PS, JMA) have no conflicts of interest to declare.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71:209–249
2. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Maattanen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A (2009) Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 360:1320–1328
3. Fränlund M, Månsson M, Godtman RA, Aus G, Holmberg E, Kollberg KS, Lodding P, Pihl CG, Stranne J, Lilja H, Hugosson J (2022) Results from 22 years of Followup in the Göteborg Randomized Population-based prostate Cancer screening trial. *J Urol* 208:292–300
4. Van Poppel H, Albrecht T, Basu P, Hogenhout R, Collen S, Roobol M (2022) Serum PSA-based early detection of prostate cancer in Europe and globally: past, present, and future. *Nat Rev Urol* 19:562–572
5. Van Poppel H, Roobol MJ, Chapple CR, Catto JWF, N'Dow J, Senksen J, Stenzl A, Wirth M (2021) Prostate-specific Antigen Testing as Part of a risk-adapted early detection strategy for prostate Cancer: European Association of Urology Position and recommendations for 2021. *Eur Urol* 80:703–711
6. Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ (2021) A European model for an organised

- risk-stratified early detection Programme for prostate Cancer. *Eur Urol Oncol* 4:731–739
7. Morote J, Borque-Fernando A, Triquell M, Celma A, Regis L, Escobar M, Mast R, de Torres IM, Semidey ME, Abascal JM, Sola C, Servian P, Salvador D, Santamaria A, Planas J, Esteban LM, Trilla E (2022) The Barcelona Predictive Model of clinically significant prostate Cancer. *Cancers (Basel)* 14:1589
 8. Morote J, Borque-Fernando A, Triquell M, Campistol M, Servian P, Abascal JM, Planas J, Méndez O, Esteban LM, Trilla E (2023) Comparison of Rotterdam and Barcelona Magnetic Resonance Imaging Risk Calculators for Predicting clinically significant prostate Cancer. *Eur Urol Open Sci* 53:46–54
 9. Jacobsen SJ, Girman CJ, Lieber MM (2001) Natural history of benign prostatic hyperplasia. *Urology* 58:5–16
 10. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA (2003) The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349:215–224
 11. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, Pettaway CA, Tammela TL, Teloken C, Tindall DJ, Somerville MC, Wilson TH, Fowler IL, Rittmaster RS, and REDUCE SG (2010) Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 362:1192–1202
 12. Thompson IM, Goodman PJ, Tangen CM, Parnes HL, Minasian LM, Godley PA, Lucia MS, Ford LG (2013) Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med* 369:603–610
 13. Goldberg H, Klaassen Z, Chandrasekar T, Flesher N (2018) Preventing clinical progression and need for treatment in patients on active surveillance for prostate cancer. *Curr Opin Urol* 28:46–54
 14. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, Grading C (2016) The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol* 40:244–252
 15. Triquell M, Campistol M, Celma A, Regis L, Cuadras M, Planas J, Trilla E, Morote J (2022) Magnetic resonance imaging-based predictive models for clinically significant prostate Cancer: a systematic review. *Cancers (Basel)* 14:4747
 16. Kim JK, Lee HJ, Hwang SI, Choe G, Kim HJ, Hong SK (2019) The effect of 5 alpha-reductase inhibitor therapy on prostate cancer detection in the era of multi-parametric magnetic resonance imaging. *Sci Rep* 9:17862
 17. Wang Z, Wang K, Ong HY, Tsang WC, Wu QH, Chiong E (2023) 5-alpha reductase inhibitors and MRI prostates: actively reducing prostate sizes and ambiguity. *BMC Urol* 23:61
 18. Falagario UG, Lantz A, Jambor I, Busetto GM, Bettocchi C, Finati M, Ricapito A, Luzzago S, Ferro M, Musi G, Totaro A, Racioppi M, Carbonara U, Ceccucci E, Manfredi M, D'Aietti D, Porcaro AB, Nordström T, Björnebo L, Oderda M, Soria F, Taimen P, Aronen HJ, Perez IM, Ettala O, Marchioni M, Simone G, Ferriero M, Brasseti A, Napolitano L, Carmignani L, Signorini C, Conti A, Ludovico G, Scarcia M, Trombetta C, Claps F, Trautner F, Montanari E, Boeri L, Maggi M, Del Giudice F, Bove P, Forte V, Ficarra V, Rossanese M, Mucciardi G, Pagliarulo V, Tafuri A, Mirone V, Schips L, Antonelli A, Gontero P, Cormio L, Sciarra A, Porpiglia F, Bassi P, Dittono P, Boström PJ, Messina E, Panebianco V, De Cobelli O, Carrieri G, and PROMOD SG (2023) Diagnosis of prostate cancer with magnetic resonance imaging in men treated with 5-alpha-reductase inhibitors. *World J Urol* 41:2967–2974
 19. Marberger M, Freedland SJ, Andriole GL, Emberton M, Pettaway C, Montorsi F, Teloken C, Rittmaster RS, Somerville MC, Castro R (2012) Usefulness of prostate-specific antigen (PSA) rise as a marker of prostate cancer in men treated with dutasteride: lessons from the REDUCE study. *BJU Int* 109:1162–1169
 20. Chang LW, Wang SS, Yang CK, Lu K, Chen CS, Cheng CL, Hung SC, Chiu KY, Hsu CY, Li JR (2023) Risk analysis of prostate Cancer Development following five-alpha reductase inhibitor treatment for benign prostate Hyperplasia. *Anticancer Res* 43:485–491
 21. Moore CM, Robertson NL, Jichi F, Damola A, Ambler G, Giganti F, Ridout AJ, Bott SR, Winkler M, Ahmed HU, Arya M, Mitra AV, McCartan N, Freeman A, Jameson C, Castro R, Gambarota G, Whitcher BJ, Allen C, Kirkham A, Emberton M (2017) The Effect of Dutasteride on magnetic resonance imaging defined prostate Cancer: MAPPED-A Randomized, Placebo Controlled, double-blind clinical trial. *J Urol* 197:1006–1013
 22. Giganti F, Moore CM, Robertson NL, McCartan N, Jameson C, Bott SRJ, Winkler M, Gambarota G, Whitcher B, Castro R, Emberton M, Allen C, Kirkham A (2017) MRI findings in men on active surveillance for prostate cancer: does dutasteride make MRI visible lesions less conspicuous? Results from a placebo-controlled, randomised clinical trial. *Eur Radiol* 27:4767–4774
 23. Giganti F, Gambarota G, Moore CM, Robertson NL, McCartan N, Jameson C, Bott SRJ, Winkler M, Whitcher B, Castro-Santamaria R, Emberton M, Allen C, Kirkham A (2018) Prostate cancer detection using quantitative T2 and T2 -weighted imaging: the effects of 5-alpha-reductase inhibitors in men on active surveillance. *J Magn Reson Imaging* 47:1646–1653
 24. Starobinets O, Kurhanewicz J, Noworolski SM (2017) Improved multiparametric MRI discrimination between low-risk prostate cancer and benign tissues in a small cohort of 5α-reductase inhibitor treated individuals as compared with an untreated cohort. *NMR Biomed* 30:e3696
 25. Forte V, Cavallo AU, Bertolo R, de Soccio V, Sperandio M, Bove P, Ciccarriello M (2021) PI-RADS score v.2 in predicting malignancy in patients undergoing 5α-reductase inhibitor therapy. *Prostate Cancer Prostatic Dis* 24:150–155
 26. Morote J, Borque-Fernando A, Triquell M, Esteban LM, Trilla E (2022) The true utility of Predictive models based on magnetic resonance imaging in selecting candidates for prostate biopsy. *Eur Urol Open Sci* 42:40–41
 27. Diniz MA (2022) Statistical methods for validation of predictive models. *J Nucl Cardiol* 29:3248–3255
 28. Nandi A, Khafa F (2022) A federated learning method for real-time emotion state classification from multi-modal streaming. *Methods* 204:340–347
 29. Strobl AN, Vickers AJ, Van Calster B, Steyerberg E, Leach RJ, Thompson IM, Ankerst DP (2015) Improving patient prostate cancer risk assessment: moving from static, globally-applied to dynamic, practice-specific risk calculators. *J Biomed Inf* 56:87–93

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Juan Morote^{1,2}  · Ángel Borque-Fernando³ · Luis M. Esteban⁴ · Natàlia Picola⁵ · Jesús Muñoz-Rodríguez⁶ · Nahuel Paesano^{2,7} · Xavier Ruiz-Plazas⁸ · Marta V. Muñoz-Rivero⁹ · Ana Celma¹ · Gemma García-de Manuel¹⁰ · Berta Miró¹¹ · José M. Abascal¹² · Pol Servian¹³

✉ Juan Morote
juan.morote@vallhebron.cat

¹ Department of Urology, Vall d'Hebron Hospital, Barcelona, Spain

² Department of Surgery, Universitat Autònoma de Barcelona, Bellaterra, Spain

³ Department of Urology, Hospital Universitario Miguel Servet, IIS-Aragon, Zaragoza, Spain

⁴ Department of Applied Mathematics, Escuela Universitaria Politécnica La Almunia, Universidad de Zaragoza, Zaragoza, Spain

⁵ Department of Urology, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain

⁶ Department of Urology, Hospital Universitari Parc Taulí, Sabadell, Spain

⁷ Clínica Creu Blanca, Barcelona, Spain

⁸ Department of Urology, Hospital Universitari Joan XXIII, Tarragona, Spain

⁹ Department of Urology, Hospital Universitari Arnau de Vilanova, Lleida, Spain

¹⁰ Department of Urology, Hospital Universitari Josep Trueta, Girona, Spain

¹¹ Unit of Statistics and Bioinformatics, Vall d'Hebron Research Institute, Barcelona, Spain

¹² Department of Urology, Parc de Salut Mar, Barcelona, Spain

¹³ Department of Urology, Hospital Germans Trias i Pujol, Badalona, Spain

5.8. PUBLICACIÓN 8

Título: Validation of the Barcelona-MRI predictive model when PI-RADS v2.1 is used with transperineal prostate biopsies.

Revista: Int Braz J Urol

Año de publicación: 2024

Volumen: 50

Páginas: 595–604

DOI: <https://doi.org/10.1590/S1677-5538.IBJU.2024.0204>

Autores: Juan Morote, Nahuel Paesano, Natàlia Picola, Jesús Muñoz-Rodríguez, Xavier Ruiz-Plazas, Marta V Muñoz-Rivero, Ana Celma, Gemma García-de Manuel, Berta Miró, Pol Servian, José M Abascal

Factor de impacto (JCR): 4.5

Cuartil (JCR): 2 (Área de Urología y Nefrología)



Validation of the Barcelona-MRI predictive model when PI-RADS v2.1 is used with transperineal prostate biopsies

Juan Morote ^{1,2}, Nahuel Paesano ^{2,3}, Natàlia Picola ⁴, Jesús Muñoz-Rodríguez ⁵, Xavier Ruiz-Plazas ⁶, Marta V. Muñoz-Rivero ⁷, Ana Celma ¹, Gemma García-de Manuel ⁸, Berta Miró ⁹, Pol Servian ¹⁰, José M. Abascal ^{11,12}

¹ Department of Urology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; ² Department of Surgery, Universitat Autònoma de Barcelona, Bellaterra, Spain; ³ Clínica Creu Blanca, Barcelona, Spain; ⁴ Department of Urology, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain; ⁵ Department of Urology, Hospital Universitari Parc Taulí, Sabadell, Spain; ⁶ Department of Urology, Hospital Universitari Joan XXIII, Tarragona, Spain; ⁷ Department of Urology, Hospital Universitari Arnau de Vilanova, Lleida, Spain; ⁸ Department of Urology, Hospital Universitari Josep Trueta, Girona, Spain; ⁹ Statistic Unit, Vall d'Hebron Research Institute, Barcelona, Spain; ¹⁰ Department of Urology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ¹¹ Department of Urology, Parc de Salut Mar, Barcelona Spain; ¹² Department of Medicine and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain

ABSTRACT

Purpose: To validate the Barcelona magnetic resonance imaging predictive model (BCN-MRI PM) in men with pre-biopsy multiparametric MRI (mpMRI) reported with the Prostate Imaging Reporting and Data System (PI-RADS) v2.1, followed by transrectal and transperineal prostate biopsies.

Materials and Methods: Prospective analysis of 3,264 men with PSA >3.0 ng/mL and/or abnormal digital rectal examination who were referred to ten participant centers in the csPCa early detection program of Catalonia (Spain), between 2021 and 2023. MpMRI was reported with the PI-RADS v2.1, and 2- to 4-core MRI-transrectal ultrasound (TRUS) fusion-targeted biopsy of suspected lesions and/or 12-core systematic biopsy were conducted. 2,295 (70.3%) individuals were referred to six centers for transrectal prostate biopsies, while 969 (39.7%) were referred to four centers for transperineal prostate biopsies. CsPCa was classified whenever the International Society of Urologic Pathology grade group was 2 or higher.

Results: CsPCa was detected in 41% of transrectal prostate biopsies and in 45.9% of transperineal prostate biopsies ($p < 0.016$). Both BCN-MRI PM calibration curves were within the ideal correlation between predicted and observed csPCa. Areas under the curve and 95% confidence intervals were 0.847 (0.830-0.857) and 0.830 (0.823-0.855), respectively ($p = 0.346$). Specificities corresponding to 95% sensitivity were 37.6 and 36.8%, respectively ($p = 0.387$). The Net benefit of the BCN-MRI PM was similar with both biopsy methods.

Conclusions: The BCN-MRI PM has been successfully validated when mpMRI was reported with the PI-RADS v2.1 and prostate biopsies were conducted via the transrectal and transperineal route.

ARTICLE INFO

Juan Morote Robles

<https://orcid.org/0000-0002-2168-323X>

Keywords:

Prostatic Neoplasms;
Magnetic Resonance Imaging;
Diagnosis

Int Braz J Urol. 2024; 50: 595-604

Submitted for publication:
January 12, 2024

Accepted after revision:
July 07, 2024

Published as Ahead of Print:
July 20, 2024

INTRODUCTION

Risk-stratified prostate cancer (PCa) screening, based on serum prostate-specific antigen (PSA) and magnetic resonance imaging (MRI), is currently recommended by the European Union (1). The new paradigm for PCa screening is focused on the early detection of clinically significant PCa (csPCa) (2). This paradigm change is based on evidence reported by the European Randomized Screening Prostate Cancer study in 2009. In this randomized trial, the hazard ratio for cause-specific death in the screening arm, and its 95% confidence interval, as compared with the control arm, reached a significance of 0.80 (0.65 to 0.98) at 8.8 years of follow up (3). This significant reduction of PCa-specific mortality has been maintained after 22 years of follow up in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial (4). The European Association of Urology currently proposes the use of risk-stratified pathways, based on predictive models, for improving csPCa screening by reducing the demand for MRI exams, maximizing the detection of csPCa, and decreasing unnecessary prostate biopsies and over-detection of insignificant PCa (iPCa) (5, 6).

The Barcelona-MRI predictive model (BCN-MRI PM) for individualizing the risk of csPCa detection in prostate biopsies was developed due to the absence of csPCa risk calculators using the Prostate Imaging Reporting and Data System (PI-RADS) v2.0, and six other independent clinical predictive variables without range limitations, namely: age (years), PCa family history (no vs. yes), type of prostate biopsy (initial vs. repeated), serum PSA (ng/mL), digital rectal examination (DRE: normal vs. suspicious), MRI-derived prostate volume (mL), and PI-RADS score from 1 to 5 (7). The BCN-MRI PM development cohort included 1,486 men, with serum PSA >3.0 ng/mL and/or suspicious DRE, who underwent pre-biopsy multiparametric MRI (mpMRI) reported with PI-RADS v2.0, followed by 2- to 4-core MRI-transrectal ultrasound (TRUS) fusion-targeted biopsy of PI-RADS >3 lesions and 12-core systematic biopsy, but only a 12-core systematic biopsy in those negative MRI (PI-RADS

1 or 2). This development cohort was prospectively recruited in a single academic institution between 2016 and 2019. Additionally, an external validation was conducted in 946 men, who underwent the same PCa suspicion criteria and diagnostic approach as those in the development cohort, in two centers from the Barcelona metropolitan area within the same period (8). The BCN-MRI risk calculator was designed for the easy and quick assessment of individual risk of csPCa, with the novelty of selecting the appropriate threshold for prostate biopsy decision, free available without cost at the <https://mrpcaprediction.shinyapps.io/MRIPCaPrediction/> (accessed on March 29, 2024). The BCN-MRI PM has been compared with the prestigious Rotterdam-MRI PM in a head-to-head analysis conducted in the external validation cohort. A better overall performance of the BCN-MRI PM was observed, especially in men with PI-RADS of 3 and 4. Additionally, it was observed that 22% of men included in this analysis presented age, serum PSA, or prostate volume out of the range accepted by the Rotterdam-MRI risk calculator (9).

Current predictive models require validation in populations where they are intended to be applied, even if the event of changes in the characteristics of the population from which the development cohort came or changes in the diagnostic procedure. These validations are necessary to ensure the ongoing accuracy of individual predictions (10).

Two relevant changes have recently been incorporated into the early diagnostic approach to csPCa. First, the PI-RADS v2.1 is currently followed for reporting MRI findings, and second, transperineal route for prostate biopsies is suggested for avoiding the infectious complications of prostate biopsies (11, 12). We hypothesise the BCN-MRI predictive model will be successfully validated in when PI-RADS v2.1 is employed for reporting pre-biopsy MRI, and prostate biopsies conducted even by transrectal and transperineal route. The present study aims to validate the BCN-MRI PM in a csPCa opportunistic screening program where the diagnostic approach employed the PI-RADS v2.1 for reporting MRI, and transperineal or transrectal prostate biopsies.

MATERIAL AND METHODS

Design, setting, and participants

This is a prospective study conducted in 3,264 men with the inclusion criteria of (i) suspicion of PCa based on serum PSA of >3.0 ng/mL and/or suspicious DRE, (ii) pre-biopsy mpMRI reported with PI-RADS v2.1, and (iii) prostate biopsy following the scheme of 2- to 4-core MRI-transrectal ultrasound (TRUS) fusion-targeted biopsies and 12-core systematic biopsy in men with PI-RADS ≥ 3 , but only a 12-core systematic biopsy in those with PI-RADS <3 . This trial was conducted in ten centers participating in the csPCa early detection program of Catalonia (Spain), a region with 7.9 million inhabitants, between January 1, 2020, and June 30, 2023. Reported cases were consecutive in each participant center. A subset of 2,295 men (70.3%) underwent prostate biopsy in six participant centers where transrectal prostate biopsy was exclusively employed, while 969 (29.7%) underwent biopsies in three other centers exclusively employing transperineal biopsies. The exclusion criteria were men with previous diagnosis of PCa, multifocal high-grade prostatic intraepithelial neoplasia, and atypical small acinar proliferation. Men recruited in one participant center where transperineal prostate biopsies followed a mapping scheme for targeted biopsies were not included in this analysis. This project was approved by the ethics committee of the coordinating center (PRAG02/2020), with participants signing an informed consent.

CsPCa suspicion and diagnostic approach

PCa suspicion was based mostly on a serum PSA >3.0 ng/mL, while 95 men (2.9%) exhibited a suspicious DRE with a serum PSA of 3.0 or lower. Men suspected of having PCa were referred to the nearest participating center of the csPCa early detection program. MpMRI was conducted at each participant center using a 1.5 or 3 Tesla scan with a pelvic phased-array surface coil. The acquisition protocol included T2-weighted imaging (T2W), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging, according to the guidelines of the European Society of Urogenital Radiology (13). MpMRI exams were read by local ex-

pert radiologists reporting with the PI-RADS v2.1 (11). All prostate biopsies were performed using freehand technique and software MRI-TRUS fusion image for targeted biopsies in 42.8%, while cognitive fusion was employed in 67.8%. Uropathologists examined the biopsy material in each pathology department and reported PCa using the International Society of Urologic Pathology grade group (GG) classification. CsPCa was considered when the GG was 2 or higher (14).

Statistical Analysis

Statistical analysis was conducted after harmonization of anonymized datasets. The data were prospectively collected and reported according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) to describe the study population (15). Quantitative variables are described using medians and interquartile ranges (25th–75th percentiles), while qualitative variables are described using numbers and percentages. Quantitative variables were compared between groups using the Mann–Whitney U test. Qualitative variables were compared between groups using Pearson's chi-square test. Relative risk (RR) of csPCa and 95% confidence intervals (CI) were assessed. Calibration of the BCN-MRI PM was conducted for both prostate biopsy routes. Discrimination of csPCa from the BCN-MRI PM in each prostate biopsy group was analyzed with receiver operating characteristic (ROC) curves, and the areas under the curve (AUC) were compared with the DeLong test. Specificities corresponding to selected sensitivities with clinical interest were compared and avoided prostate biopsies and loss of csPCa estimated. Net benefit of the BCN-MRI PM over biopsy all men was evaluated through decision curve analysis (DCAs). A p value of <0.05 was considered statistically significant. The data were analyzed using the Statistical Package for the Social Sciences (version 29.0; IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of both subsets of men who underwent transrectal or transperineal route for

prostate biopsy are summarized in Table-1. We note that baseline characteristics were similar in both subsets. The median interval from MRI exam to prostate biopsy was 27 days. However, csPCa was detected in 940 men (41%) who underwent transrectal prostate biopsy, and in 445 men (45.9%) who underwent transperineal prostate biopsy ($p = 0.016$). The rates of iPCa detection were 16.3% and 17.4%, respectively ($p = 0.441$).

Calibration of the BCN-MRI PM in both subsets was very good. Similar calibration curves between predicted risks and observed csPCa cases in transrectal and transperineal prostate biopsies were observed. Both calibration curves showed a small over-estimation in lowest predictive probabilities of csPCa and minimal under-estimation in the higher predictive probabilities of csPCa, but both were near the ideal correlation line, Figure-1 A-B.

ROC curves showed AUC (95% confidence intervals) of 0.847 (0.830–0.863) and 0.830 (0.804–0.855), in prostate biopsies conducted through transrectal and transperineal routes, respectively, ($p = 0.346$), Figure-2 A-B. Specificities corresponding to 100%, 97.5%, and 95% sensitivity of the BCN-MRI PM and thresholds were analyzed. The specificity corresponding to 100% sensitivity was 1.3 and 1.8%, from the threshold of 0.36% for transrectal biopsies and 0.49% for transperineal biopsies, $p = 0.438$. The specificities corresponding to 97.5% sensitivity were 23.7 and 22.6%, from the threshold of 5.11% and 8.58% for transrectal and transperineal prostate biopsies respectively, $p = 0.395$. Regarding the sensitivity of 95%, the specificities of the BCN-MRI-PM corresponded to 37.6 and 36.8%, from the threshold of 9.80 and 16.2% for transrectal and transperineal prostate biopsies respectively, $p = 0.387$. We note that thresholds

Table 1 - Characteristics of the study cohort according to the utilized prostate biopsy route.

Characteristic	Route of prostate biopsy		p Value
	Transrectal	Transperineal	
Number of men, n (%)	2,295 (70.3)	969 (29.7)	-
Median age, years (IQR)	68 (62-73)	68 (62-74)	0.556
Median serum PSA, ng/mL (IQR)	7.1 (5.2-11)	7.4 (5.4-10.7)	0.294
Abnormal DRE, n (%)	132 (25.7)	68 (26.0)	0.214
Median prostate volume, mL (IQR)	55 (40-79)	54 (39-76)	0.178
Prior negative prostate biopsy, n (%)	690 (30.1)	273 (28.1)	0.294
Family history of PCa, n (%)	121 (5.3%)	67 (6.9)	0.231
PI-RADS, n (%)			
1-2	230 (10.0)	83 (8.6)	0.427
3	565 (24.6)	200 (20.6)	0.235
4	987 (43.0)	459 (47.4)	0.189
5	513 (22.4)	227 (23.4)	0.201
Overall PCa detection, n (%)	1,315 (57.3)	651 (67.2)	0.001
csPCa, n (%)	940 (41.0)	445 (45.9)	0.016
iPCa, n (%)	375 (16.3)	169 (17.2)	0.441

IQR = interquartile range; n = number; PI-RADS = prostate imaging-reporting and data system; PCa = prostate cancer; csPCa = clinically significant PCa; iPCa = insignificant PCa.

Figure 1 - Calibration curves of the BCN-MRI PM in transrectal prostate biopsies (A) and transperineal prostate biopsies (B).

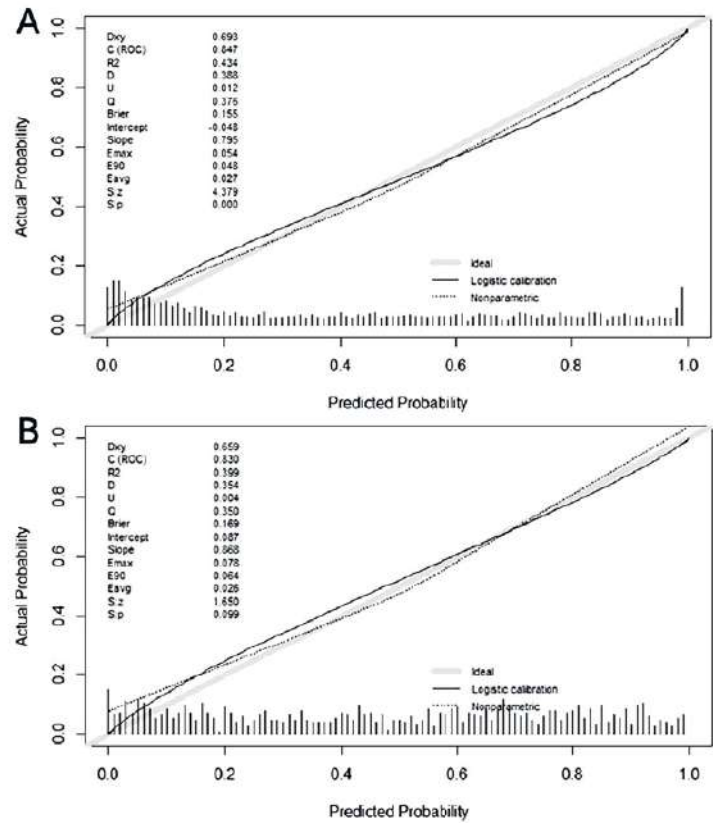
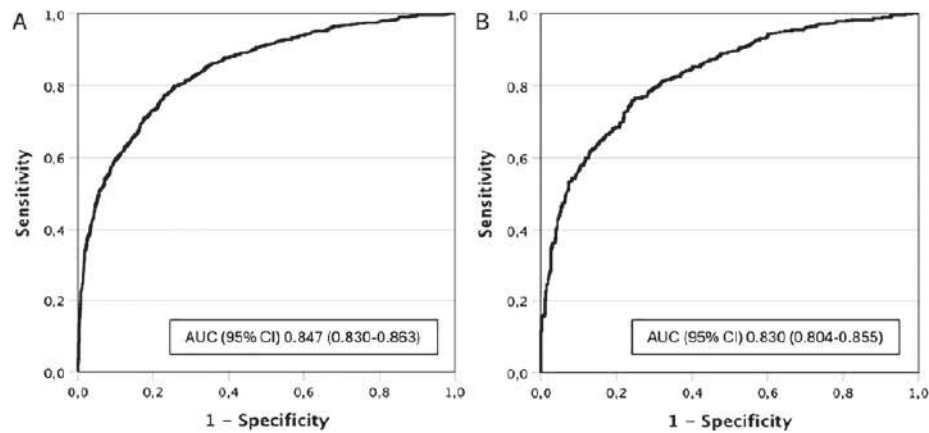


Figure 2 - Discrimination ability of the BCN-MRI PM for csPCa detection in transrectal prostate biopsies (A) and transperineal prostate biopsies (B).



of the BCN-MRI PM were higher when the transperineal route was used. The avoided prostate biopsies with 100% sensitivity of the BCN-MRI PM were 17 (0.7%) for transrectal biopsies and 9 (0.9%) for transperineal biopsies ($p = 0.438$). For csPCa 97.5% sensitivity, they were 344 (15%) and 112 (12.6%), respectively, ($p = 0.395$). For csPCa 95% sensitivity, they were 557 (24.3%) and 229 (22.6%), respectively, ($p = 0.387$).

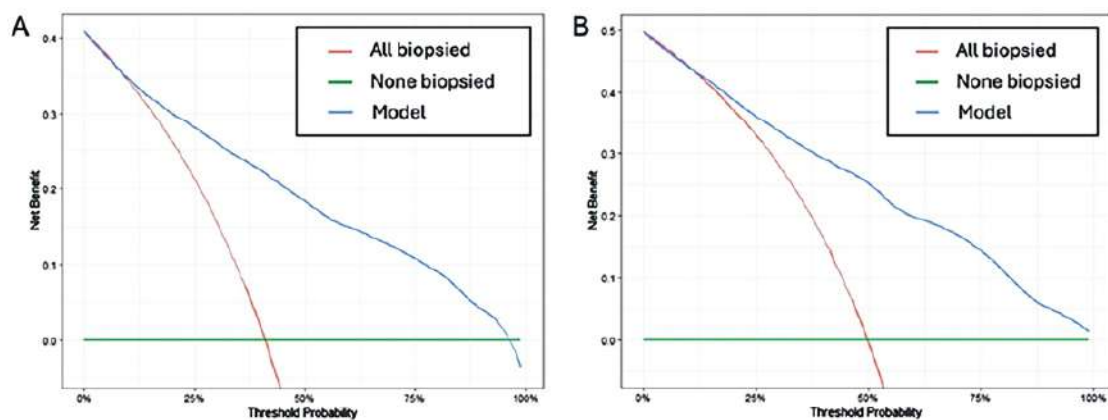
DCA's showed a similar net benefit of the BCN-MRI PM over biopsying all men with both prostate biopsy routes beginning at lower than 10% and 15% threshold probabilities of csPCa for transrectal and transperineal prostate biopsies, respectively, Figure-3 A-B.

DISCUSSION

The BCN-MRI PM is based on PI-RADS score and some clinical variables that resulted independent for csPCa prediction in prostate biopsies. PSA density was the most weighed independent predictor after MRI (16, 17), that was expressed as serum PSA and MRI derived from prostate volume to avoid the manual calculation of PSA density. The BCN-MRI PM has been satisfactorily validated in men suspected of having PCa undergoing pre-biopsy mpMRI reported with the PI-RADS v2.1, and those undergoing prostate biopsies conducted via the transrectal and transperineal routes. This is important,

since the BCN-MRI PM has been developed and validated using the PI-RADS v2.0 and transrectal biopsies. This successful validation guaranties the accuracy of the BCN-MRI PM predictions when PI-RADS v2.1 and transrectal biopsies are employed. The scheme of prostate biopsy conducted in this external validation study has been the same employed in the development cohort of the BCN-MRI PM, which obtained 2- to 4-core MRI-TRUS fusion-targeted biopsies of PI-RADS lesions ≥ 3 and/or 12-core systematic biopsy when the PI-RADS was <3 , although some current reports suggest that systematic biopsies can be reduced (18), even to biopsy only the index lesion using a mapping scheme (19). This external validation has been successful despite the improved csPCa detection observed when the transperineal route is employed to conduct prostate biopsies. We noted that transperineal prostate biopsies detected 45.9% of csPCa while 41.7% when transrectal route was used. This finding has been previously reported, especially in anterior and apical suspicious lesions (20, 21). Similar differences in csPCa detection rates were observed in the first external validation conducted in the Barcelona metropolitan area, due to differences between the baseline characteristics of the development and validation cohorts, showing the good performance of the BCN-MRI PM (8). The risk threshold for predicting the same sensitivity for csPCa detection was higher in men

Figure 3 - Net benefit of BCN-MRI PM application over biopsying all men through transrectal route (A) and transperineal route (B).



who underwent transperineal prostate biopsies than in those who underwent the transrectal route. The novelty of selecting the appropriate threshold in the BCN-MRI risk calculator to select candidates for prostate biopsy is thus very useful when csPCa individualized predictions are assessed against each prostate biopsy route (8).

External validations of predictive models are necessary before employing them in new populations with different characteristics than those observed in the development cohort, and are frequently needed to perform recalibrations or adjustments of the thresholds for assessing accurate predictions (22-26). Validations are also necessary when changes in diagnostic approach occur in the same population where the predictive model was developed or in the outcome variables (27).

The European Association of Urology currently suggests the design of risk-stratified pathways using predictive models with the objective of reducing the demand for MRI exams and selecting more appropriate candidates for prostate biopsy, while also reducing the over-detection of iPCa. This is the next step in improving the current diagnostic approach for the early detection of csPCa (28). This was the reason for developing and validating the currently named BCN-predictive model 1, which is applied before the MRI exam, using the age, PCa family history, type of prostate biopsy (initial vs. repeated), DRE (normal vs. suspicious), and DRE-prostate volume category (29). Incorporation of DRE-prostate volume category was due to the importance of prostate volume as a csPCa predictive variable, since TRUS is not currently used with only this aim (30). The corresponding BCN-risk-calculator 1 is available at the same website as the BCN-MRI risk calculator, now named the BCN-risk calculator 2. Using both BCN-risk calculators, after an initial stratification based on the serum PSA level and DRE characteristic (31), we have designed a risk-organized pathway reducing MRI exams and prostate biopsies by more than a quarter with lower loss of csPCa than the currently recommended strategy of avoiding prostate biopsies in men with PI-RADS <3 (32-34). This risk-organized pathway is more efficient than that proposed by Remmers et al., based on sequential application of the Rotterdam-risk calculator 3, and the Rotterdam-MRI risk calculator (35).

Limitations of our validation study include the use of a csPCa definition in prostate biopsies which frequently results in upgrades when the entire prostate gland is analyzed. Multicentricity of the study could produce some lack of homogeneity between both series, and probably differences in quality of MRI exams (36). Additionally, inherent limitations to the predictive models developed with the binary logistic regression algorithm exist. The BCN-MRI PM, developed from a binary logistic regression, reflects the probability of csPCa based on the specific cohort characteristics and diagnostic approach at the time of its development. Changes arising in the same development population as in others where the predictive model will be applied need validations, justifying future recalibrations and adjustments of risk thresholds to ensure accurate predictions.

The real-time updating of classically developed predictive models is a current challenge (37). Dynamic training of predictive models developed with machine learning algorithms, in the setting of federated networks, has the potential to result in continuous validated risk calculators at each partner site, ensuring accurate and lasting predictions across multiple locations (38).

CONCLUSIONS

The BCN-MRI PM has been successfully validated in men suspected of having PCa who undergo MRI exams reported with PI-RADS v2.1, and transperineal prostate biopsies. This study examined data from the csPCa early detection program of Catalonia, a region of 7.9 million inhabitants.

FUNDING

This study was funded by the Instituto de Salud Carlos III (SP) and the European Union (Grant number PI20/01666)

ACKNOWLEDGEMENTS

Pol Servian and José M. Abascal contributed similarly as first

CONFLICT OF INTEREST

None declared.

REFERENCES

1. TVan Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission. *Eur Urol*. 2021;79:327-9. doi: 10.1016/j.eururo.2020.12.010.
2. Van Poppel H, Roobol MJ, Chapple CR, Catto JWF, N'Dow J, Sønksen J, et al. Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021. *Eur Urol*. 2021;80:703-11. doi: 10.1016/j.eururo.2021.07.024.
3. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360:1320-8. doi: 10.1056/NEJMoa0810084.
4. Frånlund M, Månsson M, Godtman RA, Aus G, Holmberg E, Kollberg KS, et al. Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial. *J Urol*. 2022;208:292-300. doi: 10.1097/JU.0000000000002696.
5. Van Poppel H, Roobol MJ, Chapple CR, Catto JWF, N'Dow J, Sønksen J, et al. Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021. *Eur Urol*. 2021;80:703-11. doi: 10.1016/j.eururo.2021.07.024.
6. Van Poppel H, Albrecht T, Basu P, Hogenhout R, Collen S, Roobol M. Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future. *Nat Rev Urol*. 2022;19:562-72. doi: 10.1038/s41585-022-00638-6.
7. Triquell M, Campistol M, Celma A, Regis L, Cuadras M, Planas J, et al. Magnetic Resonance Imaging-Based Predictive Models for Clinically Significant Prostate Cancer: A Systematic Review. *Cancers (Basel)*. 2022;14:4747. doi: 10.3390/cancers14194747.
8. Morote J, Borque-Fernando A, Triquell M, Celma A, Regis L, Escobar M, et al. The Barcelona Predictive Model of Clinically Significant Prostate Cancer. *Cancers (Basel)*. 2022;14:1589. doi: 10.3390/cancers14061589.
9. Morote J, Borque-Fernando Á, Triquell M, Campistol M, Servian P, Abascal JM, et al. Comparison of Rotterdam and Barcelona Magnetic Resonance Imaging Risk Calculators for Predicting Clinically Significant Prostate Cancer. *Eur Urol Open Sci*. 2023;53:46-54. doi: 10.1016/j.euros.2023.03.013.
10. Morote J, Borque-Fernando Á, Triquell M, Esteban LM, Trilla E. The True Utility of Predictive Models Based on Magnetic Resonance Imaging in Selecting Candidates for Prostate Biopsy. *Eur Urol Open Sci*. 2022;42:40-1. doi: 10.1016/j.euros.2022.06.002.
11. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol*. 2019;76:340-51. doi: 10.1016/j.eururo.2019.02.033.
12. van den Bergh RCN, Wever L, van Melick HHE. TRECIT Is Now: Should We Abandon the Transrectal Route for Biopsy? A Three-continent Debate-Referee. *Eur Urol Open Sci*. 2021;32:43-4. doi: 10.1016/j.euros.2021.08.004.
13. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol*. 2012;22:746-57. doi: 10.1007/s00330-011-2377-y.
14. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*. 2016;40:244-52. doi: 10.1097/PAS.0000000000000530.
15. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. doi: 10.1136/bmj.h5527.
16. Rico L, Blas L, Vitagliano G, Contreras P, Rios Pita H, Ameri C. PI-RADS 3 lesions: Does the association of the lesion volume with the prostate-specific antigen density matter in the diagnosis of clinically significant prostate cancer? *Urol Oncol*. 2021;39:431.e9-431.e13. doi: 10.1016/j.urolonc.2020.11.010.
17. Rico L, Contreras P, Vitagliano G, Rios Pita H, Ameri C, Blas L. Value of prostate-specific antigen density in negative or equivocal lesions on multiparametric magnetic resonance imaging. *Turk J Urol*. 2020;46:367-72. doi: 10.5152/tud.2020.20111.

18. Lv Z, Wang J, Wang M, Hou H, Song L, Li H, et al. Is it necessary for all patients with suspicious lesions undergo systematic biopsy in the era of MRI-TRUS fusion targeted biopsy? *Int Braz J Urol.* 2023;49:359-71. doi: 10.1590/S1677-5538.IBJU.2023.0060.
19. Paesano N, Catalá V, Tcholakian L, Alomar X, Barranco M, Trilla E, et al. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. *Int Braz J Urol.* 2024;50:296-308. doi: 10.1590/S1677-5538.IBJU.2023.0558.
20. Wu Q, Tu X, Zhang C, Ye J, Lin T, Liu Z, et al. Transperineal magnetic resonance imaging targeted biopsy versus transrectal route in the detection of prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis.* 2024;27:212-21. doi: 10.1038/s41391-023-00729-4.
21. O'Callaghan ME, Roberts M, Grummet J, Mark S, Gilbourn D, Frydenberg M, et al. Trends and variation in prostate cancer diagnosis via transperineal biopsy in Australia and New Zealand. *Urol Oncol.* 2023;41:324.e13-324.e20. doi: 10.1016/j.urolonc.2023.05.011.
22. Chen R, Verbeek JFM, Yang Y, Song Z, Sun Y, Roobol MJ. Comparing the prediction of prostate biopsy outcome using the Chinese Prostate Cancer Consortium (CPCC) Risk Calculator and the Asian adapted Rotterdam European Randomized Study of Screening for Prostate Cancer (ERSPC) Risk Calculator in Chinese and European men. *World J Urol.* 2021;39:73-80. doi: 10.1007/s00345-020-03177-0.
23. De Nunzio C, Lombardo R, Baldassarri V, Cindolo L, Bertolo R, Minervini A, et al. Rotterdam mobile phone app including MRI data for the prediction of prostate cancer: A multicenter external validation. *Eur J Surg Oncol.* 2021;47:2640-5. doi: 10.1016/j.ejso.2021.04.033.
24. Petersmann AL, Remmers S, Klein T, Manava P, Huettenbrink C, Pahernik SA, et al. External validation of two MRI-based risk calculators in prostate cancer diagnosis. *World J Urol.* 2021;39:4109-16. doi: 10.1007/s00345-021-03770-x.
25. Patel HD, Remmers S, Ellis JL, Li EV, Roobol MJ, Fang AM, et al. Comparison of Magnetic Resonance Imaging-Based Risk Calculators to Predict Prostate Cancer Risk. *JAMA Netw Open.* 2024;7:e241516. doi: 10.1001/jamanetworkopen.2024.1516.
26. Kaneko M, Fujihara A, Iwata T, Ramacciotti LS, Palmer SL, Oishi M, et al. A nomogram to predict the absence of clinically significant prostate cancer in males with negative MRI. *Int Braz J Urol.* 2024;50:319-34. doi: 10.1590/S1677-5538.IBJU.2024.0084.
27. Remmers S, Nieboer D, Rijsternberg LL, Hansum T, van Leenders GJLH, Roobol MJ. Updating the Rotterdam Prostate Cancer Risk Calculator with Invasive Cribriform and/or Intraductal Carcinoma for Men with a Prior Negative Biopsy. *Eur Urol Open Sci.* 2021;36:19-22. doi: 10.1016/j.euros.2021.11.008.
28. Van Poppel H, Roobol MJ, Chandran A. Early Detection of Prostate Cancer in the European Union: Combining Forces with PRAISE-U. *Eur Urol.* 2023;84:519-22. doi: 10.1016/j.eururo.2023.08.002.
29. Morote J, Borque-Fernando Á, Triquell M, Campistol M, Celma A, Regis L, et al. A Clinically Significant Prostate Cancer Predictive Model Using Digital Rectal Examination Prostate Volume Category to Stratify Initial Prostate Cancer Suspicion and Reduce Magnetic Resonance Imaging Demand. *Cancers (Basel).* 2022;14:5100. doi: 10.3390/cancers14205100.
30. Morote J, Picola N, Muñoz-Rodríguez J, Paesano N, Ruiz-Plazas X, Muñoz-Rivero MV, et al. The Role of Digital Rectal Examination Prostate Volume Category in the Early Detection of Prostate Cancer: Its Correlation with the Magnetic Resonance Imaging Prostate Volume. *World J Mens Health.* 2024;42:441-8. doi: 10.5534/wjmh.230028.
31. Morote J, Picola N, Paesano N, Celma A, Muñoz-Rodríguez J, Asiain I, et al. Are magnetic resonance imaging and targeted biopsies needed in men with serum prostate-specific antigen over 10 ng/mL and an abnormal digital rectal examination? *Urol Oncol.* 2023;41:299-301. doi: 10.1016/j.urolonc.2023.05.003.
32. Morote J, Borque-Fernando Á, Triquell M, Abascal JM, Servian P, Planas J, et al. A risk-organised model for clinically significant prostate cancer early detection. *BJUJ Compass.* 2023;4:420-2. doi: 10.1002/bco2.230.
33. Morote J, Borque-Fernando Á, Esteban LE, Picola N, Muñoz-Rodríguez J, Paesano N, et al. Reducing the demand for magnetic resonance imaging scans and prostate biopsies during the early detection of clinically significant prostate cancer: Applying the Barcelona risk-stratified pathway in Catalonia. *Urol Oncol.* 2024;42:115.e1-115.e7. doi: 10.1016/j.urolonc.2023.09.020.

34. Morote J, Borque-Fernando Á, Esteban LM, Celma A, Campistol M, Miró B, et al. Investigating Efficient Risk-Stratified Pathways for the Early Detection of Clinically Significant Prostate Cancer. *J Pers Med.* 2024;14:130. doi: 10.3390/jpm14020130.
35. Remmers S, Kasivisvanathan V, Verbeek JFM, Moore CM, Roobol MJ, ERSPC Rotterdam Study Group PRECISION Investigators Group. Reducing Biopsies and Magnetic Resonance Imaging Scans During the Diagnostic Pathway of Prostate Cancer: Applying the Rotterdam Prostate Cancer Risk Calculator to the PRECISION Trial Data. *Eur Urol Open Sci.* 2021;36:1-8. doi: 10.1016/j.euro.2021.11.002.
36. Schmit S, Allu S, Tanzer JR, Ortiz R, Pareek G, Hyams E. Less qualitative multiparametric magnetic resonance imaging in prostate cancer can underestimate extraprostatic extension in higher grade tumors. *Int Braz J Urol.* 2024;50:37-45. doi: 10.1590/S1677-5538.IBJU.2023.0321.
37. Strobl AN, Vickers AJ, Van Calster B, Steyerberg E, Leach RJ, Thompson IM, et al. Improving patient prostate cancer risk assessment: Moving from static, globally-applied to dynamic, practice-specific risk calculators. *J Biomed Inform.* 2015;56:87-93. doi: 10.1016/j.jbi.2015.05.001.
38. Nandi A, Xhafa F. A federated learning method for real-time emotion state classification from multi-modal streaming. *Methods.* 2022;204:340-7. doi: 10.1016/j.jymeth.2022.03.005.

Correspondence address:**Juan Morote, MD, PhD**

Depart. of Urology, Vall d'Hebron University Hospital

Po Vall d'Hebron 119-129, Barcelona 08035, Spain

Telephone: +34 629 011 936

E-mail: juan.morote@uab.cat

5.9. PUBLICACIÓN 9

Título: Validation of the Barcelona Magnetic Resonance Imaging Predictive Model for Significant Prostate Cancer Detection in Men Undergoing Mapping per 0.5 mm-Core Targeted Biopsies of Suspicious Lesions and Perilesional Areas

Revista: Cancers

Año de publicación: 2025

Volumen: 17

Páginas: 473

DOI: <https://doi.org/10.3390/cancers17030473>

Autores: Nahuel Paesano, Violeta Catalá, Larisa Tcholakian, Xavier Alomar, Miguel Ángel Barranco, Jonathan Hernández-Mancera, Berta Miró, Enrique Trilla and Juan Morote.

Factor de impacto (JCR): pendiente para 2025 (en 2024: 4.4)

Cuartil (JCR): pendiente para 2025, Cuartil 2 en 2024 (Área de Oncología)



Article

Validation of the Barcelona Magnetic Resonance Imaging Predictive Model for Significant Prostate Cancer Detection in Men Undergoing Mapping per 0.5 Mm-Core Targeted Biopsies of Suspicious Lesions and Perilesional Areas

Nahuel Paesano ^{1,2,*}, Violeta Catalá ^{2,3}, Larisa Tcholakian ^{2,3}, Xavier Alomar ², Miguel Ángel Barranco ², Jonathan Hernández-Mancera ⁴, Berta Miró ⁵, Enrique Trilla ^{1,6,†} and Juan Morote ^{1,6,*} 

¹ Department of Surgery, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain; enrique.trilla@uab.cat

² Clínica Creu Blanca, 08034 Barcelona, Spain; violetacatala@uroima.com (V.C.);

larisa.tcholakian@creublanca.es (L.T.); xavier.alomar@creublanca.es (X.A.);

miguelangel.barranco@creublanca.es (M.Á.B.)

³ Uroima, 08005 Barcelona, Spain

⁴ Fundació Puigvert, 08025 Barcelona, Spain; jhemandez@fundacio-puigvert.es

⁵ Statistics Unit, Vall d'Hebron Research Institute, 08035 Barcelona, Spain; berta.miro@vhir.org

⁶ Department of Urology, Vall d'Hebron Hospital, 08035 Barcelona, Spain

* Correspondence: nahuel.paesano@uab.cat (N.P.); juan.morote@uab.cat (J.M.)

† These authors contributed equally to this work.



Academic Editor: Yasunori Minami

Received: 6 December 2024

Revised: 7 January 2025

Accepted: 28 January 2025

Published: 31 January 2025

Citation: Paesano, N.; Catalá, V.; Tcholakian, L.; Alomar, X.; Barranco, M.Á.; Hernández-Mancera, J.; Miró, B.; Trilla, E.; Morote, J. Validation of the Barcelona Magnetic Resonance Imaging Predictive Model for Significant Prostate Cancer Detection in Men Undergoing Mapping per 0.5 Mm-Core Targeted Biopsies of Suspicious Lesions and Perilesional Areas. *Cancers* **2025**, *17*, 473. <https://doi.org/10.3390/cancers17030473>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Simple Summary: The validation of predictive models is essential for informing clinical decisions, particularly in new individual populations or as diagnostic methods advance. This study evaluates the performance of the Barcelona-MRI predictive model (BCN-MRI PM) for identifying significant prostate cancer (sPCa) within the context of an advanced prostate biopsy protocol. In a cohort of 457 men suspected of having PCa, the model demonstrated high accuracy and clinical applicability, reducing unnecessary biopsies by 24.9% while maintaining a 95% detection rate for sPCa. These results validate the efficacy of the BCN-MRI PM and support its readiness for clinical implementation in this diagnostic framework.

Abstract: Background/Objectives: Validation of predictive models (PMs) is crucial to be implemented in new populations or when advances in diagnostic approaches occurred. The aim of this study is to validate the BCN-MRI PM for sPCa when a highly effective prostate biopsy protocol is used. **Methods:** A prospective cohort of 457 men suspected of having PCa, for whom MRI results were reported with the Prostate Imaging-Reporting and Data System (PI-RADS) v 2.1, underwent a per 0.5 mm-core mapping targeted biopsy of suspicious lesions and perilesional areas, followed by a 12-core-systematic biopsy. These procedures took place between 1 February 2022, and 29 February 2024, at a reference center for prostate biopsy. The individual likelihood of sPCa was assessed through the BCN-MRI risk calculator. **Results:** The overall sPCa detection rate was 58.3%. The calibration curve of the BCN-MRI PM showed an appropriate accuracy between expected and observed probabilities with a discrimination ability for sPCa yielding an area under the curve (AUC) of 0.862 (95% CI 0.828–0.896) comparable to the AUC of 0.858 (95% CI 0.833–0.883) observed in the development cohort. The application of the BCN-MRI PM provided a net benefit over performing biopsies on all men, avoiding 24.9% of prostate biopsies at 95% sensitivity for sPCa, compared to the 23.7% reduction observed in the development cohort. **Conclusions:** We conclude that the BCN-MRI PM is ready to be implemented when this biopsy protocol is employed.

Keywords: prostate biopsy; protocol; significant prostate cancer; detection

1. Introduction

Prostate cancer (PCa) is the most common malignancy in men and the third leading cause of cancer-specific death worldwide [1]. The European Randomized Screening for Prostate Cancer (ERSPC) trial reported a 20% reduction in PCa-specific mortality among men who underwent screening compared to those in the control arm after seven years of follow-up [2]. Fifteen years later, this reduction has surpassed up to 29%, attributed to the early detection and treatment of significant prostate cancer (sPCa) [3]. Consequently, the focus of early detection of PCa has shifted towards sPCa. This shift has been facilitated by the widespread of prostate-magnetic resonance imaging (MRI), which is now used to select candidates for prostate biopsy and to perform targeted biopsies of suspicious lesions identified through MRI [4]. Despite these advancements, challenges remain, including excessive unnecessary prostate biopsies and the overdiagnosis of insignificant tumors. Current predictive models, based on the Prostate Imaging Reporting and Data System (PI-RADS) and clinical variables, have become essential tools to improve the diagnostic efficiency for sPCa [5]. Since uncertain scenarios remain after the widespread use of MRI, the European Association of Urology recommends the use of risk-stratified pathways for sPCa screening, employing predictive models to guide clinical decision-making [6].

The Barcelona MRI-predictive model (BCN-MRI PM) was developed to assess individual probabilities of sPCa in 1486 men with suspected PCa, excluding those with previous PCa detection, and 5-alpha reductase inhibitors (5-ARI) treatment of symptomatic benign prostatic hyperplasia due to the known modifications of serum PSA levels [7]. All men underwent pre-biopsy multiparametric MRI (mpMRI) reported with the Prostate Imaging-Reporting and Data System (PI-RADS) v 2.0 followed by a 2- to 4-core targeted biopsy of suspicious lesions and/or 12-core systematic biopsies via transrectal route, conducted between 1 January 2016 and 31 December 2019, at one academic institution [8,9]. The predictive variables for sPCa included in this model were age (years), PCa family history (no vs. yes), type of prostate biopsy (initial vs. repeated), serum PSA level (ng/mL), digital rectal examination (normal vs. suspicious), MRI-based prostate volume (mL), and PI-RADS score (1 to 5). A risk calculator was designed being available at the web site <https://mrpcaprediction.shinyapps.io/MRIPCAPrediction/>. The model development was conducted at a single academic institution, and a subsequent initial external validation was conducted in a cohort of 946 men suspected of having PCa who followed the same diagnostic approach employed in the development cohort at two institutions in the metropolitan area of Barcelona [10]. The BCN-MRI was the first predictive model for sPCa including the PI-RADS score v 2.0, having no limitation on age, serum PSA level, or prostate volume. The BCN-MRI PM was evaluated for each PI-RADS score, along with the risk calculator incorporating the selection of an appropriate threshold [10,11]. The BCN-MRI PM exhibited higher clinical utility than the prestigious Rotterdam MRI PM in the external validation cohort [12].

Validation of predictive models is critical before their implementation in new populations or when significant changes in the diagnostic approach are introduced to ensure that predictions accurately reflect the true risk of the event occurring [13,14].

Our aim is to validate the BCN-MRI PM in a cohort of men suspected of having PCa, for whom MRI results were assessed with the PI-RADS v 2.1 score, and prostate biopsies were performed using a mapping per 0.5 mm-core targeted biopsy of suspicious lesions and perilesional areas, followed by a 12-core systematic biopsy protocol.

2. Materials and Methods

2.1. Design, Participants, and Setting

A prospective study was conducted involving 457 men suspected of having PCa who were referred for prostate biopsy to the Creu Blanca reference center in Barcelona, Spain, between 1 February 2022, and 29 February 2024. This study received the approval from the ethics committee of Vall d'Hebron Hospital (PRAG-02/2021).

2.2. Diagnostic Approach for sPCa Detection in Prostate Biopsies

Men suspected of having PCa were initially identified based on a serum PSA exceeding 3.0 ng/mL and/or a suspicious DRE. These individuals underwent external multiparametric MRI (mpMRI) with those exhibiting a PI-RADS score of 3 to 5 referred for transperineal prostate biopsy at Creu Blanca reference center. Additionally, some men with a PI-RADS 2 and a high risk of PCa were also referred for biopsy.

Biparametric MRI (bMRI) was performed at Creu Blanca to segment suspicious lesions using a Siemens Verio™ 3 Tesla MRI scanner (Siemens Healthcare, Erlangen, Germany) equipped with a pelvic-phased array coil. The imaging protocol included T2-weighted transverse sections, along with coronal and sagittal T2-weighted sequences (both 2D and 3D). Diffusion-weighted imaging was acquired with b-values of 1600, 2000, and 3000 s/mm², complemented by apparent diffusion coefficient mapping. An expert uro-radiologist with 15 years of experience and an annual interpretation volume of more than 1000 MRIs, reclassified external mpMRI lesions following the PI-RADS v2.1 criteria [15]. The ProFuse™ system (Eigen, Grass Valley, California, USA) was employed for semi-automatic segmentation of up to three suspicious lesions that satisfied the European Society of Urogenital Radiology standards [16]. Men whose lesions were reclassified to a PI-RADS score of 2 underwent the same biopsy protocol as those with both targeted and systematic biopsies. External mpMRIs were deemed diagnostically adequate, with Prostate Imaging Quality scores of 3 or higher [17,18].

The prostate biopsies were performed via transperineal route under general anesthesia by experienced urologists. Targeted biopsies were obtained every 0.5 mm from suspicious lesions and perilesional areas, followed by a 12-core systematic biopsy using the Artemis™ robotic arm system (Eigen, Gars Valley, CA, USA) and the Aloka Noblus™ ultrasound system (Hitachi, Wilton, CT, USA).

The diagnosis of sPCa was established by an experienced uro-pathologist when the International Society of Urologic Pathology (ISUP) grade group was 2 or higher [19,20].

2.3. Assessment of Individual sPCa Likelihood

The endpoint variable of the study was the individual likelihood of sPCa, which was prospectively assessed with the BCN-MRI risk calculator, accessible at the web site <https://mriscaprediction.shinyapps.io/MRIPCaPrediction/>. The predictive variables in the BCN-MRI risk calculator include age (in years), first-degree family history of PCa (no vs. yes), type of biopsy (initial vs. repeated), serum PSA level (ng/mL), DRE status (normal vs. suspicious), MRI-based prostate volume (mL), and PI-RADS v2.1 scores (from 1 to 5).

2.4. Statistical Analysis

Quantitative variables were described as medians with interquartile ranges (IQR), while qualitative variables were expressed as percentages. Descriptive variables were compared with the Mann-Whitney U test and the Chi-square test. Calibration of the predictive model was assessed. Discrimination power of the BCN-MRI PM was determined using the receiver operating characteristic (ROC) curve and the area under the curve (AUC).

The net benefit of using the BCN-MRI PM for identifying prostate biopsy candidates was compared to biopsying all men through decision curve analysis (DCA). The clinical utility of the model was determined using the clinical utility curves (CUC), which explored the potential rates of missed sPCa detection and the avoidable prostate biopsies. Specificities at sensitivity threshold of 100%, 97.5%, 95%, 92.5%, and 90% were analyzed. The efficacies analyzed with the Youden index, and clinically the rates of saved prostate biopsies and undetected sPCa were analyzed. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statements were followed [21]. Statistical analyses were computed using R programming language v.4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS v.24 (IBM, statistical package for social sciences, San Francisco, CA, USA).

3. Results

3.1. Characteristics of the Validation Cohort

The most relevant characteristics of the validation cohort, consisting of 457 men suspected of having PCa, are presented in Table 1. The age of participants ranged from 32 to 88 years, with 151 being older than 70 (33%) and 3 (0.6%) younger than 45. Serum PSA levels were below 3.0 ng/mL in one case (2.8 ng/mL) and above 10 ng/mL in 82 cases (17.9%). The MRI-derived prostate volume was up to 50 mL in 260 men (56.9%), between 51 and 100 mL in 152 cases (33.7%), and above 100 mL in 45 (9.8%).

Table 1. Characteristics of the validation cohort.

Characteristic	Measure
Number of men	457
Median age, years (IQR)	67 (56–72)
Median serum PSA, ng/mL (IQR)	6.0 (4.8–9.0)
Suspicious DRE, <i>n</i> (%)	61 (13.3)
PCa family history, <i>n</i> (%)	80 (17.5)
Repeated prostate biopsies, <i>n</i> (%)	107 (23.4)
Median prostate volume, ml (IQR)	47 (34–63)
PI-RADS score 2, <i>n</i> (%)	73 (16.0)
PI-RADS score 3, <i>n</i> (%)	106 (23.2)
PI-RADS score 4, <i>n</i> (%)	175 (38.3)
PI-RADS score 5, <i>n</i> (%)	103 (22.5)
Significant PCa detection, <i>n</i> (%)	267 (58.4)

IQR: 25–75 percentiles; *n*: number; PSA: prostate-specific antigen; DRE: digital rectal examination; PCa: prostate cancer; PI-RADS: prostate imaging-reporting and data system.

There was one suspicious lesion in 360 cases (78.8%), two lesions in 93 (20.4%) and three lesions in four cases (0.9%). The median size of the index lesion was 12 mm (IQR 4–44). In 298 cases (65.2%), the index lesion was in the peripheral zone of the prostate gland; in 148 cases (32.4%), it was in the central/transitional zone; and in 11 cases (2.4%), it was in the fibromuscular anterior zone. The median overall number of core-obtention per case was 21 (IQR 19–24) ranging from 14 to 35. The overall detection rate of sPCa was 58.4%, and those according to the PI-RADS category of the index lesion were 2.7% in PI-RADS 2, 33% in PI-RADS 3, 80% in PI-RADS 4, and 87.4% in PI-RADS 5.

3.2. Calibration of the BCN-MRI PM in the Validation Cohort

Calibration of the BCN-MRI PM in this validation cohort of 457 men suspected of having PCa, in whom 267 sPCa (58.4%) were detected, is presented in Figure 1. The calibration curve closely aligns with the ideal curve, with a slight over detection of sPCa at

the median threshold points. Calibration curves obtained in the development cohort of the BCN-MRI PM (B), and the initial external validation cohort (C) are also shown.

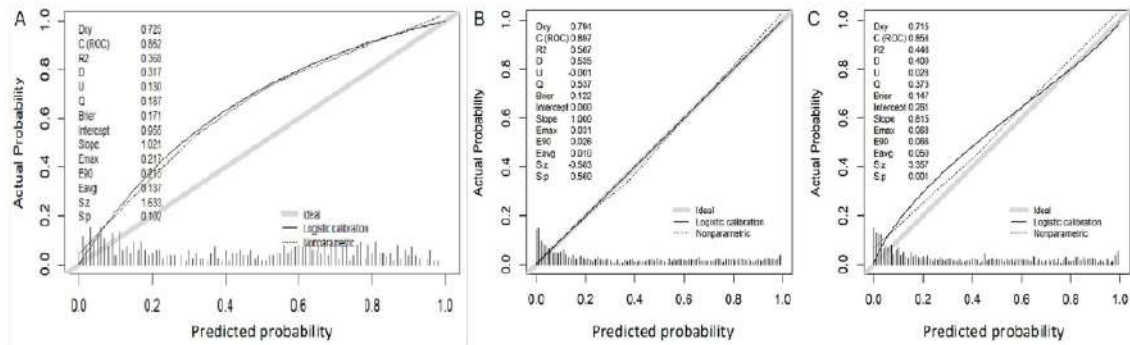


Figure 1. Calibration curve of the BCN-MRI predictive model in the present validation cohort (A), in the development cohort (B), and in the initial external validation cohort (C).

3.3. Discrimination Ability, Net Benefit, and Clinical Utility of the BCN-MRI PM for sPCa Detection

The discriminatory ability for sPCa of the BCN-MRI PM, represented with ROC curves, showed an AUC of 0.862 (95% CI 0.828–0.896) in this validation cohort, Figure 2A. This result was comparable with the AUC of 0.842 (95% CI 0.822–0.861) observed in the development cohort of the BCN-MRI PM, and better than 0.743 (95% CI: 0.711–0.776) observed in the initial validation cohort ($p = 0.008$), Figure 2B [10].

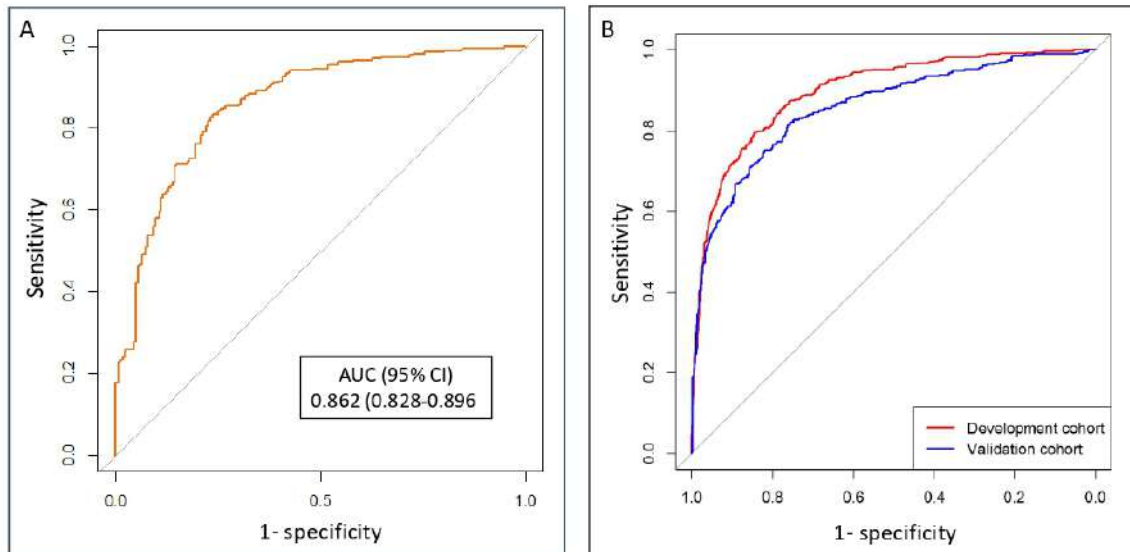


Figure 2. Discrimination ability of the BCN-MRI predictive model for significant PCa detection in prostate biopsy in this validation cohort (A), referenced to those observed in the development cohort and the initial external validation cohort (B) [10].

The DCA showed a net benefit of the BCN-MRI PM over biopsy for all men, beginning at a threshold probability of 12%, Figure 3A. This benefit was comparable with that observed in the development cohort and the initial validation cohort, Figure 3B [10].

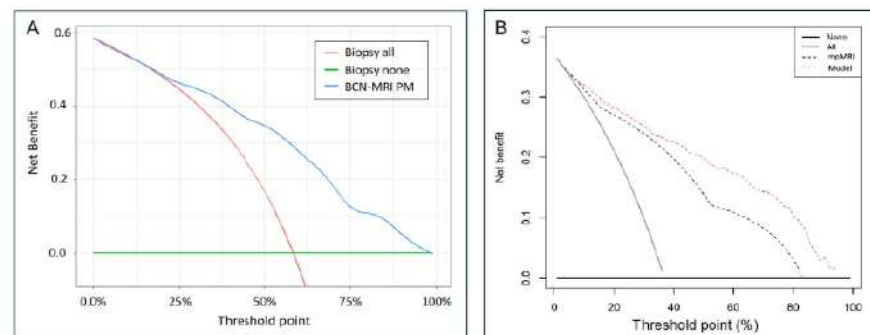


Figure 3. Net benefit of the BCN-MRI predictive model, represented through Decision Curve Analysis (DCA), in which ‘y axis’ represents to biopsy all men and ‘x axis’ represents to biopsy any of them. The DCA showed a net benefit of the BCN-MRI PM over biopsy for all men, beginning at a threshold probability of 12%, (A). This benefit was comparable with that observed in the development cohort and the initial validation cohort, (B) [10].

The clinical utility of the BCN-MRI PM, based on the estimation of the percentages of saved biopsies and undetected sPCa for 5% threshold intervals, is presented in Table 2.

Table 2. Clinical efficacy of the BCN-MRI predictive model showing the rate of undetected sPCa and saved biopsies to each 5% threshold from 0 to 100 percent.

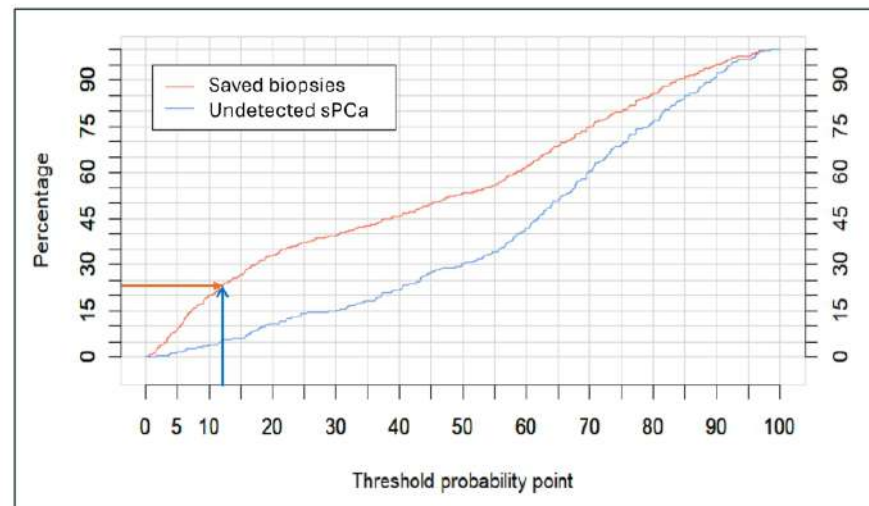
Threshold (%)	Undetected sPCa (%)	Saved Biopsies (%)
0	0.0	0.0
5	1.5	9.2
10	3.7	20.1
15	6.0	26.7
20	10.9	33.0
25	14.2	37.2
30	15.0	39.4
35	18.4	42.7
40	21.7	45.7
45	27.3	49.9
50	30.3	53.4
55	34.1	56.0
60	41.9	61.7
65	50.9	68.7
70	60.3	74.8
75	68.9	79.9
80	76.8	85.8
85	84.3	90.8
90	91.4	95.0
95	96.6	98.0
100	100.0	100.0

Table 3 displays the specificities and 95% confidence intervals of the BCN-MRI PM at sensitivities of 100%, 97.5%, 95%, 92.5%, and 90% for sPCa, as these represent the most relevant clinical scenarios. The efficacy measured by the Youden index, and the corresponding percentage of avoided biopsies are also presented. If we choose to allow up to 5% of sPCa to go undetected, the specificity of the BCN-MRI PM will be 48.4% (95% CI, 42.3–51.6), the Youden index will be 43.6, and 24.9% of prostate biopsies will be avoided.

Table 3. Specificities estimated from 90 to 100% sensitivities of the BCN-MRI predictive model, efficacy of the model 'Youden index' and saved biopsies with these thresholds.

Sensitivity (%)	Threshold (%)	Specificity (%) (95% CI)	Youden Index	Saved Biopsies (%)
100	1.6	5.3 (3.8–6.1)	5.3	1.6
97.5	7.8	34.3 (30.4–40.2)	25.8	17.1
95	11.9	48.4 (42.3–51.6)	43.6	24.9
92.5	16.5	59.5 (53.4–63.5)	52.0	30.2
90	18.7	62.6 (59.7–65.7)	52.9	32.6

Clinical utility curves (CUCs), representing the differential percentage between undetected sPCa and saved prostate biopsies across a continuous evolution of the threshold probability point from 0 to 100%, are shown in Figure 4. A highly relevant scenario, based on the detection of at least 95% of sPCa, is highlighted with arrows corresponding to the application of the 12% threshold of the BCN-MRI PM, which saves almost 25% of prostate biopsies.

**Figure 4.** Analysis of clinical utility of the BCN-MRI predictive model, represented by clinical utility curves (CUCs) showing the undetected rate of significant PCa and avoided prostate biopsies according to the continuous threshold point. Arrows indicate the rate of saved biopsies at the 12% threshold corresponding to the 95% sensitivity for significant PCa detection.

3.4. Potential Clinical Utility of the BCN-MRI PM According to the PI-RADS v 2.1 Score

Analyzing the potential clinical utility of the BCN-MRI PM in individuals with PI-RADS 2, the probability of sPCa ranged from 0.22% to 26.70% among the 73 cases analyzed. The probabilities in the two cases with significant PCa (sPCa) detected were 11.28% and 22.99%, with respective PSA densities of 0.14 and 0.17, and normal digital rectal examinations in both. By applying an 11% threshold for recommending biopsy in PI-RADS 2 cases, a 100% sensitivity for sPCa cases would be detected, while prostate biopsies using this threshold would be indicated in 16 cases (21.9%) within this subgroup.

For PI-RADS 3 (the most uncertain scenario), 35 cases of sPCa were identified among 106 individuals. By applying a 10% threshold, 36 prostate biopsies (40%) could be avoided while 8 sPCa cases (22.8%) would be missed, representing a global loss of 3% among the 267 significant PCa cases diagnosed in the overall series.

For PI-RADS 4 and 5, no threshold was founded for allowing to avoid prostate biopsies in these subsets without missing sPCa cases.

4. Discussion

The BCN-MRI PM for sPCa has been successfully validated in men suspected of having PCa through a highly effective transperineal prostate biopsy protocol. This approach involved obtaining core obtention cores at 0.5 mm intervals from suspicious lesions and perilesional areas, along with a 12-core systematic biopsy [22–24]. Among individuals with a PI-RADS score 2, sPCa was detected in 2.7% of cases, a rate lower than the 9% (95% CI 5–13) reported in the meta-analysis by Oerther et al. on sPCa detection rates across PI-RADS v2.1 assessment categories. Conversely, a detection rate of 33% was observed in men with a PI-RADS score of 3, which is notably higher than the referenced rate of 16% (95% CI: 7–27). For those with a PI-RADS score of 4, this approach identified sPCa in 80% of cases, surpassing the 59% (95% CI: 39–78) reported in the meta-analysis. Finally, in men with a PI-RADS score of 5, the protocol achieved an sPCa detection rate of 87.4%, placing it at the upper end of the range reported in the meta-analysis, which cited a rate of 85% (95% CI: 73–94) [25].

The clinical characteristics of the analyzed cohort differed from those of the development cohort and the initial external validation cohort of the BCN-MRI PM in several aspects, including age, serum PSA level, prostate volume, percentage of suspicious DRE findings, proportion of biopsy naïve men, family history of PCa, and the distribution of PI-RADS scores. Notably, the most significant difference was observed in the outcome variable of the BCN-MRI PM. The rate of sPCa detected in the present validation cohort was 58.3% compared to 36.9% in the development cohort and 40.8% in the initial external validation cohort. The latter utilized PI-RADS v2.0 and employed a biopsy protocol consisting of 2-to 4-core targeted biopsies of suspicious lesions alongside a 12-core systematic biopsy performed via transrectal route [10]. Despite these differences, the performance of the BCN-MRI PM under these challenging conditions was comparable to its performance in the initial external validation. The model demonstrated discrimination abilities with an AUC of 0.862 (IQR 0.828–0.896) and 0.858 (IQR 0.833–0.883), respectively. In both validation cohorts, applying the BCN-MRI PM provided a net benefit compared to performing biopsies on all men, beginning at a threshold of approximately 12%. Furthermore, the clinical utility of the BCN-MRI PM, as indicated by the percentage of saved prostate biopsies at 95% sensitivity, was 24.9% in the present cohort compared to 23.7% in the initial external validation. Thus, we conclude that the BCN-MRI PM performed slightly better in the current cohort, where enhanced biopsy effectiveness was observed compared to the protocol used in the development and initial external validation cohorts [10].

In recent years, several significant changes have been introduced to the diagnostic pathway for sPCa, potentially influencing the effectiveness of prostate biopsy. The currently utilized PI-RADS version 2.1 differs from version 2.0, which was employed in the development and initial validation cohort of the BCN-MRI PM [9,16]. Additionally, the currently recommended approach for performing prostate biopsies is the transperineal route, whereas the transrectal route was used during the development and initial external validation of the BCN-MRI PM [26]. These updates underscore the need to validate the BCN-MRI PM under these revised conditions. Since the development and initial external validation excluded men receiving 5-alpha reductase inhibitors (5-ARI) for symptomatic benign prostatic hyperplasia due to their impact on serum PSA levels, the BCN-MRI PM has now been validated in a cohort of men suspected of having PCa who are undergoing 5-ARI treatment [27,28]. Furthermore, the predictive model has been validated in contexts where version 2.1 of the PI-RADS score is used in MRI reports and prostate biopsies are performed via transperineal route [29]. Lastly, given that an optimal prostate biopsy protocol has not yet been defined, and evidence suggests that mapping biopsies of targeted suspicious

lesions and perilesional areas may enhance biopsy effectiveness [29,30], we validated the BCN-MRI PM in a cohort of men undergoing this biopsy protocol.

The BCN-MRI PM has been successfully validated in men suspected of having PCa who underwent targeted biopsy of lesional and perilesional following a 0.5 mm-core mapping protocol in combination with a 12-core systematic biopsy. Its potential clinical utility of the BCN-MRI PM was specifically evaluated across different PI-RADS v2.1 categories. We found that in individuals with PI-RADS 2, using a 11% threshold, it could detect 100% of existing clinically significant prostate cancers (sPCa) in this group by biopsying only 22%. Similarly, for PI-RADS 3, using a 10% threshold, it could potentially avoid 40% of prostate biopsies, although this would result in missing 23% of detected sPCa, representing a 3% reduction in the overall sPCa detection rate in this series. For PI-RADS 4 and 5, no threshold was identified that would allow avoiding biopsies without missing some sPCa cases.

Several limitations can be attributed to this study. Performing biopsies on men reclassified as PI-RADS core 2 may introduce a bias into the detection rate of sPCa. Nevertheless, this approach may also be considered a strength, as it provides an opportunity to assess the effectiveness of applying the BCN-MRI PM in a subset of men who are rarely subjected to prostate biopsy. A validation conducted in a cohort referred from a non-structured, opportunistic screening effort for early sPCa detection does not necessarily guarantee successful validation in the contexts of a population-based screening program. Additionally, it was not possible to assess the specific number and contribution of perilesional cores in detecting sPCa, as cores obtained from each suspicious lesion and its perilesional area were collectively analyzed. A limitation of the BCN-MRI PM lies in its reliance on the definition of sPCa based on findings from prostate biopsies, which may not fully represent the true pathology of the entire prostate gland. It is important to acknowledge the inherent constraints associated with predictive models. These models estimate individual probabilities of a condition based on the characteristics on the development cohort. Since PI-RADS score is incorporated in MRI PMs, its potential utility should be analyzed in each category to identify the scenarios in which they are effective [10,31]. We have observed that the BCN-MRI PM has potential utility to select candidates for prostate biopsy with PI-RADS 2 and 3. However, in PI-RADS 4 and 5, in which sPCa detection was very high, no potential saving biopsies was observed without missing sPCa.

The sequenced application of the BCN PMs (BCN-1 PM prior MRI and BCN-MRI PM) for the early detection sPCa represents a cost-effective approach. This strategy is advantageous when compared to the recommended practice of performing MRI for all men suspected of having PCa and conducting biopsies on those with PI-RADS 3 or higher, as well with the systematic use of novel tumor markers [32].

Predictive models face challenges due to the ongoing changes in the characteristics of the populations where they are implemented, often requiring recalibration and readjustment to maintain accuracy [30]. Achieving real-time updates for predictive models remains a significant challenge for the future risk calculators [33]. Establishing a continuous feedback loop incorporating new cases, leveraging appropriate machine learning algorithms, and utilizing federated networks risk calculators to undergo continuous updates at each participating site, thereby ensuring sustained accuracy [34]. Moreover, the broader applications of novel imaging techniques and predictive modelling in cancer detection are expected to contribute to the future prediction of sPCa [35–47].

5. Conclusions

The BCN-MRI PM has been successfully validated in men suspected of having PCa using an effective prostate biopsy protocol that includes 0.5 mm mapping-core targeted biopsies of suspicious lesions and 12-core systematic biopsy.

Author Contributions: Conceptualization, N.P. and J.M.; methodology, B.M., J.M. and N.P.; data curation, V.C., L.T., X.A., M.Á.B. and J.H.-M.; writing—original draft preparation, J.M. and N.P.; writing—review and editing, E.T.; supervision, J.M.; project administration, J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Instituto de Salud Carlos III (SP) and the European Union (PI20/01666).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Vall d’Hebron Hospital (PRAG-02/2021) approved on 12 February 2021.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Database is available under request to corresponding author.

Conflicts of Interest: Author Violeta Catalá and Larisa Tcholakian were employed by the company Uroima. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]
- Schroder, F.H.; Hugosson, J.; Roobol, M.J.; Tammela, T.L.; Ciatto, S.; Nelen, V.; Kwiatkowski, M.; Lujan, M.; Lilja, H.; Zappa, M.; et al. Screening and prostate-cancer mortality in a randomized European study. *New Engl. J. Med.* **2009**, *360*, 1320–1328. [CrossRef] [PubMed]
- Fränlund, M.; Månsson, M.; Godtman, R.A.; Aus, G.; Holmberg, E.; Kollberg, K.S.; Lodding, P.; Pihl, C.G.; Stranne, J.; Lilja, H.; et al. Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial. *J. Urol.* **2022**, *208*, 292–300. [CrossRef] [PubMed]
- Barentsz, J.O.; Richenberg, J.; Clements, R.; Choyke, P.; Verma, S.; Villeirs, G.; Rouviere, O.; Logager, V.; Futterer, J.J. ESUR prostate MR guidelines 2012. *Eur. Radiol.* **2012**, *22*, 746–757. [CrossRef]
- Alberts, A.R.; Roobol, M.J.; Verbeek, J.F.M.; Schoots, I.G.; Chiu, P.K.; Osses, D.F.; Tijsterman, J.D.; Beerlage, H.P.; Mannaerts, C.K.; Schimmöller, L.; et al. Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators. *Eur. Urol.* **2019**, *75*, 310–318. [CrossRef]
- Van Poppel, H.; Hogenhout, R.; Albers, P.; van den Bergh, R.C.N.; Barentsz, J.O.; Roobol, M.J. A European Model for an Organised Risk-stratified Early Detection Programme for Prostate Cancer. *Eur. Urol. Oncol.* **2021**, *4*, 731–739. [CrossRef]
- Jacobsen, S.J.; Girman, C.J.; Lieber, M.M. Natural history of benign prostatic hyperplasia. *Urology* **2001**, *58*, 5–16. [CrossRef]
- Weinreb, J.C.; Barentsz, J.O.; Choyke, P.L.; Cornud, F.; Haider, M.A.; Macura, K.J.; Margolis, D.; Schnall, M.D.; Shtern, F.; Tempny, C.M.; et al. PI-RADS Prostate Imaging—Reporting and Data System: 2015, Version 2. *Eur. Urol.* **2016**, *69*, 16–40. [CrossRef]
- Mottet, N.; Confort, P.; van den Bergh, R.C.N.; Briers, E.D.; Eberli, D.; De Meerleer, G.; De Santis, M.; Gillessen, S.; Grummet, J.; Henry, A.M.; et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. 2019. Available online: <https://d56bochluxqnz.cloudfront.net/documents/EAU-Pocket-Prostate-Cancer-2019.pdf> (accessed on 12 September 2024).
- Morote, J.; Borque-Fernando, A.; Triquell, M.; Celma, A.; Regis, L.; Escobar, M.; Mast, R.; de Torres, I.M.; Semidey, M.E.; Abascal, J.M.; et al. The Barcelona Predictive Model of Clinically Significant Prostate Cancer. *Cancers* **2022**, *14*, 1589. [CrossRef]
- Triquell, M.; Campistol, M.; Celma, A.; Regis, L.; Cuadras, M.; Planas, J.; Trilla, E.; Morote, J. Magnetic Resonance Imaging-Based Predictive Models for Clinically Significant Prostate Cancer: A Systematic Review. *Cancers* **2022**, *14*, 4747. [CrossRef]
- Morote, J.; Borque-Fernando, A.; Triquell, M.; Campistol, M.; Servian, P.; Abascal, J.M.; Planas, J.; Méndez, O.; Esteban, L.M.; Trilla, E. Comparison of Rotterdam and Barcelona Magnetic Resonance Imaging Risk Calculators for Predicting Clinically Significant Prostate Cancer. *Eur. Urol. Open. Sci.* **2023**, *53*, 46–54. [CrossRef] [PubMed]
- Krstajic, D.; Buturovic, L.J.; Leahy, D.E.; Thomas, S. Cross-validation pitfalls when selecting and assessing regression and classification models. *J. Cheminform.* **2014**, *6*, 10. [CrossRef] [PubMed]
- Diniz, M.A. Statistical methods for validation of predictive models. *J. Nuc. Cardiol.* **2022**, *29*, 3248–3255. [CrossRef]
- Turkbey, B.; Rosenkrantz, A.B.; Haider, M.A.; Padhani, A.R.; Villeirs, G.; Macura, K.J.; Tempny, C.M.; Choyke, P.L.; Cornud, F.; Margolis, D.J.; et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur. Urol.* **2019**, *76*, 340–351. [CrossRef] [PubMed]

16. Roethke, M.C.; Kuru, T.H.; Schultze, S.; Tichy, D.; Kopp-Schneider, A.; Fenchel, M.; Schlemmer, H.P.; Hadaschik, B.A. Evaluation of the ESUR PI-RADS scoring system for multiparametric MRI of the prostate with targeted MR/TRUS fusion-guided biopsy at 3.0 Tesla. *Eur. Radiol.* **2014**, *24*, 344–352. [\[CrossRef\]](#)
17. Giganti, F.; Allen, C. Imaging quality and prostate MR: It is time to improve. *Br. J. Radiol.* **2021**, *94*, 20200934. [\[CrossRef\]](#)
18. Giganti, F.; Kirkham, A.; Kasivisvanathan, V.; Papoutsaki, M.-V.; Punwani, S.; Emberton, M.; Moore, C.M.; Allen, C. Understanding PI-QUAL for prostate MRI quality: A practical primer for radiologists. *Insights. Imag.* **2021**, *12*, 59. [\[CrossRef\]](#)
19. Epstein, J.I.; Egevad, L.; Amin, M.B.; Delahunt, B.; Srigley, J.R.; Humphrey, P.A.; Grading, C. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am. J. Surg. Pathol.* **2016**, *40*, 244–252. [\[CrossRef\]](#)
20. Epstein, J.I.; Zelefsky, M.J.; Sjöberg, D.D.; Nelson, J.B.; Egevad, L.; Magi-Galluzzi, C.; Vickers, A.J.; Parwani, A.V.; Reuter, V.E.; Fine, S.W.; et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur. Urol.* **2016**, *69*, 428–435. [\[CrossRef\]](#)
21. Collins, G.S.; Reitsma, J.B.; Altman, D.G.; Moons, K.G. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): The TRIPOD Statement. *Br. J. Surg.* **2015**, *102*, 148–158. [\[CrossRef\]](#)
22. Morote, J.; Paesano, N.; Picola, N.; Miró, B.; Abascal, J.M.; Servian, P.; Trilla, E.; Méndez, O. Comparing Two Targeted Biopsy Schemes for Detecting Clinically Significant Prostate Cancer in Magnetic Resonance Index Lesions: Two- to Four-Core versus Saturated Transperineal Targeted Biopsy. *Cancers* **2024**, *16*, 2306. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Sanguedolce, F.; Lauwers, C.N.G.; Tedde, A.; Basile, G.; Chernysheva, D.; Uleri, A.; Baboudjian, M.; Giannarini, G.; Panebianco, V.; Madonia, M.; et al. Regional Versus Systematic Biopsy in Addition to Targeted Biopsy: Results from a Systematic Review and Meta-analysis. *Eur. Urol. Oncol.* **2024**, *10*, 1016. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Brisbane, W.G.; Priester, A.M.; Ballon, J.; Kwan, L.; Delfin, M.K.; Felker, E.R.; Sisk, A.E.; Hu, J.C.; Marks, L.S. Targeted Prostate Biopsy: Umbra, Penumbra, and Value of Perilesional Sampling. *Eur. Urol.* **2022**, *82*, 303–310. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Oerther, B.; Engel, H.; Bamberg, F.; Sigle, A.; Gratzke, C.; Benndorf, M. Cancer detection rates of the PI-RADSv2.1 assessment categories: Systematic review and meta-analysis on lesion level and patient level. *Prostate Cancer Prostatic Dis.* **2022**, *25*, 256–263. [\[CrossRef\]](#)
26. Comford, P.; Tilki, D.; Bergh, R.C.N.V.D.; Briers, E.; Ebtli, D.; Meerleer, G.D.; Santis, M.D.; Gillessen, A.; Leeders, A.M.H.V.; Oldenburg, J.; et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. 2024. Available online: <http://uroweb.org/guidelines/compilations-of-all-guidelines/> (accessed on 15 September 2024).
27. Marberger, M.; Freedland, S.J.; Andriole, G.L.; Emberton, M.; Pettaway, C.; Montorsi, F.; Teloken, C.; Rittmaster, R.S.; Somerville, M.C.; Castro, R. Usefulness of prostate-specific antigen (PSA) rise as a marker of prostate cancer in men treated with dutasteride: Lessons from the REDUCE study. *BJU. Int.* **2012**, *109*, 1162–1169. [\[CrossRef\]](#)
28. Morote, J.; Borque-Fernando, Á.; Esteban, L.M.; Picola, N.; Muñoz-Rodríguez, J.; Paesano, N.; Ruiz-Plazas, X.; Muñoz-Rivero, M.V.; Celma, A.; Manuel, G.G.; et al. External validation of the Barcelona magnetic resonance imaging predictive model for detecting significant prostate cancer including men receiving 5-alpha reductase inhibitors. *World J. Urol.* **2024**, *42*, 393. [\[CrossRef\]](#)
29. Morote, J.; Paesano, N.; Picola, N.; Muñoz-Rodríguez, J.; Ruiz-Plazas, X.; Muñoz-Rivero, M.V.; Celma, A.; García-de Manuel, G.; Miró, B.; Servian, P.; et al. Validation of the Barcelona-MRI predictive model when PI-RADS v2.1 is used with trans-perineal prostate biopsies. *Int. Braz. J. Urol.* **2024**, *50*, 595–604. [\[CrossRef\]](#)
30. Paesano, N.; Catalá, V.; Tcholakian, L.; Alomar, X.; Barranco, M.; Trilla, E.; Morote, J. The effectiveness of mapping-targeted biopsies on the index lesion in transperineal prostate biopsies. *Int. Braz. J. Urol.* **2024**, *50*, 119–131. [\[CrossRef\]](#)
31. Morote, J.; Borque-Fernando, Á.; Triquell, M.; Esteban, L.M.; Trilla, E. The True Utility of Predictive Models Based on Magnetic Resonance Imaging in Selecting Candidates for Prostate Biopsy. *Eur. Urol. Open. Sci.* **2022**, *42*, 40–41. [\[CrossRef\]](#)
32. Morote, J.; Borque-Fernando, Á.; Esteban, L.M.; Celma, A.; Campistol, M.; Miró, B.; Méndez, O.; Trilla, E. Investigating Efficient Risk-Stratified Pathways for the Early Detection of Clinically Significant Prostate Cancer. *J. Pers. Med.* **2024**, *14*, 130. [\[CrossRef\]](#)
33. Nandi, A.; Xhafa, F. A federated learning method for real-time emotion state classification from multi-modal streaming. *Methods* **2022**, *204*, 340–347. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Strobl, A.N.; Vickers, A.J.; Van Calster, B.; Steyerberg, E.; Leach, R.J.; Thompson, I.M.; Ankerst, D.P. Improving patient prostate cancer risk assessment: Moving from static, globally-applied to dynamic, practice-specific risk calculators. *J. Biomed. Inform.* **2015**, *56*, 87–93. [\[CrossRef\]](#)
35. Li, W.; Wu, J.; Zhang, J.; Wang, J.; Xiang, D.; Luo, S.; Liu, X. Puerarin-loaded PEG-PE micelles with enhanced anti-apoptotic effect and better pharmacokinetic profile. *Drug Deliv.* **2018**, *25*, 827–837. [\[CrossRef\]](#)
36. Gao, X.; Tang, J.; Liu, H.; Liu, L.; Liu, Y. Structure–activity study of fluorine or chlorine-substituted cinnamic acid derivatives with tertiary amine side chain in acetylcholinesterase and butyrylcholinesterase inhibition. *Drug Dev. Res.* **2019**, *80*, 438–445. [\[CrossRef\]](#)
37. Lu, Q.; Chen, Y.; Liu, H.; Yan, J.; Cui, P.; Zhang, Q.; Liu, Y. Nitrogen-containing flavonoid and their analogs with diverse B-ring in acetylcholinesterase and butyrylcholinesterase inhibition. *Drug Dev. Res.* **2020**, *81*, 1037–1047. [\[CrossRef\]](#)

38. Sun, T.; Lv, J.; Zhao, X.; Li, W.; Zhang, Z.; Nie, L. In vivo liver function reserve assessments in alcoholic liver disease by scalable photoacoustic imaging. *Photoacoustics* **2023**, *34*, 100569. [\[CrossRef\]](#)
39. Du, Y.; Chen, L.; Yan, M.; Wang, Y.; Zhong, X.; Xu, C.; Cheng, Y. Neurometabolite levels in the brains of patients with autism spectrum disorders: A meta-analysis of proton magnetic resonance spectroscopy studies (N = 1501). *Mol. Psychiatry* **2023**, *28*, 3092–3103. [\[CrossRef\]](#)
40. He, Y.; Bao, M.; Chen, Y.; Ye, H.; Fan, J.; Shi, G. Accuracy characterization of Shack–Hartmann sensor with residual error removal in spherical wavefront calibration. *Light Adv. Manuf.* **2024**, *4*, 393–403. [\[CrossRef\]](#)
41. Xu, X.; Luo, Q.; Wang, J.; Song, Y.; Ye, H.; Zhang, X.; Shi, G. Large-field objective lens for multi-wavelength microscopy at mesoscale and submicron resolution. *Opto-Electron. Adv.* **2024**, *7*, 230212. [\[CrossRef\]](#)
42. Zou, Y.; Zhu, S.; Kong, Y.; Feng, C.; Wang, R.; Lei, L.; Chen, L. Precision matters: The value of PET/CT and PET/MRI in the clinical management of cervical cancer. *Strahlenther. Onkol.* **2024**. Online ahead of print. [\[CrossRef\]](#)
43. Yao, X.; Zhu, Y.; Huang, Z.; Wang, Y.; Cong, S.; Wan, L.; Hu, Z. Fusion of shallow and deep features from 18F-FDG PET/CT for predicting EGFR-sensitizing mutations in non-small cell lung cancer. *Quant. Imaging Med. Surg.* **2024**, *14*, 5460–5472. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Xiang, Y.; Jialing, W.; Jianhao, L.; Jiangpeng, A.; Feizhou, D.; Rui, J. Bi-Parametric Magnetic Resonance Imaging Analysis of Biochemical Recurrence of Prostate Cancer after Radical Surgery and Its Predictive Value: A Retrospective Study. *Arch. Esp. Urol.* **2024**, *77*, 598–604.
45. Lan, Z.; Tan, F.; He, J.; Liu, J.; Lu, M.; Hu, Z.; Huang, Y. Curcumin-primed olfactory mucosa-derived mesenchymal stem cells mitigate cerebral ischemia/reperfusion injury-induced neuronal PANoptosis by modulating microglial polarization. *Phytomedicine* **2024**, *129*, 155635. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Wang, Y.; Xu, Y.; Song, J.; Liu, X.; Liu, S.; Yang, N.; Zhang, Y. Tumor Cell-Targeting and Tumor Microenvironment-Responsive Nanoplatforams for the Multimodal Imaging-Guided Photodynamic/Photothermal/Chemodynamic Treatment of Cervical Cancer. *Int. J. Nanomed.* **2024**, *19*, 5837–5858. [\[CrossRef\]](#)
47. Wang, H.; Yan, Z.; Yang, W.; Liu, R.; Fan, G.; Gu, Z.; Tang, Z. A strategy of monitoring acetylcholinesterase and screening of natural inhibitors from *Uncaria* for Alzheimer's disease therapy based on near-infrared fluorescence probe. *Sens. Actuators B Chem.* **2025**, *424*, 136895. [\[CrossRef\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

6. RESUMEN GLOBAL DE RESULTADOS

El primer aspecto de mejoría en el procedimiento diagnóstico del csPCa que hemos analizado en nuestro proyecto ha sido la interpretación del PI-RADS por parte del radiólogo. Se llevó a cabo la evaluación de la concordancia entre las puntuaciones PI-RADS asignadas por radiólogos no expertos utilizando mpMRI y aquellas determinadas por un radiólogo experto mediante bpMRI, en 222 hombres con sospecha de PCa. La mediana de edad de los pacientes fue de 67 años y la mediana del PSA sérico fue de 6.8 ng/mL. La detección global de cáncer fue del 68,5%, y del 53,2% para csPCa, **Tabla 1 (art.1)**. La concordancia global entre las puntuaciones PI-RADS de la lesión índice fue baja (49,1%), con un índice Kappa de 0.288, lo que indica una pobre correlación entre las lecturas de radiólogos no expertos y expertos. En el 45,9% de los casos, la lectura experta redujo la categoría PI-RADS, mientras que en solo un 5,0% se incrementó ($p < .001$). La concordancia aumentó de forma significativa conforme aumentaba la categoría PI-RADS del informe no experto: fue del 30,8% en PI-RADS 3, del 43,6% en PI-RADS 4 y del 83,7% en PI-RADS 5, **Tabla 2 (art.1)**. Desde un punto de vista clínico, la lectura experta permitió reclasificar 64 imágenes sospechosas inicialmente categorizadas como PI-RADS ≥ 3 por radiólogos no expertos a PI-RADS 2. Esta reclasificación podría haber evitado el 28,8% de las biopsias, en contraste con solo un 1,8% si se hubiese seguido el criterio no experto ($p = .021$). La omisión de estas biopsias habría resultado en la pérdida de detección de 5 csPCa (4,2%) según lectura experta, frente a 4 (3,4%) según la lectura no experta ($p = .669$). Además, la lectura experta permitió reducir en un 29,4% la sobredetección de iPCa, mientras que la lectura no experta no evitó ningún caso de sobrediagnóstico ($p = .034$), **Tabla 3 (art.1)**. El análisis histopatológico demostró una mejor correlación entre la categorización PI-RADS y el grado ISUP en la lectura experta. De los 64 casos reclasificados como PI-RADS 2 por el experto, el 76,6% no presentaban cáncer y un 15,6% eran PCa de bajo grado (ISUP GG1), lo que respalda el valor discriminativo de la lectura experta, **Tabla 4 (art.1)**. Además, la lectura experta mostró una clara correlación entre el aumento en la puntuación PI-RADS y una mayor tasa de detección de csPCa, relación que no se observó en las lecturas no expertas, **Figura 3 (art.1)**. Dos ejemplos ilustrativos de discordancia entre lecturas se presentan en las **Figuras 4A y 4B (art.1)**. En ambos casos, lesiones categorizadas como PI-RADS 4 por el radiólogo no experto fueron recategorizadas como PI-RADS 2 por el radiólogo experto tras identificar signos compatibles con prostatitis o hallazgos benignos, con biopsias

negativas en ambos. Finalmente, el análisis multivariante identificó dos predictores independientes de concordancia entre las lecturas: la puntuación PI-RADS inicial del radiólogo no experto (OR 3.925, IC 95% 1.888–8.160, $p < 0.001$) y el volumen prostático (OR 0.359, IC 95% 0.162–0.795, $p = 0.012$). Específicamente, la concordancia fue menor en próstatas de mayor volumen, especialmente en casos categorizados como PI-RADS 4 por el lector no experto, **Tabla 5 (art.1)**.

En segundo lugar, se analizó la precisión diagnóstica de las biopsias prostáticas dirigidas (TB) y sistemáticas (SB) para detectar el csPCa y además se desarrolló un modelo predictivo para valorar la omisión parcial de biopsias sistemáticas en varones con sospecha de PCa y puntuaciones PI-RADS ≥ 3 . La cohorte analizada estuvo compuesta por 2.122 hombres con sospecha de cáncer de próstata, con una mediana de edad de 68 años y PSA de 7.3 ng/mL. El 60,6% de las biopsias se realizaron por vía transperineal y el 70,5% con resonancia 3.0 Tesla. La distribución de PI-RADS fue de 22,9% (PI-RADS 3), 54,0% (PI-RADS 4) y 23,1% (PI-RADS 5), **Tabla 1 (art.2)**. El PCa fue detectado en el 67,1% de los pacientes, siendo csPCa en el 48,4%. La concordancia entre TB y SB para la detección de csPCa fue del 76%: en el 24,4% de los casos se detectó por ambas técnicas, y en el 51,6% no se detectó por ninguna. Sin embargo, en el 24% de los casos hubo discordancia: el 17,3% de los csPCa fueron detectados únicamente por TB y el 6,7% solo por SB, **Tabla 2 (art.2)**. Considerando exclusivamente los 1,026 casos de csPCa, el 35,7% fueron detectados solo por TB y el 13,9% solo por SB. El grado ISUP predominante en ambas situaciones fue el 2, aunque también se detectaron tumores de alto grado ($GG \geq 3$) exclusivamente por una de las dos vías. El análisis multivariado identificó como predictores independientes de mayor concordancia: edad >68 años (OR 1.48; $p < 0.001$), menor volumen prostático (OR 0.582; $p < 0.001$), resonancia 3T (OR 1.463; $p = 0.002$), puntuaciones PI-RADS más altas (OR 1.590; $p < 0.001$), uso de fusión software (OR 1.333; $p = 0.020$) y vía transperineal (OR 1.335; $p = 0.018$), **Tabla 3 (art.2)**. La discordancia fue mayor en hombres mayores y con resonancia 3T, y menor en próstatas grandes. Se observó una tendencia creciente de detección exclusiva por TB a medida que aumentaba la puntuación PI-RADS: del 4,9% en PI-RADS 3 al 25,9% en PI-RADS 5. En contraste, la detección exclusiva por SB se mantuvo estable entre 5,1% y 7,5%, **Tablas 4 y 5 (art.2)**. A partir de los factores predictivos independientes identificados, se desarrolló un modelo para estimar la capacidad de las TB de detectar csPCa. El AUC de la curva ROC fue de 0.741 (IC 95%: 0.721–0.762), **Figura 1 (art.2)**. Tras evaluar los umbrales de

sensibilidad del 100%, 97,5% y 95% para la detección de csPCa, las especificidades correspondientes fueron del 5,8%, 22,5% y 27,4%, respectivamente. Con estos parámetros, se observó que podían evitarse 11 biopsias sistemáticas sin omitir ningún caso de csPCa cuando se aplicaba una sensibilidad del 100%. Con un umbral de sensibilidad del 97,5%, se evitaban 312 biopsias sistemáticas (14,7%) con 25 casos de csPCa no detectados (2,4%). Finalmente, con una sensibilidad del 95%, se evitaban 368 SB (18,3%) a costa de no detectar 47 casos de csPCa (4,6%), **Tabla 6 (art.2)**.

Comparamos también la eficacia diagnóstica de csPCa según el abordaje realizado en la biopsia prostática ya que actualmente se recomienda realizar la vía transperineal. Para ello se diseñó un estudio multicéntrico pareado que evaluó la eficacia diagnóstica de las biopsias prostáticas transperineales y transrectales (TRB) en la detección de csPCa, mediante biopsias dirigidas a lesiones sospechosas identificadas por mpMRI. Además, se analizó el valor añadido de las biopsias sistemáticas según la vía de abordaje. De los 4.029 hombres inicialmente evaluados, se seleccionaron 1.376 con datos completos sobre tamaño y localización de la lesión índice. Para minimizar sesgos, se construyó un grupo pareado de 325 pares de casos según la vía de utilizada para la biopsia, con variables clínicas y técnicas equilibradas, **Tabla 1 y Figura 1 (art.3)**. Globalmente, la detección de sPCa fue del 41,3% mediante biopsias dirigidas y del 29,7% mediante biopsias sistemáticas. En el grupo pareado, las TPB mostraron tasas superiores de detección de csPCa tanto en el diagnóstico global (49,5% vs. 40,6%; $p = 0.027$) como en las biopsias dirigidas a la lesión índice (44,6% vs. 30,8%; $p < 0.001$), **Tabla 3 (art. 3)**. Sin embargo, la detección de csPCa mediante biopsias sistemáticas fue mayor en la vía transrectal (35,1%) frente a la TPB (24,3%) ($p = 0.003$), y los casos detectados únicamente por biopsia sistemática fueron significativamente más frecuentes con TRB (10,5%) que con TPB (4,9%) ($p = 0.012$), **Tabla 4 (art.3)**. La localización de la lesión índice tuvo un impacto directo sobre la eficacia diagnóstica. En lesiones localizadas en la zona central a nivel de la base media, la TPB detectó csPCa en el 33,3% de los casos frente al 5,9% con TRB ($p = 0.003$); en la zona anterior a nivel medio, las tasas fueron de 47,8% con TPB frente a 20,8% con TRB ($p = 0.039$); y en la zona anterior apical, del 52,9% frente a 24,2%, respectivamente ($p = 0.024$). En cambio, para las lesiones situadas en la zona periférica, tanto en base como en ápex, no se observaron diferencias significativas entre ambas vías de abordaje, **Tabla 5 (art. 3)**. Por último, el análisis multivariante identificó como predictores independientes de mayor probabilidad de detección de csPCa variables

como la edad avanzada, PSA elevado, tacto rectal sospechoso, menor volumen prostático, uso de resonancia 3T, fusión software, y puntuaciones PI-RADS más altas, **Tabla 2 (art.3)**.

Desarrollamos un estudio retrospectivo en un centro de referencia en Barcelona con el objetivo de evaluar la eficacia de las biopsias dirigidas por mapeo exclusivamente sobre la lesión índice en la detección de csPCa, utilizando la plataforma de biopsia de próstata por fusión transperineal Artemis™. El análisis incluyó a 309 hombres con sospecha de cáncer de próstata, todos sometidos a mpMRI y biopsias sistemáticas de 12 cilindros además de las biopsias dirigidas. La cohorte presentó una mediana de edad de 67 años y un PSA de 6.3 ng/mL, con un volumen prostático mediano de 53 cc. El 62,1% de los hombres fueron diagnosticados con csPCa, y un 12.3% con iPCa, **Tabla 1 (art.4)**. La tasa de detección de csPCa se incrementó significativamente con el aumento en la puntuación PI-RADS: 6,3% en PI-RADS 2, 26,8% en PI-RADS 3, 87,3% en PI-RADS 4, y 93,1% en PI-RADS 5 ($p < 0.001$), mientras que la detección de iPCa disminuyó en los niveles más altos, **Tabla 1 y Figura 2 (art.4)**. Las biopsias dirigidas a la lesión índice detectaron 185 de los 192 casos de csPCa (96.3%), mientras que solo tres casos (1.6%) fueron detectados exclusivamente en las biopsias sistemáticas y cuatro (2.1%) en una segunda lesión sospechosa, **Tabla 2 (art.4)**. No se identificó ningún csPCa adicional en las biopsias dirigidas a una tercera lesión. El índice de concordancia entre biopsias dirigidas y sistemáticas fue bajo ($Kappa = 0.239$), y en la mayoría de los casos (43%) el csPCa fue detectado únicamente por la biopsia dirigida, **Figura 2B (art.4)**. Desde el punto de vista del rendimiento diagnóstico, el estudio mostró que restringir la biopsia exclusivamente a la lesión índice reduciría en un 63,6% el número total de cilindros (de 6.573 a 2.392). Esta reducción aumentaría hasta el 72,8% si se aplicara el modelo predictivo desarrollado para estimar la probabilidad de detección de csPCa mediante biopsias dirigidas al índice. Un modelo, basado en regresión logística, identificó como predictores independientes el PSA (OR: 1.136; $p = 0.033$), el volumen prostático (OR: 0.978; $p < 0.001$) y la puntuación PI-RADS de la lesión índice (OR: 7.285; $p < 0.001$), **Tabla 3 (art.4)**. El modelo presentó un elevado poder discriminativo del csPCa, con un AUC de 0.918 (IC 95%: 0.887–0.950), **Figura 3A (art. 4)**, y un beneficio clínico neto frente a la estrategia de biopsiar a todos los varones, **Figura 3B (art.4)**. Con una sensibilidad del 100%, el modelo permitiría evitar el 23,3% de las biopsias dirigidas al índice sin omitir nuevos casos de csPCa.

Con el objetivo comparar la eficacia del esquema de muestreo cada 0.5 mm frente al esquema clásico que obtiene entre dos y cuatro muestras por lesión para detectar csPCa, se realizó un estudio prospectivo multicéntrico en Cataluña que comparó la eficacia diagnóstica de dos esquemas de biopsias TPB dirigidas a las lesiones sospechosa en la mpMRI. El análisis principal se realizó sobre una cohorte pareada por puntuación de propensión que incluyó a 522 hombres con lesiones PI-RADS 3 a 5, distribuidos equitativamente entre ambos esquemas, **Tabla 3 (art.5)**. La tasa de detección de csPCa en las biopsias dirigidas a la lesión índice fue significativamente mayor con el esquema de saturación (71,9%) en comparación con el esquema de dos a cuatro cilindros (47,9%) ($p < 0.001$). En contraste, la detección de iPCa fue menor con el esquema saturado (11,1%) frente al convencional (18,8%) ($p = 0.019$), **Figura 2 (art.5)**. La superioridad del esquema de saturación fue especialmente evidente en lesiones con puntuaciones PI-RADS más altas. En lesiones PI-RADS 4, la tasa de detección de csPCa fue del 87,3% frente al 47,4% con el esquema convencional ($p < 0.001$), y en PI-RADS 5, del 90,3% frente al 77,8% ($p < 0.001$). En PI-RADS 3 no se alcanzó significación estadística, aunque también se observó una tendencia favorable (26,8% vs. 18,3%; $p = 0.158$), **Figura 1 (art.5)**. Respecto de las biopsias sistemáticas de 12 cilindros realizadas en todos los casos, no se observaron diferencias significativas en la detección de csPCa según el esquema de biopsia dirigida utilizado (28.0% en el grupo convencional vs. 26,8% en el grupo saturado; $p = 0.228$). Sin embargo, la detección de csPCa exclusivamente en la biopsia sistemática fue significativamente menor cuando se utilizó el esquema saturado (1,5% vs. 5,0%; $p = 0.035$), **Figura 3 (art.5)**. El análisis multivariante identificó que, además del esquema de biopsia, variables como la edad, el PSA, el volumen prostático, la puntuación PI-RADS, el tamaño y la localización de la lesión índice fueron predictores independientes de la detección de csPCa, **Tabla 2 (art.5)**. En particular, el esquema saturado mostró una Odds Ratio de 2.137 (IC 95%: 1.869–3.439; $p < 0.001$) para detección de csPCa en comparación con el esquema convencional.

Para contextualizar los hallazgos previos en un escenario en el que se utilizan diferentes plataformas de fusión de imágenes de MRI-TRUS para realizar biopsias prostáticas transperineales, realizamos una revisión sistemática de la literatura con el objetivo de analizar la eficacia diagnóstica de las distintas plataformas así como explorar la utilidad complementaria de las biopsias sistemáticas en combinación con las dirigidas. Esta revisión incluyó estudios publicados hasta febrero de 2023, seleccionados mediante los

criterios PRISMA y PICO, y fue registrada en PROSPERO (CRD42022375619). Se incluyeron finalmente 30 estudios que analizaron los resultados de biopsias en 11.313 pacientes, **Figura 1 (art.6)**. Las características demográficas globales mostraron una edad media de 66.5 años, un PSA promedio de 7.8 ng/mL, volumen prostático medio de 45.4 cc y densidad de PSA media de 0.17 (rango: 0.12–0.27). Se analizaron 10.457 lesiones, predominantemente PI-RADS 3 (2748), PI-RADS 4 (4126) y PI-RADS 5 (2339), con un 22% de tacto rectal anormal reportado en las series que lo consignaban, **Tabla 3 (art.6)**. En cuanto a las características técnicas, todas las biopsias fueron transperineales en posición de litotomía. Se utilizaron diversos tipos de anestesia: local en 11 estudios, general en 15, sedación en dos y raquídea en dos. La segmentación prostática fue realizada por el urólogo en la mayoría de los casos, aunque en algunos estudios fue efectuada por el radiólogo o ambos, **Tabla 4 (art.6)**. Las plataformas más utilizadas fueron Koelis, Biopsee, UroNav y iSR'obot Mona Lisa, distribuidas entre fusiones rígidas (14 estudios) y elásticas (16 estudios). Los resultados de detección global de PCa y csPCa fueron del 61,4% y 47,8%, respectivamente. La tasa de detección de csPCa varió según la categoría PI-RADS: 24.5% en PI-RADS 3, 55.9% en PI-RADS 4 y 81.5% en PI-RADS 5, **Tabla 6 (art.6)**. La contribución adicional de la biopsia sistemática, definida como la detección de csPCa únicamente mediante esta técnica, fue reportada en 14 estudios, con una media del 9.5% (rango: 0,8% a 22,1%). Este hallazgo confirma que la complementariedad entre biopsia dirigida y sistemática también es válida en la vía transperineal. Cuando se compararon los tipos de software, las biopsias guiadas por fusión elástica mostraron una tasa global de detección de PCa del 64,8% y de csPCa del 50,3%, mientras que con software de fusión rígida las tasas fueron de 57,9% y 45,4%, respectivamente. En poblaciones homogéneas, se observó que la fusión rígida ofrecía mejores resultados en detección de csPCa, especialmente en pacientes con vigilancia activa o biopsia previa negativa, **Tablas 7 y 8 (art.6)**. Finalmente, no se hallaron diferencias significativas entre los distintos tipos de robots analizados. El sistema ArtemisTM no contaba con publicaciones sobre su rendimiento por vía transperineal. Las series más recientes también reflejan una tendencia creciente al uso de anestesia local, lo que demuestra la factibilidad de la técnica en condiciones ambulatorias.

En una segunda parte de nuestro proyecto, se evaluó el rendimiento del modelo predictivo de Barcelona que incorpora la información de la MRI (BCN-MRI PM) en un entorno clínico del programa de diagnóstico precoz del csPCa de Cataluña, con el propósito de

validar su capacidad predictiva para la detección de csPCa en varones con sospecha de PCa tratamiento con inhibidores de la 5-alfa reductasa (5-ARI). El análisis incluyó a 2.212 hombres con sospecha de PCa atendidos en 10 centros durante el año 2022, de los cuales 120 (5,4%) estaban recibiendo tratamiento con 5-ARI desde hacía más de un año. La mediana de edad fue mayor en los usuarios de 5-ARI (72 vs. 68 años; $p < 0.001$), al igual que el volumen prostático (69 vs. 53 cc; $p < 0.001$), mientras que el PSA fue comparable entre ambos grupos (8.0 vs. 7.3 ng/mL; $p = 0.107$), **Tabla 1 (art.7)**. La distribución de las puntuaciones PI-RADS fue similar, predominando las categorías 4 y 5 en ambos subgrupos. La detección global de PCa fue del 63,4%, siendo csPCa en el 44,6% e iPCa en el 18,8%. No se observaron diferencias significativas en la tasa de detección de csPCa entre los hombres tratados y no tratados con 5-ARI (42,5% vs. 44,7%; $p = 0.706$). En cuanto al rendimiento del modelo BCN-MRI PM, su capacidad discriminativa fue elevada tanto en hombres sin tratamiento (AUC: 0.824; IC 95%: 0.783–0.842) como en aquellos bajo tratamiento con 5-ARI (AUC: 0.848; IC 95%: 0.806–0.916), sin diferencias significativas entre ambos ($p = 0.157$), **Figura 1A y 1D (art.7)**. Las curvas de calibración mostraron un leve exceso de detección de csPCa en las probabilidades bajas en los hombres sin tratamiento, mientras que en los tratados con 5-ARI se observó un mejor ajuste a la curva ideal, **Figura 1A y 1B (art.7)**. La aplicación clínica del modelo, evaluada mediante curvas de utilidad clínica, demostró que en los hombres sin tratamiento de 5-ARI, el uso del BCN-MRI PM permitiría evitar el 17,3% de las biopsias prostáticas con una pérdida del 2,5% de csPCa (sensibilidad del 97,5%). En cambio, en los usuarios de 5-ARI, el modelo permitiría evitar el 25% de las biopsias sin omitir ningún caso de csPCa, incluso aplicando un umbral de sensibilidad del 100%, **Figura 2 y 3 (art.7)**. El análisis de beneficio clínico neto mediante análisis curvas de decisión mostró que el uso del BCN-MRI PM aporta un beneficio neto superior que la estrategia de biopsiar a todos los pacientes con resonancia positiva, tanto en hombres tratados como no tratados con 5-ARI, **Figura 1 (art. 7)**.

Realizamos un estudio prospectivo en un centro de referencia de Barcelona con el objetivo de validar el modelo predictivo BCN-MRI PM para la detección de csPCa en hombres con sospecha de PCa, empleando un protocolo avanzado de biopsia por mapeo dirigido cada 0.5 mm sobre lesiones sospechosas y sus áreas perilesionales, seguido de una biopsia sistemática de 12 cilindros. El estudio incluyó a 457 hombres biopsiados entre febrero de 2022 y febrero de 2024. La tasa global de detección de csPCa fue del 58,4%.

Según la categoría PI-RADS v2.1 de la lesión índice, las tasas de detección fueron de 2,7% (PI-RADS 2), 33% (PI-RADS 3), 80% (PI-RADS 4) y 87,4% (PI-RADS 5), **Tabla 1 (art.8)**. La mayoría de las lesiones índice (65.2%) se localizaban en la zona periférica y el tamaño mediano de la lesión fue de 12 mm. El número total de cilindros por paciente tuvo una mediana de 21 (rango intercuartil 19–24). La calibración del modelo BCN-MRI PM fue adecuada, mostrando una buena concordancia entre las probabilidades esperadas y observadas y comparable con la cohorte de desarrollo, y la primera validación externa, **Figura 1 (art.8)**. La capacidad discriminativa del modelo fue elevada, con un área bajo la curva (AUC) de 0.862 (IC 95%: 0.828–0.896), superior al AUC de 0.743 (IC 95%: 0.711–0.776) observado en la validación del BCN-MRI PM ($p = 0.008$), **Figura 2 (art.8)**. El análisis de curvas de decisión mostró un beneficio clínico neto del modelo a partir de umbrales del 12% en adelante, comparable al de cohortes previas, **Figura 3 (art.8)**. En términos de utilidad clínica, con un umbral del 12% de probabilidad de csPCa, el modelo permitiría evitar el 24.9% de las biopsias prostáticas con una sensibilidad del 95%, **Tabla 3 y Figura 4 (art.8)**. A mayores umbrales, se incrementaba el porcentaje de biopsias evitadas, pero también los casos de csPCa no detectados, **Tabla 2 (art.8)**. Por ejemplo, al permitir una omisión del 5% de los casos de csPCa, se lograría evitar el 24.9% de las biopsias, con una especificidad del 48.4% y un índice de Youden de 43.6, **Tabla 3 (art.8)**. Al analizar subgrupos por categoría PI-RADS, se observó que en los hombres con PI-RADS 2, un umbral del 11% permitía detectar el 100% de los csPCa (2 casos) evitando biopsiar al 78,1% del subgrupo. En los PI-RADS 3, un umbral del 10% evitaría el 40% de las biopsias, pero a costa de omitir el 22,8% de los csPCa, lo que representa una pérdida global del 3% de csPCa en la cohorte total. En los PI-RADS 4 y 5 no se identificó ningún umbral que permitiera evitar biopsias sin perder diagnósticos de csPCa. En conjunto, el modelo BCN-MRI PM mostró un rendimiento robusto incluso bajo un protocolo de biopsia más exhaustivo que el usado en su desarrollo, validando su aplicabilidad clínica en contextos actuales que utilizan PI-RADS v2.1 y biopsias transperineales con mapeo dirigido y sistemático.

En el contexto del programa de detección precoz de csPCa en Cataluña, se desarrolló un estudio prospectivo multicéntrico con el objetivo de validar el BCN-MRI PM en una cohorte de 3.264 hombres con resonancia pre-biopsia informada según PI-RADS v 2.1 y sometidos a biopsias prostáticas por vía transrectal o transperineal. Los hombres incluidos presentaban un PSA >3 ng/mL y/o un tacto rectal sospechoso. Del total, 2.295 (70,3%) fueron sometidos a biopsias transrectales y 969 (29,7%) a biopsias transperineales. Las características clínicas y radiológicas iniciales fueron comparables entre ambos grupos, incluyendo edad, PSA, volumen prostático, distribución de puntuaciones PI-RADS y proporción de antecedentes familiares y biopsias previas, **Tabla 1 (art.9)**. La tasa de detección global de csPCa fue mayor con la vía transperineal (45,9%) que con la transrectal (41,0%) ($p = 0.016$). No hubo diferencias significativas en la detección de iPCa (17,4% vs. 16,3%; $p = 0.441$). La calibración del modelo fue buena para ambas vías de abordaje, con curvas de calibración próximas a la línea de correlación ideal, y sólo una leve sobrestimación en las probabilidades más bajas y subestimación en las más altas, **Figura 1 (art.9)**. La capacidad discriminativa del modelo fue elevada en ambos grupos: AUC de 0.847 (IC 95%: 0.830–0.863) en biopsias transrectales y 0.830 (IC 95%: 0.804–0.855) en biopsias transperineales, sin diferencias estadísticamente significativas ($p = 0.346$), **Figura 2 (art.9)**. El análisis de umbrales del modelo según sensibilidad mostró que, para una sensibilidad del 100%, las especificidades fueron del 1,3% (umbral 0,36%) en biopsias transrectales y 1,8% (umbral 0,49%) en transperineales ($p = 0.438$). A una sensibilidad del 97,5%, las especificidades fueron del 23,7% y 22,6%, respectivamente ($p = 0.395$), y para una sensibilidad del 95%, del 37,6% y 36,8% ($p = 0.387$). Con estos umbrales, el modelo permitiría evitar 17 (0,7%) y 9 (0,9%) biopsias prostáticas sin omitir ningún caso de csPCa; 344 (15,0%) y 112 (12,6%) con pérdida del 2,5%; y 557 (24,3%) y 229 (22,6%) con pérdida del 5%, respectivamente para las rutas transrectal y transperineal ($p > 0.3$ en todos los casos). Las curvas de decisión clínica mostraron un beneficio neto del modelo sobre la estrategia de biopsiar a todos los pacientes, tanto en la vía transrectal (a partir de un umbral del 10%) como en la transperineal (a partir del 15%), **Figura 3 (art.9)**. En conjunto, los resultados confirman la validez del BCN-MRI PM cuando se utiliza PI-RADS v2.1 y se realizan biopsias tanto transrectales como transperineales, reforzando su aplicabilidad como herramienta de estratificación de riesgo en el abordaje diagnóstico del csPCa en entornos clínicos contemporáneos.

Tabla 5. Relación entre los objetivos secundarios, las publicaciones incluidas y los principales hallazgos de la tesis.

Objetivo secundario	Publicación	Diseño	Muestra	Resultado principal	Conclusión práctica
Analizar el impacto de la lectura experta de la MRI	Publicación 1	Prospectivo	222 pacientes	La lectura experta redujo un 28,8% las biopsias sin perder csPCa	La interpretación experta mejora la selección de candidatos a biopsia
Limitar las biopsias sistemáticas mediante un modelo predictivo	Publicación 2	Multicéntrico prospectivo	2.122 pacientes	Se evitaron el 18,3% de biopsias sistemáticas con pérdida <5% de csPCa	Los modelos predictivos permiten individualizar la indicación de biopsia sistemática
Comparar la biopsia transrectal y transperineal	Publicación 3	Estudio pareado multicéntrico	650 pacientes	Mayor detección de csPCa por vía transperineal	La vía transperineal debe considerarse el abordaje de referencia
Evaluar el protocolo mapping cada 0,5 mm	Publicación 4	Prospectivo	309 pacientes	Detección del 96,3% de csPCa	El mapping permite focalizar la biopsia en la lesión índice y área perilesional
Comparar el mapping frente al protocolo convencional	Publicación 5	Estudio pareado multicéntrico	261 pacientes	71,9% vs. 47,9% de detección de csPCa	El mapping mejora significativamente el rendimiento diagnóstico
Analizar las plataformas MRI-TRUS	Publicación 6	Revisión sistemática	>11.000 pacientes	Mejor rendimiento de plataformas con registro rígido	La tecnología de fusión influye en la eficacia diagnóstica
Validar el BCN-MRI PM en pacientes tratados con 5-ARI	Publicación 7	Validación multicéntrica	120 pacientes	AUC 0,824	El modelo mantiene su utilidad clínica
Validar el BCN-MRI PM en biopsias transperineales	Publicación 8	Validación multicéntrica	969 pacientes	AUC 0,830	El modelo es aplicable a la vía transperineal
Validar el BCN-MRI PM utilizando PI-RADS v2.1 y mapping	Publicación 9	Validación prospectiva	457 pacientes	AUC 0,862	El modelo mantiene su rendimiento en escenarios diagnósticos avanzados

7. RESUMEN GLOBAL DE LA DISCUSIÓN

La evolución del diagnóstico precoz del csPCa ha estado marcada por el desafío de alcanzar una precisión elevada, al mismo tiempo que una reducción de procedimientos invasivos innecesarios y riesgos asociados al sobrediagnóstico. La introducción de la MRI como herramienta de primera línea en la evaluación del riesgo de csPCa ha transformado profundamente la estrategia diagnóstica (164). Sin embargo, su incorporación plena en la práctica clínica requiere resolver una serie de cuestiones relacionadas con su estandarización, interpretación experta, integración tecnológica y la definición de umbrales clínicos que permitan individualizar la indicación de biopsia prostática.

La definición de experiencia en la interpretación de la MRI prostática carece de criterios uniformes. Algunos autores la establecen en función del número de estudios interpretados, fijando el umbral en 500 o 1000 casos, mientras que otros la asocian al tiempo de práctica, situándola entre tres y doce años de actividad en el área (165–167). Alternativamente, se ha propuesto valorar la experiencia a partir de la retroalimentación histopatológica y del volumen acumulado de casos evaluados (168,169). Existe una escasez de estudios que comparen de forma sistemática la variabilidad inter-observador y sus consecuencias clínicas. Hemos analizado la concordancia entre las lecturas realizadas por radiólogos no expertos y la reinterpretación efectuada por una radióloga experta utilizando MRI sin contraste (bpMRI). Encontramos la misma clasificación con el PI-RADS v 2.1 en el 49,1% de los estudio, lo que debemos entender como pobre en línea con las publicaciones previas que reportan una consistencia limitada entre lectores (170). Esta discrepancia se atribuye a una tendencia sistemática de los radiólogos no especializados a sobrestimar el riesgo, clasificando como PI-RADS 3 ó 4 lesiones que, tras evaluación experta, fueron reclasificadas como benignas (PI-RADS 2). Esta reclasificación habría permitido evitar la realización del 28,8% de las biopsias, con una pérdida diagnóstica de csPCa del 4,2%. De los 64 hombres cuyas lesiones fueron reclasificadas como PI-RADS 2 por el experto, 49 (76,6%) no presentaron PCa y 10 (15,6%) fueron diagnosticados de PCa insignificante (iPCa). Nuestra observación es consistente con publicaciones previas, donde la lectura experta permitió reclasificar 45 de 116 lesiones índice como PI-RADS < 3, evitando así la realización de biopsias innecesarias, sin comprometer el rendimiento diagnóstico (171). En consonancia con estos estudios, una mayor experiencia del lector reduce significativamente la tendencia a sobre-diagnosticar el iPCa. Boschheidgen et al. llevaron a cabo un estudio que comparó la lectura entre expertos y no expertos en MRI, en hombres de 45 años, observando una

reducción del 71% en la detección de iPCa al utilizar PI-RADS ≥ 4 como umbral para indicar la biopsia (172). El volumen prostático se presenta como una variable modificadora en la interpretación de la MRI. Las glándulas prostáticas pequeñas y heterogéneas se asocian a menor precisión diagnóstica por parte de lectores poco expertos, lo que sugiere una interacción entre el tamaño prostático y la experiencia del lector (173). Por otra parte, la interpretación experta de bpMRI, conforme a PI-RADS v 2.1, permite prescindir del uso de contraste en lesiones PI-RADS 3 localizadas en la zona periférica, donde predomina la secuencia de difusión (174). Esta práctica podría explicar la mayor proporción de lesiones PI-RADS 3 observadas en nuestra serie tras la lectura experta, sin que ello implique necesariamente una mayor indicación de biopsia. Estos hallazgos refuerzan la necesidad de profesionalizar e institucionalizar la lectura experta de la MRI prostática. Este hecho permitirá mayor eficiencia de la biopsia prostática. En esta línea, se plantea la conveniencia de centralizar la lectura de MRI en centros de referencia, formar radiólogos especializados en la interpretación de MRI prostática, y desarrollar algoritmos de inteligencia artificial que puedan asistir o replicar la lectura experta en entornos sin acceso a radiólogos expertos. En conjunto, estas medidas permitirían mejorar la eficiencia diagnóstica y reducir los riesgos inherentes a la biopsia prostática.

Ante la necesidad de optimizar el rendimiento diagnóstico de la biopsia prostática y reducir procedimientos innecesarios, nuestro proyecto se ha sumado para generar evidencia respecto de la necesidad de combinar biopsias sistemáticas y dirigidas (175). Si bien las biopsias dirigidas han demostrado ser más sensibles que las sistemáticas, sigue existiendo un porcentaje no despreciable de casos de csPCa que son identificados exclusivamente en la biopsia sistemática, especialmente cuando existen csPCa en lesiones no visibles en la MRI o por errores en su localización (176,177). Nuestro estudio, realizado en 2.122 varones con sospecha de PCa sometidos a biopsia prostática sistemática en 10 centros de Cataluña, puso de manifiesto que el 13,9% de los csPCa se detectaron exclusivamente en la biopsia sistemática, el 35,7% únicamente en las biopsias dirigidas, y el 50,4% en ambas. Este resultado evidencia la complementariedad diagnóstica entre ambos tipos de biopsia en nuestro medio. La literatura sugiere que los csPCa pueden estar presentes hasta en el 9,2% de las biopsias sistemáticas realizadas en casos con PI-RADS < 3 (178, 179). Por tanto, eliminar esta modalidad de muestreo puede comprometer la sensibilidad global del proceso diagnóstico. Estudios emblemáticos como

PROMIS y PRECISION han demostrado, con evidencia de nivel uno, que las biopsias dirigidas presentan mayor sensibilidad que las sistemáticas (180, 181). En PROMIS, la sensibilidad para csPCa se incrementó del 48% (IC 95%: 42–55%) al 93% (IC 95%: 88–96%) al utilizar biopsias dirigidas. En el estudio PRECISION, la tasa de detección de csPCa fue del 38% con biopsias dirigidas frente al 26% con biopsias sistemáticas. No obstante, investigaciones como MRI-First y PAIREDCAP concluyeron que ninguna técnica por sí sola asegura una sensibilidad diagnóstica óptima, observando que entre el 11,5% y el 33,3% de los casos pueden pasar desapercibidos si se emplea un único enfoque (182, 183). Nuestro estudio también evidenció que existen factores clínicos y técnicos influyen en la detección de csPCa en las biopsias dirigidas. Tal como indicaron Williams et al., errores en la localización de las lesiones, lesiones no visibles y omisiones interpretativas son causas frecuentes de falsos negativos en biopsias dirigidas (184). Así mismo, se ha observado que la discordancia entre ambas biopsias aumenta con la edad y el volumen prostático, y que la detección exclusiva mediante biopsia dirigida se incrementa con puntuaciones PI-RADS más elevadas, mientras que la detección exclusiva mediante biopsia sistemática se mantiene relativamente constante (185). También se ha identificado una mayor discordancia al utilizar MRI con campo magnético de 3 Tesla, un hallazgo novedoso que no había sido previamente descrito en la literatura, a pesar de que estudios previos no habían demostraron un aumento consistente en la tasa de detección de csPCa con mayor intensidad de campo (186). En nuestro estudio, desarrollamos un modelo predictivo para estimar la probabilidad de detección de csPCa exclusivamente en las biopsias dirigidas. Este modelo, que incorporó variables como la edad, volumen prostático, tipo de fusión TRUS-RM, vía de abordaje y campo magnético de la MRI, mostró un AUC de 0,741 (IC 95%: 0,721–0,762). Aunque su rendimiento global fue moderado, permitió evitar hasta el 18,3% de las biopsias sistemáticas, dejando de detectar menos del 5% csPCa. Avances tecnológicos como la combinación de MRI con Ga⁶⁸PSMA-PET (187), el uso de biopsias dirigidas robotizadas, y mejoras en la fusión de imágenes TRUS-MRI pueden reducir aún más la necesidad realizar biopsias sistemáticas y minimizar el sobrediagnóstico de iPCa (188). Sin embargo, en la actualidad, las biopsias sistemáticas siguen siendo necesarias para garantizar la máxima detección de csPCa (62).

La reciente recomendación de realizar la biopsia prostática por vía transperineal se llevado a cabo con el objetivo de reducir las severas complicaciones infecciosas de la vía

transrectal y el excesivo consumo de antibióticos (189). Sin embargo, la eficacia diagnóstica del csPCa en ambas vías no ha sido evaluada de manera exhaustiva. Por ello, a partir de la serie amplia de biopsias recogidas en nuestro grupo multicéntrico, realizamos un estudio pareado, en el que se eliminaron variables confusoras, reforzándose la eficacia del abordaje transperineal en el contexto de biopsias dirigidas por fusión de imágenes. En comparación con el abordaje transrectal, la biopsia transperineal mostró tasas significativamente más altas de detección de csPCa tanto en las lesiones índice (44,6% vs. 30,8%), como en biopsias combinadas sistemáticas y dirigidas (49,5% vs. 40,6%). Estos hallazgos coinciden con series recientes que identifican a la biopsia transperineal como un predictor independiente de mayor rendimiento diagnóstico (190), y contrastan con otros estudios en los que no se observaron diferencias significativas entre ambas rutas (191,192). La complementariedad entre las biopsias sistemáticas y dirigidas continúa existiendo cuando se utiliza el abordaje transperineal. Nuestros datos fortalecen esa afirmación, al mostrar que cada método contribuye de manera independiente a la detección del csPCa. Un hallazgo llamativo en nuestro estudio fue mayor detección de csPCa exclusivamente en la biopsia sistemática cuando el abordaje fue transrectal (10,5 frente al 4,9%) que cuando se realizó la biopsia por vía transperineal. Esta diferencia podría deberse a variaciones en el volumen prostático, ya que en las glándulas próstáticas menores a 30 ml. de nuestra serie existió mejor rendimiento de la biopsia transrectal, mientras que el volumen medio global fue de 60 ml. La localización de las lesiones parece influir en la eficacia de cada abordaje. La vía transperineal fue superior para detectar csPCa en lesiones anteriores, apicales, centrales y en la base media, mientras que el acceso transrectal mostró ventajas en las lesiones posteriores. Este patrón de detección fue coherente con el metaanálisis de Uleri et al. que verificó la superioridad de las biopsias transperineales para tumores anteriores y apicales, y su equivalencia con las biopsias transrectales en tumores periféricos (193). Nuestro estudio complementa y refuerza la evidencia presentada en análisis previos, al demostrar que la elección de la vía de abordaje, la localización tumoral y el volumen prostático son factores clave que condicionan la efectividad diagnóstica de la biopsia prostática en función de su abordaje transrectal o transperineal.

La detección precoz del csPCa continúa mejorando gracias a la introducción de nuevos softwares de fusión entre imágenes de MRI y TRUS para realizar biopsias dirigidas (194), estrategias innovadoras de robotización y la recomendación del abordaje transperineal

(62). En este contexto, nuestro proyecto ha incorporado un estudio inédito en el que se analiza el rendimiento de la biopsia prostática dirigida por saturación, mediante un mapeo realizado cada 0.5 mm, de las lesiones sospechosas y áreas perilesionales, complementado con biopsias sistemáticas obteniendo 12 cilindros. En esta serie en la que se utilizó el PI-RADS v 2.1 se obtuvo una tasa global de detección de PCa del 74,4%, 62,1% de csPCa y 12,3% de iPCa. En el contexto de la medicina de precisión, la multifocalidad tumoral plantea importantes desafíos diagnósticos (195), y diversos protocolos de biopsia buscan optimizar la precisión con la menor agresividad posible, como evitar la zona de transición (196), utilizar biopsias de saturación (197), seleccionar pacientes según la densidad de PSA (PSAD) (198), aplicar estrategias del tipo umbra/penumbra (177,199), reducir el número de cilindros (200) o eliminar la biopsia sistemática (201). No obstante, el valor añadido de biopsiar lesiones secundarias y realizar biopsias sistemáticas sigue en evaluación. Rachubinski et al. demostraron que la biopsia de lesiones secundarias aporta valor diagnóstico en la mayoría de los casos (202). En nuestro estudio, la biopsia dirigida sobre la lesión índice detectó el 96,3% de los csPCa mientras que la biopsia de la segunda lesión aportó un 2,1% adicional, y la biopsia sistemática un 1,6%. Biopsiar una tercera lesión no mejoró el rendimiento diagnóstico. Petov et al. (203) concluyeron que ambas técnicas presentan tasas comparables de detección de csPCa, mientras que Marra et al. (204) destacaron su carácter complementario. La revisión Cochrane también respalda esta combinación, aunque los datos disponibles sobre el abordaje transperineal siguen siendo limitados (51). Porpiglia et al. observaron que la biopsia dirigida no fue inferior a la combinación con biopsia sistemática en este contexto (205). En nuestra serie, solo tres casos (1%) de csPCa fueron detectados exclusivamente mediante biopsias sistemáticas. En nueve pacientes, la biopsia sistemática identificó iPCa no detectados en las biopsias dirigidas lo que incrementó su sobrediagnóstico. En tres casos la biopsia sistemática permitió reclasificar el grupo de grado tumoral. A partir de estos hallazgos, desarrollamos un modelo predictivo que fue capaz de evitar casi una cuarta parte de las biopsias sin dejar de detectar casos de csPCa. Se evitó el 72,8% de los 6.573 cilindros tomados, lo que redujo significativamente la agresividad del procedimiento. Desde una perspectiva práctica, la implementación de un protocolo de biopsia dirigida mediante mapping cada 0,5 mm debería realizarse en centros que dispongan de resonancia magnética prostática de alta calidad, interpretación radiológica experimentada y experiencia en biopsia prostática transperineal guiada por fusión de imágenes. La adecuada identificación de las lesiones sospechosas y la precisión

en su muestreo constituyen elementos fundamentales para reproducir los beneficios observados en esta tesis. Por ello, esta estrategia debe aplicarse en un entorno que garantice la calidad de la evaluación radiológica y de la técnica de biopsia dirigida.

En el marco de la optimización de las estrategias diagnósticas del csPCa, llevamos a cabo un estudio prospectivo y multicéntrico en cohortes pareadas para comparar la eficacia de las biopsias dirigidas por saturación de lesiones sospechosas y áreas perilesionales frente al protocolo clásico que recomienda la obtención entre 2 y 4 punciones. Nuestros resultados respaldan el uso de esquemas de biopsia dirigida por saturación. En particular, se observó mayor eficacia de biopsia por saturación. Este incremento fue evidente en todas las categorías PI-RADS y especialmente en las categorías 4 y 5. Las tasas de sobredetección de iPCa también se redujeron al aplicar el esquema de saturación. Finalmente, también se redujo el porcentaje de csPCa identificado exclusivamente en biopsias sistemáticas. Estos hallazgos coinciden con estudios previos en los que se ha observado un aumento en la tasa de detección de csPCa al incrementar el número de punciones dirigidas (206–208), aunque algunos autores han señalado que esquemas más reducidos podrían ofrecer una eficacia diagnóstica comparable en determinados contextos clínicos (209, 210). En conjunto, la evidencia actual sugiere que la obtención sistemática de muestras adicionales en las lesiones sospechosas y áreas perilesionales no solo mejora la sensibilidad diagnóstica del csPCa, sino que también podría permitir prescindir de las biopsias sistemáticas reduciendo el sobrediagnóstico y las complicaciones asociadas al excesivo número de punciones. Globalmente existe una tendencia progresiva a utilizar modelos diagnósticos más precisos y personalizados en plataformas robóticas y abordajes transperineal. En consonancia con los hallazgos de ensayos multicéntricos previamente discutidos, como PROMIS, PRECISION, MRI-FIRST y PAIREDCAP (180–183), se ha consolidado el valor añadido de la biopsia dirigida, sin que ello implique, por el momento abandonar por completo la biopsia sistemática.

Llegados a este punto, nos preguntamos si todas las plataformas que permiten la biopsia dirigida por fusión entre imágenes de MRI y TRUS a través del abordaje transperineal permiten igual eficacia para detectar el csPCa. Para ello, se realizó una revisión sistemática que reportó publicaciones de todos los dispositivos aprobados por la FDA y la EMA, con excepción del sistema Artemis™, que no disponía de publicaciones sobre su efectividad diagnóstica por vía transperineal hasta ese momento. Si bien no se identificaron diferencias relevantes entre las distintas plataformas, los sistemas con

registro rígido mostraron tasas de detección superiores respecto a los de registro elástico, existiendo una concordancia con los hallazgos de Görtz et al. (86). También observamos una adopción creciente de estas plataformas en contextos ambulatorios bajo anestesia local, como lo demuestran las técnicas descritas por Fletcher et al. (211) y Kaneco et al. (212). Esta transición tecnológica requiere superar desafíos vinculados a la estandarización del proceso de segmentación prostática, aún poco documentado, y a la formación específica del operador, factores que inciden directamente en la precisión diagnóstica y en la optimización de recursos.

La literatura más reciente continúa analizando el valor añadido de la biopsia sistemática en el contexto de las biopsias dirigidas. Si bien algunos estudios, como el de Porpiglia et al. (205), sugieren que la biopsia dirigida por sí sola no es inferior en determinados escenarios, nuestra revisión reveló que en el 9,5% de los casos el csPCa se detectó únicamente mediante biopsia sistemática, con un rango entre 0,8% y 22,1%. Este hallazgo subraya la necesidad de una evaluación cuidadosa y personalizada en cada paciente. La decisión de omitir la biopsia sistemática debe basarse en variables como la experiencia del operador, el volumen prostático, la localización tumoral y la calidad de la imagen (185, 213, 214).

La integración clínica de las estrategias diagnósticas previamente comentadas requiere de herramientas capaces de estimar de manera personalizada el riesgo de csPCa antes de realizar una biopsia y mejorar la selección de candidatos. En este contexto, el BCN-MRI PM ha representado un avance sustancial. Este modelo fue desarrollado a partir de las variables clínicas predictoras independiente edad, antecedentes familiares de PCa, existencia de biopsias previas negativas, tacto rectal sospechoso, nivel sérico de PSA, y las basadas en la MRI volumen prostático y puntuación PI-RADS v 2.0, realizándose la biopsia por vía transrectal con un esquema basado en obtener entre 2 y 4 punciones de las lesiones sospechosas y/o una biopsia sistemática obteniendo 12 punciones cuando en PI-RADS fue inferior a 3. Por tanto, el BCN-MRI PM precisa ser validado en pacientes con hiperplasia benigna sintomática tratados con inhibidores de la 5-alfa reductasa (5-ARI) que tienen sospecha de PCa, cuando se analiza la MRI con la versión 2.1 del PI-RADS, cuando se utiliza la vía transperineal para realizar la biopsia prostática y una modalidad de biopsia altamente eficaz basada en la biopsia dirigida a través de un *mapping* cada 0.5 mm de las lesiones sospechosas y áreas perilesionales complementada por biopsia sistemática.

El BCN-MRI PM fue validado satisfactoriamente pacientes tratados 5-ARIs. Su capacidad discriminatoria del csPCa en la cohorte de pacientes tratado con 5-ARIs fue similar a la de los varones pareados no tratados, con AUC de 0.848 y 0.824, respectivamente. Este hecho puede justificarse por la homogeneidad del tejido prostático inducido por estos fármacos y por la mejor delimitación de las lesiones sospechosas en la MRI (163). Al aplicar el modelo con un umbral de sensibilidad del 100%, fue posible evitar el 25% de las biopsias en esta la cohorte tratada con 5-ARIs. Esta observación adquiere especial relevancia ya que los pacientes tratados con 5-ARI suelen presentar próstatas de mayor volumen, concentraciones de PSA inferiores y perfiles clínicos de bajo riesgo, lo que dificulta la interpretación de la MRI. En nuestro estudio, la cohorte de pacientes tratados con 5-ARIs presentó niveles séricos de PSA similares a los de la cohorte de varones no sometidos al tratamiento. Este hallazgo estuvo en consonancia con estudios previos en los que también se reportaron valores de PSA sérico comparables (215, 216). El estudio PROMOD, que incluyó a más de 7.600 pacientes, evidenció que el PSA medio en los pacientes tratados con 5-ARIs fue 6,0 ng/mL frente a 6,5 ng/mL en los no tratados (217). Este resultado contrasta con la recomendación clínica de monitorizar el PSA tras alcanzar el nadir en el primer año de tratamiento y considerar sospechoso cualquier incremento confirmado superior a 0,3 ng/mL (218). Por tanto, sería necesario un seguimiento más estricto del PSA en pacientes tratados con 5-ARI, a fin de evitar retrasos en el diagnóstico de tumores de alto grado (219). Desde el punto de vista radiológico, el estudio MAPPED aportó datos preliminares sobre el efecto de la exposición a dutasteride durante seis meses, observándose un aumento del coeficiente de difusión aparente (ADC) y una menor visibilidad tumoral en las secuencias de difusión (DWI), sin cambios en las imágenes en T2 (220). Estos hallazgos abren la posibilidad de que los 5-ARI puedan mejorar la diferenciación entre tejido benigno y tumoral en la zona periférica (221), aunque la evidencia sobre su impacto en la clasificación PI-RADS y su correlación con la detección de csPCa sigue siendo limitada y contradictoria (222). Falagario et al. informaron que el uso de 5-ARI no afecta la asociación entre PI-RADS y csPCa, aunque sí observaron una mayor frecuencia de tumores de alto grado en usuarios con PI-RADS 5 (217).

Ya que actualmente se recomienda utilizar la v 2.1 del PI-RADS y la vía transperineal para realizar las biopsias protáticas, y el BCN-MRI PM fue desarrollados en una cohorte en la que la MRI se reportó con el PI-RADS v 2.0 y la biopsia rearealizó por vía

transrectal, se llevó a cabo una nueva validación del modelo BCN-MRI PM en varones con sospecha de PCa sometidos a biopsia transperineal, utilizando el sistema PI-RADS v2.1 (55). La capacidad discriminatoria del BCN-MRI PM fue comparable en ambos abordajes, con un área bajo la curva (AUC) de 0,830 para la vía transperineal y de 0,847 para la transrectal. Además, el análisis de las curvas de decisión clínica mostró que el modelo proporciona un beneficio neto en umbrales de riesgo entre el 10% y el 15%, superando la estrategia convencional de biopsiar a todos los varones con sospecha de PCa y MRI con PI-RADS > 3. Es importante destacar que, en este estudio de validación, la tasa de detección de csPCa fue del 45,9% para la vía transperineal y del 41,7% para la vía transrectal. La posibilidad que ofrece el BCN-MRI PM de seleccionar diferentes umbrales de riesgo lo convierte en una herramienta flexible y adaptativa, capaz de ajustarse tanto a distintas vías de abordaje como a diversos entornos clínicos (223). De hecho, el umbral requerido para alcanzar una sensibilidad del 95% fue más alto en la vía transperineal, lo que subraya su capacidad de individualización según la técnica empleada, constituyendo una ventaja relevante para su aplicación práctica.

Finalmente, el BCN-MRI PM ha sido validado satisfactoriamente en una cohorte de varones con sospecha de PCa evaluados mediante el PI-RADS v 2.1 y sometidos a biopsia transperineal con un protocolo que incluyó un mapeo con cilindros obtenidos cada 0.5 mm de las lesiones sospechosas y sus áreas perilesionales, además de una biopsia sistemática de 12 cilindros. En este contexto técnico más exigente, se observó una tasa de detección global de csPCa del 58,3%, muy superior a la registrada en la cohorte de desarrollo (36,9%) y en la validación externa inicial (40,8%). A pesar de las diferencias entre las cohortes respecto a la edad, niveles séricos de PSA, volumen prostático, hallazgos en el tacto rectal, proporción de pacientes con biopsia previa negativa y distribución según de las categorías PI-RADS, el modelo mantuvo un rendimiento discriminativo del csPCa robusto mostrando un AUC de 0.862, comparable o incluso superior al observado en validaciones previas (225-227). Al analizar los resultados por categoría PI-RADS según la versión 2.1, el rendimiento del modelo se confirma como clínicamente útil. En pacientes con PI-RADS 3, la tasa de detección de csPCa alcanzó el 33%, en comparación con el 16% (IC 95%: 7–27) reportado en el metaanálisis de Oerther et al. (224). En las categorías PI-RADS 4 y 5, las tasas de detección fueron del 80% y 87,4%, respectivamente, que fueron superiores al 59% y 85%, reportados previamente. Estos hallazgos refuerzan la capacidad del BCN-MRI PM para identificar correctamente

a los varones con mayor riesgo de csPCa, incluso bajo condiciones técnicas de incorporación reciente y escenarios clínicos de mayor complejidad. El BCN-MRI PM permitió establecer umbrales de riesgo específicos según la categoría PI-RADS. En varones con PI-RADS 2, un umbral del 11% permitió evitar el 78,1% de las biopsias sin dejar de identificar ningún csPCa. En PI-RADS 3, se logró evitar el 40% de las biopsias utilizando un umbral del 10%, con una pérdida diagnóstica limitada (3% del total de csPCa). En cambio, en PI-RADS 4 y 5 no se identificaron umbrales clínicamente seguros que permitieran evitar la biopsia sin riesgo de omitir casos con csPCa. Las curvas de decisión clínica confirmaron que el BCN-MRI PM proporciona un beneficio neto a partir de umbrales de riesgo cercanos al 12%. Además, al aplicar el umbral que determinó del 95% de sensibilidad, fue posible evitar el 24,9% de biopsias sin comprometer la detección de csPCa, lo cual representa una mejoría respecto al 23,7% alcanzado en la validación inicial (163). Estos resultados sugieren que el BCN-MRI PM conserva su eficacia diagnóstica en contexto en el que se utiliza la v 2.1 del PI-RADS y una biopsia por mapeo en un protocolo de biopsia umbra-penumbra con abordajes transperineal.

Limitaciones del proyecto

Este enfoque escalonado basado en modelos de riesgo ha demostrado ser más eficiente que esquemas previos, como el propuesto por Remmers et al., que utiliza la aplicación secuencial de la calculadora de riesgo de Rotterdam (228). Sin embargo, es fundamental reconocer las limitaciones de la validación realizada. En primer lugar, la definición de csPCa se basa en los resultados de la biopsia, los cuales pueden subestimar el verdadero grado tumoral. Además, la naturaleza multicéntrica del estudio podría haber introducido cierta variabilidad entre las distintas series, incluyendo diferencias en la calidad de las imágenes de resonancia magnética empleadas.

Nuestro proyecto, a pesar de haberse llevado a cabo sobre una amplia cohorte y multicéntrica de más de 4.000 varones con sospecha de PCa, evaluados en el marco del programa catalán de diagnóstico precoz de csPCa, presenta limitaciones que impiden clasificar sus hallazgos con un nivel de evidencia tipo I (229). No se realizó una asignación aleatoria, lo que implica una posible influencia de variables confusoras. Para mitigar este sesgo, en algunos de los análisis requirieron de grupos pareados.

Si bien los 10 centros participantes aplicaron criterios homogéneos de sospecha clínica de PCa, existieron divergencias en sus protocolos de diagnóstico. Estas diferencias, sin embargo, fueron aprovechadas como una oportunidad para efectuar comparaciones entre estrategias diagnósticas. En todos los casos se empleó una definición consensuada de csPCa, definida por un ISUP grupo de grado igual o superior a 2. Aun así, es ampliamente conocido que la valoración del ISUP-GG en la biopsia puede no reflejar adecuadamente la agresividad real del tumor, con tasas relevantes de infragradación cuando se analiza la glándula prostática completa tras una prostatectomía radical.

Por último, cabe señalar que los modelos predictivos enfrentan el desafío permanente de adaptarse a los cambios en las características poblacionales y a las modificaciones diagnósticas. Esta necesidad de actualización continua limita su aplicabilidad universal, especialmente en contextos clínicos para los cuales no han sido específicamente validados. La imposibilidad actual de adaptar los modelos predictivos en redes federadas en tiempo real constituye una restricción importante para su uso amplio y sostenido a pesar de su indudable utilidad clínica.

Entre las limitaciones de esta tesis debe considerarse que la mayoría de los estudios incluidos presentan un diseño observacional, lo que limita la capacidad para establecer relaciones causales definitivas. Asimismo, la naturaleza multicéntrica de gran parte de las cohortes analizadas introduce una heterogeneidad inherente relacionada con la selección de pacientes, la interpretación de la resonancia magnética, las plataformas de fusión utilizadas y las técnicas de biopsia empleadas. Por otra parte, la estrategia diagnóstica propuesta depende en gran medida de la experiencia radiológica y de la disponibilidad de recursos tecnológicos específicos, especialmente en lo referente a la interpretación experta de la resonancia magnética prostática y a la realización de biopsias transperineales dirigidas mediante protocolos de saturación. En consecuencia, la extrapolación de estos resultados a centros con menor experiencia o diferente infraestructura tecnológica debe realizarse con cautela. No obstante, la consistencia de los hallazgos observados en distintos escenarios clínicos y cohortes de pacientes respalda la solidez de las conclusiones alcanzadas.

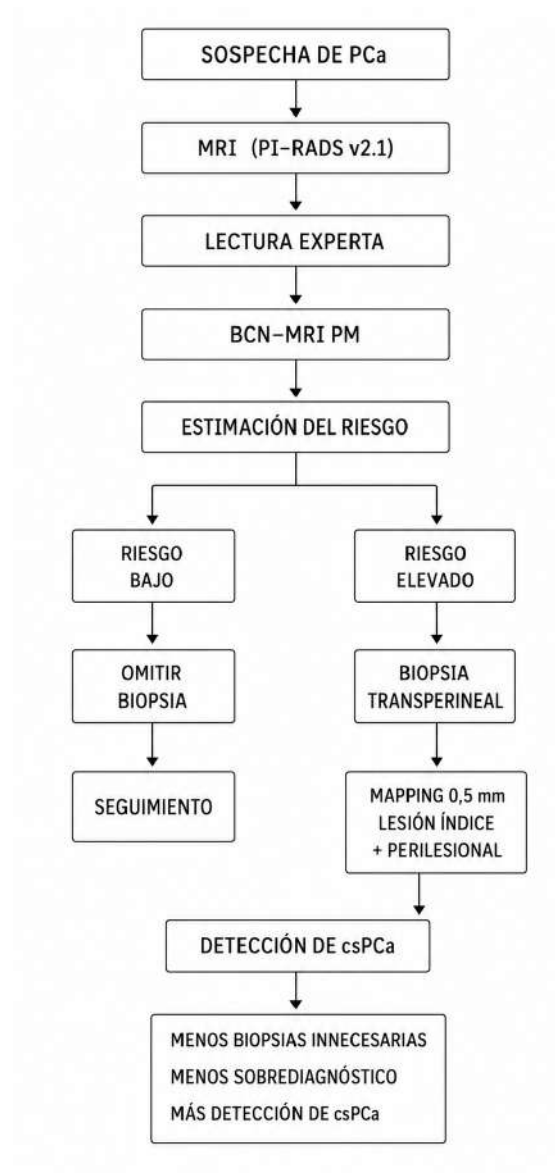


Figura 5. Estrategia integrada propuesta para la optimización del diagnóstico precoz del cáncer de próstata clínicamente significativo.

8. CONCLUSIONES

1. La lectura experta de la MRI mejora la clasificación de las lesiones evaluadas con el PI-RADS v 2.1 permitiendo reducir el número de biopsias prostáticas innecesarias sin comprometer la detección del csPCa.
2. La biopsia prostática sistemática tiene un valor residual cuando se utiliza un modelo predictivo específico, desarrollado a partir de la edad, volumen prostático, potencia de la MRI, categoría del PI-RADS, técnica de fusión de imágenes y vía de abordaje de la biopsia.
3. El abordaje transperineal para realizar la biopsia prostática mejora la detección del csPCa respecto de la vía transrectal, especialmente en localizaciones anterior y apical.
4. El protocolo de biopsia por saturación mediante *mapping* cada 0.5 mm, dirigido a las lesiones sospechosas, incluida la lesión índice y sus áreas perilesionales, mejora la detección del csPCa en comparación con el protocolo estándar basado en la obtención de dos a cuatro cilindros por lesión. Además, permite omitir la biopsia del resto de las lesiones sospechosas y la biopsia sistemática, con una pérdida diagnóstica de csPCa inferior al 5%, y demuestra una mayor eficiencia global que el protocolo convencional recomendado.
5. La revisión sistemática de la literatura, realizada para evaluar las plataformas que permiten realizar biopsias por fusión de imágenes MRI-TRUS por vía transperineal, sugiere mayor eficacia clínica de aquellas que utilizan registro de imagen rígido frente a las que utilizan registro elástico. La complementariedad de las biopsias sistemáticas se sugiere en todas las plataformas analizadas.
6. El BCN-MRI PM ha sido validado satisfactoriamente en pacientes con sospecha de PCa sometidos a tratamiento con 5-ARI, cuando se utiliza el PI-RADS v 2.1, la vía de abordaje transperineal, y un protocolo de biopsias dirigidas mediante *mapping* cada 0.5 mm de lesiones sospechosas y áreas perilesionales.

9. LÍNEAS DE FUTURO

Esta tesis doctoral se enmarca en la línea de investigación en cáncer de próstata del Grupo de Investigación en Urología del Instituto de Investigación Vall d'Hebron (VHIR), donde desde hace más de una década se desarrollan proyectos sobre el diagnóstico precoz del csPCa.

Hasta el momento, se ha recibido financiación del Instituto de Salud Carlos III y co-financiación por el Fondo Europeo para el Desarrollo Regional “Un camino para hacer Europa” (PI20/01666). Red Federada para Acelerar la Aplicación de la Inteligencia Artificial en el Sistema Sanitario Español (TARTAGLIA), Ministerio de Asuntos Económicos y Transformación Digital (MIA. 2021.M02.0005). Federated Learning and mUlti-party computation Techniques for prostatE cancer (FLUTE), European Commission Horizon Europe (HORIZON-HLTH-2022-IND-13-02-101095382).

A partir de estos proyectos ya se han presentado dos tesis doctorales y otras dos están en desarrollo. A partir de los hallazgos de nuestro proyecto de tesis doctoral, se plantean las siguientes líneas de futuro:

1. Validación de la integración de los aspectos metodológicos analizados en nuestra tesis para optimizar el diagnóstico precoz del csPCa. Idealmente, se requerirá la realización de un ensayo clínico prospectivo, randomizado y multicéntrico entre centros que integren los avances de nuestro estudio (grupo estudio) y otros centros donde no estén integrados estos avances (grupo control).
2. Desarrollo de una validación in situ y en tiempo real del BCN-MRI PM. Los modelos predictivos actuales, basados en regresión logística, ofrecen predicciones estáticas aplicables únicamente a las cohortes de desarrollo y requieren validaciones externas complejas en cada escenario nuevo donde vayan a implementarse. La integración de algoritmos de aprendizaje automático en redes federadas representa una solución innovadora que permitiría retroalimentar localmente el modelo con nuevos datos generados en cada centro participante, posibilitando una evolución diferenciada del modelo en cada nodo de la red y validaciones automáticas, dinámicas y descentralizadas. La utilización de algoritmos de aprendizaje automático en el contexto de redes federadas debe permitir la retroalimentación local del algoritmo con nuevos casos en la red. A través de esta retroalimentación específica el modelo tendrá una diferente evolución, en cada lugar, validándose en cada uno de los nodos de participación en la red federada.

3. Comparación entre la regresión logística y algoritmos de aprendizaje automático en el desarrollo de modelos predictivos que no utilizan megadatos. Se comparará la efectividad clínica del BCN-MRI PM desarrollado mediante algoritmos de aprendizaje regresión logística tradicional. Este análisis permitirá establecer si la complejidad adicional de los modelos no lineales se traduce en un beneficio clínico real.
4. Definir la aportación del análisis radiómico de las MRI prostáticas respecto de la clasificación PI-RADS v 2.1. Si se confirma la superioridad de la radiómica respecto del PI-RADS (establecido visualmente por radiólogos) el BCN-MRI PM, ahora sí debería desarrollarse a través de un algoritmo aprendizaje automático ya que el análisis de texturas de la MRI reportará un conjunto de *bigdata* no evaluable mediante regresión logística. Será necesario también analizar si el modelo radiómico se complementa con el PI-RADS y mejora al considerar variable clínicas.
5. Respecto de la evaluación de la agresividad tumoral del PCa y la definición biológica del csPCa, los análisis multiómicos deberían reportar datos para mejorar su definición actual, basada en la clasificación del grado de diferenciación glandular, descrito por Gleason en 1974.
6. Definir un nuevo modelo organizado de riesgo que permita mejorar el árbol de decisiones basado la secuencia del BCN-PM 1 y 2, a través de algoritmos de inteligencia artificial para que integren los megadatos procedentes de los análisis radiómicos y multiómicos que definan el csPCa.
7. Definir el protocolo más eficaz y menos agresivo de biopsia prostática. En una perspectiva de futuro prevemos que diagnóstico precoz del PCa y su agresividad puedan establecerse a través de la imagen ($\text{Ga}^{68}\text{PSMA-PET-MRI}$) y datos clínicos analizados mediante inteligencia artificial sin ser necesaria la biopsia prostática.
8. Las futuras líneas de investigación deberán centrarse en la validación prospectiva de la estrategia diagnóstica integrada propuesta en esta tesis dentro de programas asistenciales reales, evaluando su impacto sobre la toma de decisiones clínicas y los resultados oncológicos. Asimismo, serán necesarios estudios de coste-efectividad que permitan determinar el beneficio económico derivado de la utilización de modelos predictivos basados en MRI, la reducción de biopsias innecesarias y la optimización de los recursos diagnósticos. Del mismo modo, resultará fundamental realizar validaciones externas internacionales que confirmen la reproducibilidad de estos hallazgos en diferentes

sistemas sanitarios y poblaciones. Finalmente, se precisan estudios con seguimiento a largo plazo de aquellos pacientes en los que el BCN-MRI PM recomiende la omisión de la biopsia prostática, con el objetivo de confirmar la seguridad oncológica de esta estrategia.

10. BIBLIOGRAFÍA

1. Bray F, Laversanne M, Sung H, Ferlat J, Siegel R, Jemal A et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024; 74:229-263.
2. Haas GP, Delongchamps N, Brawley OW, Wang CY, de la Roza G. The Worldwide Epidemiology of Prostate Cancer: Perspectives from Autopsy Studies. *Can J Urol.* 2008; 15:3866.
3. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol.* 2012; 61:1079-1092.
4. Culp MBB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. *Eur Urol.* 2020; 77:38–52.
5. Rawla P. Epidemiology of Prostate Cancer. *World J Oncol.* 2019; 10:63–89.
6. SEOM: Sociedad Española de Oncología Médica. El cáncer en cifras 2023.
7. Bell KJL, del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *Int J Cancer.* 2015; 137:1749–1757.
8. Hemminki K. Familial risk and familial survival in prostate cancer. *World J Urol.* 2012; 30:143-148.
9. Beebe-Dimmer JL, Kapron AL, Fraser AM, Smith KR, Cooney KA. Risk of Prostate Cancer Associated With Familial and Hereditary Cancer Syndromes. *J Clin Oncol.* 2020; 38:1807-1813.
10. al Olama AA, Dadaev T, Hazelett DJ, Li Q, Leongamornlert D, Saunders EJ, et al. Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans. *Hum Mol Genet.* 2015; 24:5589–5602.
11. Pritchard CC, Mateo J, Walsh MF, de Sarkar N, Abida W, Beltran H, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *NEJM.* 2016; 375:443-453.
12. Giri VN, Hegarty SE, Hyatt C, O’Leary E, Garcia J, Knudsen KE, et al. Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. *Prostate.* 2019; 79:333–339.

13. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of Dutasteride on the Risk of Prostate Cancer. *NEJM*. 2010; 362:1192–1202.
14. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. *NEJM*. 2003; 349:215–224.
15. Hu X, Wang YH, Yang ZQ, Shao YX, Yang WX, Li X. Association of 5- alpha-reductase inhibitor and prostate cancer incidence and mortality: a meta-analysis. *Transl Androl Urol*. 2020; 9:2519–2532.
16. Knijnik PG, Brum PW, Cachoeira ET, Paludo A de O, Gorgen ARH, Burtet LM, et al. The impact of 5-alpha-reductase inhibitors on mortality in a prostate cancer chemoprevention setting: a meta-analysis. *World J Urol*. 2021; 39:365–376.
17. Haider A, Zitzmann M, Doros G, Isbarn H, Hammerer P, Yassin A. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. *J Urol*. 2015; 193:80–86.
18. Watts EL, Appleby PN, Perez-Cornago A, Bueno-de-Mesquita HB, Chan JM, Chen C, et al. Low Free Testosterone and Prostate Cancer Risk: A Collaborative Analysis of 20 Prospective Studies. *Eur Urol*. 2018; 74:585–594.
19. Carthon B, Sibold HC, Blee S, D. Pentz R. Prostate Cancer: Community Education and Disparities in Diagnosis and Treatment. *Oncologist*. 2021; 26:537–548.
20. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. *Clin Epidemiol*. 2012; 4:1-11.
21. Hugosson J, Roobol MJ, Månsson M, Tammela TLJ, Zappa M, Nelen V, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. *Eur Urol*. 2019; 76:43–51.
22. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur Urol*. 2021; 79:263–282.
23. Hara M, Koyanagi Y, Inoue T, Fukuyama T. Some physico-chemical characteristics of “seminoprotein”, an antigenic component specific for human seminal plasma. Forensic immunological study of body fluids and secretion. VII. *Nihon Hoigaku Zasshi*. 1971; 25:322–324.

24. Yousef GM, Diamandis EP. The new human tissue kallikrein gene family: structure, function, and association to disease. *Endocr Rev.* 2001; 22:184-204.
25. Digby M, Zhang XY, Richards RI. Human prostate specific antigen (PSA) gene: structure and linkage to the kallikrein-like gene, hGK-1. *Nucleic Acids Res.* 1989; 17:2137.
26. Henttu P, Liao SS, Vihko P. Androgens up-regulate the human prostate- specific antigen messenger ribonucleic acid (mRNA), but down-regulate the prostatic acid phosphatase mRNA in the LNCaP cell line. *Endocrinology.* 1992; 130:766-772.
27. Wang MC, Papsidero LD, Kuriyama M, Valenzuela LA, Murphy GP, Chu TM. Prostate antigen: a new potential marker for prostatic cancer. *Prostate.* 1981; 2:89-96.
28. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate. *NEJM.* 1987; 317:909–916.
29. Semonjow A, Brandt B, Oberpenning F, Roth S, Hertle L. Discordance of assay methods creates pitfalls for the interpretation of prostate-specific antigen values. Discordance of assay methods creates pitfalls for the interpretation of prostate-specific antigen values. *Prostate Suppl.* 1996; 16:3–16.
30. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter. *NEJM.* 2004; 350:2239–2246.
31. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA guideline. *J Urol.* 2013; 190:419–426.
32. Vickers AJ, Ulmert D, Sjoberg DD, Bennette CJ, Bjork T, Gerdtsson A, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long-term risk of metastasis: case-control study. *BMJ.* 2013; 346:2023–2023.
33. Gelfond J, Choate K, Ankerst DP, Hernandez J, Leach RJ, Thompson IM. Intermediate-Term Risk of Prostate Cancer is Directly Related to Baseline Prostate Specific Antigen: Implications for Reducing the Burden of Prostate Specific Antigen Screening. *J Urol.* 2015; 194:46–51.
34. Stephan C, Lein M, Jung K, Schnorr D, Loening SA. The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients

- with prostate carcinoma and benign prostate hyperplasia. *Cancer*. 1997; 79:104–109.
35. Huang Y, Li ZZ, Huang YL, Song HJ, Wang YJ. Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10 ng/mL. *Medicine*. 2018; 97:e0249.
 36. Morote J, Campistol M, Triquell M, Celma A, Regis L, de Torres I, et al. Improving the Early Detection of Clinically Significant Prostate Cancer in Men in the Challenging Prostate Imaging-Reporting and Data System 3 Category. *Eur Urol Open Sci*. 2022; 37:38–44.
 37. Moyer VA, U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012; 157:120-134.
 38. Kelly SP, Anderson WF, Rosenberg PS, Cook MB. Past, Current, and Future Incidence Rates and Burden of Metastatic Prostate Cancer in the United States. *Eur Urol Focus*. 2018; 4:121–127.
 39. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019; 69:7–34.
 40. Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018; 319:1901-1913.
 41. Májek O, Babjuk M, Roobol MJ, Bratt O, Van Poppel H, Zachoal R, et al. How to follow the new EU Council recommendation and improve prostate cancer early detection: the Prostaforum 2022 declaration. *Eur Urol Open Sci*. 2023; 53:106–108.
 42. Frånlund M, Månsson M, Godtman RA, Aus G, Holmberg E, Hugosson J, et al. Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial. *J Urol*. 2022; 208:292-300.
 43. Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology*. 1993; 42:365–374.
 44. Naji L, Randhawa H, Sohani Z, Dennis B, Lautenbach D, Kavanagh O, et al. Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A

- Systematic Review and Meta-Analysis. *The Annals of Family Medicine*. 2018; 16:149–154.
45. Gosselaar C, Roobol MJ, Roemeling S, Schröder FH. The Role of the Digital Rectal Examination in Subsequent Screening Visits in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. *Eur Urol*. 2008; 54:581–588.
 46. Prebay ZJ, Medeiros R, Doolittle J, Langenstroer P, Jacobsohn K, See WA, et al. The prognostic value of digital rectal exam for the existence of advanced pathologic features after prostatectomy. *Prostate*. 2021; 81:1064– 1070.
 47. Berlin A, Brierley J, Cornford P, Chung P, Giannopoulos E, Mason M, et al. TNM Staging of Prostate Cancer: Challenges in Securing a Globally Applicable Classification. *Eur Urol*. 2022; 82:52–53.
 48. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *The Lancet*. 2017; 389:815–822.
 49. Smeenge M, Barentsz J, Cosgrove D, de la Rosette J, de Reijke T, Eggener S, et al. Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel. *BJU Int*. 2012; 110:942–948.
 50. Bratan F, Niaf E, Melodelima C, Chesnais AL, Souchon R, Mège- Lechevallier F, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. *Eur Radiol*. 2013; 23:2019–2029.
 51. Drost FJH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database of Systematic Reviews*. 2019;4: CD012663.
 52. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2. *Eur Urol*. 2016; 69:16–40.
 53. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of

- Prostate Imaging Reporting and Data System Version 2. *Eur Urol.* 2019; 76:340–351.
54. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al. Magnetic Resonance Imaging for the Detection, Localisation, and of Prostate Cancer: Recommendations from a European Consensus Meeting. *Eur Urol.* 2011; 59:477–494.
 55. Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. *Radiology.* 2019; 292:464–474.
 56. Kang HC, Jo N, Bamashmos AS, Ahmed M, Sun J, Ward, J, et al. Accuracy of prostate magnetic resonance imaging: reader experience matters. *Eur Urol Open Sci.* 2021; 27:53–60.
 57. Goldberg H, Ahmad AE, Chandrasekar T, Klotz L, Emberton M, Haider MA, et al. Comparison of Magnetic Resonance Imaging and Transrectal Ultrasound Informed Prostate Biopsy for Prostate Cancer Diagnosis in Biopsy Naïve Men: A Systematic Review and Meta-Analysis. *J Urol.* 2020; 203:1085–1093.
 58. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège- Lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol.* 2019; 20:100–109.
 59. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *Eur Urol.* 2019; 75:570–578.
 60. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *NEJM.* 2018; 378:1767–1777.
 61. Panebianco V, Barchetti G, Simone G, Del Monte M, Ciardi A, Grompone MD, et al. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? *Eur Urol.* 2018; 74:48–54.

62. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. 2021; 79:243–262.
63. Porter KK, King A, Galgano SJ, Sherrer RL, Gordetsky JB, Rais-Bahrami S. Financial implications of biparametric prostate MRI. *Prostate Cancer Prostatic Dis*. 2020; 23:88–93.
64. Haghighi M, Shah S, Taneja SS, Rosenkrantz AB. Prostate Cancer. *J Comput Assist Tomogr*. 2013; 37:980–988.
65. Tan CH, Hobbs BP, Wei W, Kundra V. Dynamic contrast-enhanced MRI for the detection of prostate cancer: meta-analysis. *AJR*. 2015; 204:439-448.
66. Greer MD, Shih JH, Lay N, Barrett T, Kayat Bittencourt L, Borofsky S, et al. Validation of the Dominant Sequence Paradigm and Role of Dynamic Contrast-enhanced Imaging in PI-RADS Version 2. *Radiology*. 2017; 285:859–869.
67. Kang Z, Min X, Weinreb J, Li Q, Feng Z, Wang L. Abbreviated Biparametric Versus Standard Multiparametric MRI for Diagnosis of Prostate Cancer: A Systematic Review and Meta-Analysis. *AJR*. 2019; 212:357-365.
68. Gleason DF, Mellinger GT, Veterans Administration Cooperative Urological Research Group. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. 1974. *J Urol*. 2002; 167:953–959.
69. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005; 29:1228-1242.
70. Harnden P, Shelley MD, Coles B, Staffurth J, Mason MD. Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. *Lancet Oncol*. 2007; 8:411–419.
71. Saeter T, Vlatkovic L, Waaler G, Servoll E, Nesland JM, Axcrona K, et al. Intraductal Carcinoma of the Prostate on Diagnostic Needle Biopsy Predicts Prostate Cancer Mortality: A Population-Based Study. *Prostate*. 2017; 77:859–865.

72. Van der Kwast T, Bubendorf L, Mazerolles C, Raspollini MR, Van Leenders GJ, Pihl CG, et al. Guidelines on processing and reporting of prostate biopsies: the 2013 update of the pathology committee of the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Virchows Archiv*. 2013; 463:367–377.
73. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*. 2016; 40:244-252.
74. van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2020; 44:87–99.
75. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic Value of Systematic Biopsy Methods in the Investigation of Prostate Cancer: A Systematic Review. *J Urol*. 2006; 175:1605–1612.
76. Kenigsberg AP, Renson A, Rosenkrantz AB, Huang R, Wysock JS, Taneja SS, et al. Optimizing the Number of Cores Targeted During Prostate Magnetic Resonance Imaging Fusion Target Biopsy. *Eur Urol Oncol*. 2018; 1:418–425.
77. Arsov C, Rabenalt R, Blondin D, Quentin M, Hiester A, Godehardt E, et al. Prospective Randomized Trial Comparing Magnetic Resonance Imaging (MRI)-guided In-bore Biopsy to MRI-ultrasound Fusion and Transrectal Ultrasound-guided Prostate Biopsy in Patients with Prior Negative Biopsies. *Eur Urol*. 2015; 68:713–720.
78. Watts KL, Frechette L, Muller B, Ilinksy D, Kovac E, Aboumohamed A, et al. Systematic review and meta-analysis comparing cognitive vs. image-guided fusion prostate biopsy for the detection of prostate cancer. *Urol Oncol*. 2020; 38:734. e19-734.e25.
79. Wegelin O, van Melick HHE, Hooft L, Bosch JLHR, Reitsma HB, Barentsz JO, et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? *Eur Urol*. 2017; 71:517–531.

80. Tu X, Liu Z, Chang T, Qiu S, Xu H, Bao Y, et al. Transperineal Magnetic Resonance Imaging–Targeted Biopsy May Perform Better Than Transrectal Route in the Detection of Clinically Significant Prostate Cancer: Systematic Review and Meta-analysis. *Clin Genitourin Cancer*. 2019; 17:860–870.
81. Pradere B, Veeratterapillay R, Dimitropoulos K, Yuan Y, Omar MI, MacLennan S, et al. Nonantibiotic Strategies for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta-Analysis. *J Urol*. 2021; 205:653–663.
82. Bennett H, Roberts MJ, Doi S, Gardiner R. The global burden of major infectious complications following prostate biopsy. *Epidemiol Infect*. 2016; 144:1784–1791.
83. Pilatz A, Dimitropoulos K, Veeratterapillay R, Yuan Y, Omar MI, MacLennan S, et al. Antibiotic Prophylaxis for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta- Analysis. *J Urol*. 2020; 204:224–230.
84. Jue JS, Rastinehad AR. MRI Fusion Transperineal Prostate Biopsy Instructions and Troubleshooting. *J Endourol*. 2021; 35:2-6.
85. Ippoliti S, Fletcher P, Orecchia L, Miano R, Kastner C, Barrett T. Optimal biopsy approach for detection of clinically significant prostate cancer. *Br J Radiol*. 2022; 95:20210413.
86. Görtz M, Nyarangi-Dix JN, Pursche L, Schütz V, Reimold P, Radtke JP, et al. Impact of Surgeon's Experience in Rigid versus Elastic MRI/TRUS-Fusion Biopsy to Detect Significant Prostate Cancer Using Targeted and Systematic Cores. *Cancers (Basel)*. 2022; 14:886.
87. Venderink W, de Rooij M, Sedelaar JPM, Huisman HJ, Fütterer JJ. Elastic Versus Rigid Image Registration in Magnetic Resonance Imaging-transrectal Ultrasound Fusion Prostate Biopsy: A Systematic Review and Meta-analysis. *Eur Urol Focus*. 2018; 4:219-227.
88. Franks LM. Latent carcinoma of the prostate. *J Pathol Bacteriol*. 1954; 68:603–616.
89. Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, Epstein JI. Do adenocarcinomas of the prostate with Gleason score (GS) ≤ 6 have the potential to metastasize to lymph nodes? *Am J Surg Pathol*. 2012; 36:1346– 1352.

90. Anderson BB, Oberlin DT, Razmaria AA, Choy B, Zagaja GP, Shalhav AL, et al. Extraprostatic Extension Is Extremely Rare for Contemporary Gleason Score 6 Prostate Cancer. *Eur Urol*. 2017; 72:455–460.
91. Sauter G, Clauditz T, Steurer S, Wittmer C, Büscheck F, Krech T, et al. Integrating Tertiary Gleason 5 Patterns into Quantitative Gleason Grading in Prostate Biopsies and Prostatectomy Specimens. *Eur Urol*. 2018; 73:674–683.
92. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecomnet E, Freeman A, et al. Characterizing Clinically Significant Prostate Cancer Using Template Prostate Mapping Biopsy. *J Urol*. 2011; 186:458–464.
93. Matoso A, Epstein JI. Defining clinically significant prostate cancer on the basis of pathological findings. *Histopathology*. 2019; 74:135–145.
94. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019; 17:479-505.
95. Jo JK, Hong SK, Byun SS, Lee SE, Lee S, Oh JJ. Prognostic Significance of the Disparity Between Biopsy and Pathologic Gleason Score After Radical Prostatectomy in Clinical Candidates for Active Surveillance According to the Royal Marsden Criteria. *Clin Genitourin Cancer*. 2016;14:e329-333.
96. Loeb S, Vonesh EF, Metter EJ, Carter HB, Gann PH, Catalona WJ. What Is the True Number Needed to Screen and Treat to Save a Life with Prostate- Specific Antigen Testing? *J Clin Oncol*. 2011; 29:464–467.
97. Klotz L. Active surveillance for prostate cancer: for whom? *J Clin Oncol*. 2005; 23:8165–8169.
98. Bruinsma SM, Roobol MJ, Carroll PR, Klotz L, Pickles T, Moore CM, et al. Expert consensus document: Semantics in active surveillance for men with localized prostate cancer - results of a modified Delphi consensus procedure. *Nat Rev Urol*. 2017; 14:312–322.
99. Albertson PC. Editorial comment on: Insignificant prostate cancer and active surveillance: from definition to clinical implications. *Eur Urol*. 2009; 55:1331–1332.
100. Selvadurai ED, Singhera M, Thomas K, Mohammed K, Woode-Amissah R, Horwich A, et al. Medium-term Outcomes of Active Surveillance for Localised Prostate Cancer. *Eur Urol*. 2013; 64:981–987.

101. Musunuru HB, Yamamoto T, Klotz L, Ghanem G, Mamedov A, Sethukavalan P, et al. Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. *J Urol*. 2016; 196:1651–1658.
102. Dall’Era MA, Konety BR, Cowan JE, Shinohara K, Stauf F, Cooperberg MR, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*. 2008; 112:2664–2670.
103. Komisarenko M, Martin LJ, Finelli A. Active surveillance review: contemporary selection criteria, follow-up, compliance and outcomes. *Transl Androl Urol*. 2018; 7:243–255.
104. Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al. Active Surveillance for Low-Risk Prostate Cancer Worldwide: The PRIAS Study. *Eur Urol*. 2013; 63:597–603.
105. Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. *BJU Int*. 2008; 101:165-169.
106. Tosoian JJ, Mamawala M, Epstein JI, Landis P, Wolf S, Trock BJ, et al. Intermediate and Longer-Term Outcomes From a Prospective Active- Surveillance Program for Favorable-Risk Prostate Cancer. *J Clin Oncol*. 2015; 33:3379–3385.
107. Adamy A, Yee DS, Matsushita K, Maschino A, Cronin A, Vickers A, et al. Role of Prostate Specific Antigen and Immediate Confirmatory Biopsy in Predicting Progression During Active Surveillance for Low-Risk Prostate Cancer. *J Urol*. 2011; 185:477–482.
108. Lam TBL, MacLennan S, Willemse PPM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). *Eur Urol*. 2019; 76:790–813.
109. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. *NEJM*. 2018; 379:2319–2329.
110. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *NEJM*. 2016; 375:1415–1424.

111. Bryant RJ, Oxley J, Young GJ, Lane JA, Metcalfe C, Davis M, et al. The ProtecT trial: analysis of the patient cohort, baseline risk stratification and disease progression. *BJU Int.* 2020; 125:506–514.
112. Mazzone E, Stabile A, Pellegrino F, Basile G, Cignoli D, Cirulli GO, et al. Positive Predictive Value of Prostate Imaging Reporting and Data System Version 2 for the Detection of Clinically Significant Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol Oncol.* 2021; 4:697–713.
113. Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *J Urol.* 1992; 147:815–816.
114. Lujan M, Paez A, Llanes L, Miravalles E, Berenguer A. Prostate specific antigen density. Is there a role for this parameter when screening for prostate cancer? *Prostate Cancer Prostatic Dis.* 2001; 4:146–149.
115. Omri N, Kamil M, Alexander K, Alexander K, Edmond S, Ariel Z, et al. Association between PSA density and pathologically significant prostate cancer: The impact of prostate volume. *Prostate.* 2020; 80:1444–1449.
116. Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. *Prostate Cancer Prostatic Dis.* 2018; 21:57–63.
117. Yusim I, Krenawi M, Mazor E, Novack V, Mabjeesh NJ. The use of prostate specific antigen density to predict clinically significant prostate cancer. *Sci Rep.* 2020; 10:20015.
118. Hansen NL, Barrett T, Koo B, Doble A, Gnanapragasam V, Warren A, et al. The influence of prostate-specific antigen density on positive and negative predictive values of multiparametric magnetic resonance imaging to detect Gleason score 7–10 prostate cancer in a repeat biopsy setting. *BJU Int.* 2017; 119:724–730.
119. Washino S, Okochi T, Saito K, Konishi T, Hirai M, Kobayashi Y, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naïve patients. *BJU Int.* 2017; 119:225–233.
120. Pagniez MA, Kasivisvanathan V, Puech P, Drumez E, Villers A, Olivier J. Predictive Factors of Missed Clinically Significant Prostate Cancers in Men with

- Negative Magnetic Resonance Imaging: A Systematic Review and Meta-Analysis. *J Urol*. 2020; 204:24–32.
121. Morote J, Celma A, Diaz F, Regis L, Roche S, Mast R, et al. Prostatic-specific antigen density behavior according to multiparametric magnetic resonance imaging result. *Urol Oncol*. 2020; 38:410–417.
 122. Schoots IG, Padhani AR. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation. *BJU Int*. 2021; 127:175–178.
 123. Roobol MJ, Schröder FH, Hugosson J, Jones JS, Kattan MW, Klein EA, et al. Importance of prostate volume in the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators: results from the prostate biopsy collaborative group. *World J Urol*. 2012; 30:149–155.
 124. Morote J, Triquell M, Campistol M, Abascal JM, Servian P, Trilla E. Stratifying the initial prostate cancer suspicion to avoid magnetic resonance exams by sequencing men according to serum prostate-specific antigen, digital rectal examination and the prostate-specific antigen density based on digital rectal prostate volume category. *BJUI Compass*. 2023; 4:266–268.
 125. Schoots IG, Roobol MJ. Multivariate risk prediction tools including MRI for individualized biopsy decision in prostate cancer diagnosis: current status and future directions. *World J Urol*. 2020; 38:517–529.
 126. de la Calle C, Patil D, Wei JT, Scherr DS, Sokoll L, Chan DW, et al. Multicenter Evaluation of the Prostate Health Index to Detect Aggressive Prostate Cancer in Biopsy Naïve Men. *J Urol*. 2015; 194:65–72.
 127. Zappala SM, Scardino PT, Okrongly D, Linder V, Dong Y. Clinical performance of the 4Kscore Test to predict high-grade prostate cancer at biopsy: A meta-analysis of us and European clinical validation study results. *Rev Urol*. 2017; 19:149–155.
 128. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, et al. A Multicenter Study of [-2] Pro-Prostate Specific Antigen Combined With Prostate Specific Antigen and Free Prostate Specific Antigen for Prostate Cancer Detection in the 2.0 to 10.0 ng/ml Prostate Specific Antigen Range. *J Urol*. 2011; 185:1650–1655.

129. Nordström T, Vickers A, Assel M, Lilja H, Grönberg H, Eklund M. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. *Eur Urol.* 2015; 68:139–146.
130. Campistol M, Triquell M, Regis L, Celma A, Trilla E, Morote J, et al. Relationship between Proclarix and the Aggressiveness of Prostate Cancer. *Mol Diagn Ther.* 2023; 27:487-498.
131. Durand X, Moutereau S, Xylinas E, de la Taille A. Progensa™ PCA3 test for prostate cancer. *Expert Rev Mol Diagn.* 2011; 11:137–144.
132. Gittelman MC, Hertzman B, Bailen J, Williams T, Koziol I, Henderson RJ, et al. PCA3 Molecular Urine Test as a Predictor of Repeat Prostate Biopsy Outcome in Men with Previous Negative Biopsies: A Prospective Multicenter Clinical Study. *J Urol.* 2013; 190:64–69.
133. Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PFA, et al. Clinical Utility of the PCA3 Urine Assay in European Men Scheduled for Repeat Biopsy. *Eur Urol.* 2008; 54:1081–1088.
134. Van Neste L, Hendriks RJ, Dijkstra S, Trooskens G, Cornel EB, Jannink SA, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker–Based Risk Score. *Eur Urol.* 2016; 70:740–748.
135. Hendriks RJ, van der Leest MMG, Israël B, Hannink G, YantiSetiasti A, Cornel EB, et al. Clinical use of the SelectMDx urinary-biomarker test with or without mpMRI in prostate cancer diagnosis: a prospective, multicenter study in biopsy-naïve men. *Prostate Cancer Prostatic Dis.* 2021; 24:1110–1119.
136. Tomlins SA, Aubin SMJ, Siddiqui J, Lonigro RJ, Sefton-Miller L, Miick S, et al. Urine TMPRSS2: ERG fusion transcript stratifies prostate cancer risk in men with elevated serum PSA. *Sci Transl Med.* 2011;3:94ra72.
137. Hessels D, Smit FP, Verhaegh GW, Witjes JA, Cornel EB, Schalken JA. Detection of TMPRSS2-ERG Fusion Transcripts and Prostate Cancer Antigen 3 in Urinary Sediments May Improve Diagnosis of Prostate Cancer. *Clin Can Res.* 2007; 13:5103–5108.
138. Roumiguié M, Ploussard G, Nogueira L, Bruguière E, Meyrignac O, Lesourd M, et al. Independent Evaluation of the Respective Predictive Values for High-Grade Prostate Cancer of Clinical Information and RNA Biomarkers after Upfront MRI and Image-Guided Biopsies. *Cancers (Basel).* 2020; 12:285.

139. James G, Witten D, Hastie T, Tibshirani R. An Introduction to Statistical Learning. Springer New York. 2013.
140. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. Wiley. 2013.
141. Hastie T, Tibshirani R, Friedman J. The Elements of Statistical Learning. Springer New York. 2009.
142. Adam A, Hellig JC, Perera M, Bolton D, Lawrentschuk N. “Prostate Cancer Risk Calculator” mobile applications (Apps): a systematic review and scoring using the validated user version of the Mobile Application Rating Scale (uMARS). *World J Urol.* 2018; 36:565–573.
143. Vickers AJ, Cronin AM, Aus G, Pihl CG, Becker C, Pettersson K, et al. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: Data from the European Randomized Study of Prostate Cancer Screening in Göteborg, Sweden. *BMC Med.* 2008; 6:1–10.
144. Cestari A. Predictive Models in Urology. *Urologia.* 2013; 80:42–45.
145. Roobol MJ, Kerkhof M, Schröder FH, Cuzick J, Sasieni P, Hakama M, et al. Prostate Cancer Mortality Reduction by Prostate-Specific Antigen–Based Screening Adjusted for Nonattendance and Contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol.* 2009; 56:584–591.
146. van Leeuwen PJ, Connolly D, Gavin A, Roobol MJ, Black A, Bangma CH, et al. Prostate cancer mortality in screen and clinically detected prostate cancer: Estimating the screening benefit. *Eur J Cancer.* 2010; 46:377–383.
147. Roobol MJ, Steyerberg EW, Kranse R, Wolters T, van den Bergh RCN, Bangma CH, et al. A Risk-Based Strategy Improves Prostate-Specific Antigen–Driven Detection of Prostate Cancer. *Eur Urol.* 2010; 57:79–85.
148. <https://www.prostatecancer-riskcalculator.com/>.
149. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst.* 2006; 98:529–534.
150. Virtanen A, Gomari M, Kranse R, Stenman UH. Estimation of prostate cancer probability by logistic regression: free and total prostate-specific antigen, digital

- rectal examination, and heredity are significant variables. *Clin Chem.* 1999; 45:987–994.
151. Karakiewicz PI, Benayoun S, Kattan MW, Perrotte P, Valiquette L, Scardino PT, et al. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. *J Urol.* 2005; 173:1930–1934.
 152. Garzotto M, Hudson RG, Peters L, Hsieh YC, Barrera E, Mori M, et al. Predictive modeling for the presence of prostate carcinoma using clinical, laboratory, and ultrasound parameters in patients with prostate specific antigen levels ≤ 10 ng/mL. *Cancer.* 2003; 98:1417–1422.
 153. Ankerst DP, Thompson IM. Merging digital rectal exam, family history, age and prostate-specific antigen to create a decision-making tool. *Arch Ital Urol Androl.* 2006; 78:143–146.
 154. Grönberg H, Eklund M, Picker W, Aly M, Jäderling F, Adolfsson J, et al. Prostate Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric Magnetic Resonance Imaging. *Eur Urol.* 2018; 74:722–728.
 155. Ruffion A, Devonec M, Champetier D, Decaussin-Petrucci M, Rodriguez-Lafrasse C, Paparel P, et al. PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy. *Int J Mol Sci.* 2013; 14:17767–17780.
 156. Verbeek JFM, Bangma CH, Kweldam CF, van der Kwast TH, Kümmerlin IP, van Leenders GJLH, et al. Reducing unnecessary biopsies while detecting clinically significant prostate cancer including cribriform growth with the ERSPC Rotterdam risk calculator and 4Kscore. *Urol Oncol.* 2019; 37:138–144.
 157. Roobol MJ, Vedder MM, Nieboer D, Houlgatte A, Vincendeau S, Lazzeri M, et al. Comparison of Two Prostate Cancer Risk Calculators that Include the Prostate Health Index. *Eur Urol Focus.* 2015; 1:185–190.
 158. Schoots IG, Padhani AR. Personalizing prostate cancer diagnosis with multivariate risk prediction tools: how should prostate MRI be incorporated? *World J Urol.* 2020; 38:531–545.
 159. Van Poppel H, Albrecht T, Basu P, Hogenhout R, Collen S, Roobol M. Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future. *Nat Rev Urol.* 2022; 19:562–572.

160. van Harten MJ, Roobol MJ, van Leeuwen PJ, Willemse PM, van den Bergh RCN. Evolution of European prostate cancer screening protocols and summary of ongoing trials. *BJU Int.* 2024; 134:31-42.
161. Yamashiro JR, de Riese WTW. Any Correlation Between Prostate Volume and Incidence of Prostate Cancer: A Review of Reported Data for the Last Thirty Years. *Res Rep Urol.* 2021; 13:749–757.
162. Roobol MJ, van Vugt HA, Loeb S, Zhu X, Bul M, Bangma CH, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. *Eur Urol.* 2012; 61:577–583.
163. Morote J, Borque-Fernando A, Triquell M, Celma A, Regis L, Trilla E, et al. The Barcelona Predictive Model of Clinically Significant Prostate Cancer. *Cancers (Basel).* 2022 Mar 21; 14:1589.
164. Stabile A, Giganti F, Rosenkrantz AB, Moore C, Gill I, Taneja S, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. *Nat Rev Urol.* 2020; 17:41–61.
165. Giganti F, Kirkham A, Kasivisvanathan V, Papoutsaki M, Punwani S, Emberton M, et al. Understanding PI-QUAL for prostate MRI quality: a practical primer for radiologists. *Insights Imag.* 2021; 12:59.
166. Giganti F, Allen C. Imaging quality and prostate MR: it is time to improve. *Br J Radiol.* 2021; 94:20200934.
167. Epstein JI, Zelefsky MJ, Sjoberg DD, Vickers A, Parwani A, Klein E, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur. Urol.* 2016; 69:428–435.
168. Pickersgill NA, Vetter JM, Raval NS, Andriole G, Ippolito J, Kim E, et al. The accuracy of prostate magnetic resonance imaging interpretation: impact of the individual radiologist and clinical factors. *Urology.* 2019; 127:68–73.
169. Overduin CG, Fütterer JJ, Barentsz JO. MRI-guided biopsy for prostate cancer detection: a systematic review of current clinical results. *Curr Urol Rep.* 2013; 14:209-213.
170. Tamada T, Kido A, Yamamoto A, Takeuchi M, Miyaji Y, Sone T, et al. Comparison of Biparametric and Multiparametric MRI for Clinically Significant Prostate Cancer Detection With PI-RADS Version 2.1. *J Magn Reson Imaging.* 2021; 53:283-291.

171. Stabile A, Sorce G, Barletta F, Cirulli G, Gandaglia G, Briganti A, et al. Impact of prostate MRI central review over the diagnostic performance of MRI-targeted biopsy: should we routinely ask for an expert second opinion? *World J Urol.* 2023; 41:3231–3237.
172. Boschheidgen M, Albers P, Schlemmer HP, Hellms S, Antoch G, Becker N, et al. Multiparametric magnetic resonance imaging in prostate cancer screening at the age of 45 years: results from the first screening round of the PROBASE trial. *Eur Urol.* 2024; 85:105–111.
173. Sonn GA, Fan RE, Ghanouni P, Wang N, Brooks J, Leppert J, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. *Eur Urol Focus.* 2019; 5:592–599.
174. Asif A, Nathan A, Ng A, Emberton M, Deeks J, Moore C, et al. Comparing biparametric to multiparametric MRI in the diagnosis of clinically significant prostate cancer in biopsy-naïve men (PRIME): a prospective, international, multicentre, non-inferiority within-patient, diagnostic yield trial protocol. *BMJ Open.* 2023; 13:070280.
175. Connor MJ, Gorin MA, Eldred-Evans D, Bass EJ, Desai A, Ahmed HU, et al. Landmarks in the evolution of prostate biopsy. *Nat. Rev. Urol.* 2023; 20: 241–258.
176. Thomson A, Li M, Grummet J, Sengupta S. Transperineal prostate biopsy: a review of technique. *Transl Androl Urol.* 2020; 9:3009-3017.
177. Brisbane WG, Priester AM, Ballon J, Kwan L, Delfin MK, Felker ER, et al. Targeted Prostate Biopsy: Umbra, Penumbra, and Value of Perilesional Sampling. *Eur. Urol.* 2022; 82:303–310.
178. Kasivisvanathan V, Stabile A, Neves JB, Giganti F, Valerio M, Shanmugabavan V, et al. Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis. *Eur. Urol.* 2019; 76:284–303.
179. Elwenspoek MMC, Sheppard AL, McInnes MDF, Bryant R, Donovan J, Whiting, P, et al. Comparison of Multiparametric Magnetic Resonance Imaging and Targeted Biopsy with Systematic Biopsy Alone for the Diagnosis of Prostate Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2019; 2:198427.

180. Killock D. Prostate cancer: Improving diagnosis - can MP-MRI fulfil its PROMIS? *Nat Rev Clin Oncol.* 2017; 14:137.
181. Martini A, Kumarasamy S, Tewari AK. MRI-Targeted Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med.* 2018; 379:589.
182. Jayadevan R, Marks LS. Exclusive MRI-targeted biopsy: not so fast. *Lancet Oncol.* 2019; 20:9-10.
183. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, et al. Comparison of Targeted vs. Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. *JAMA Surg.* 2019; 154:811–818.
184. Williams C, Ahdoot M, Daneshvar MA, Hague C, Wilbur AR, Gomella PT, et al. Why Does Magnetic Resonance Imaging-Targeted Biopsy Miss Clinically Significant Cancer. *J. Urol.* 2022; 207:95–107.
185. Zattoni F, Marra G, Kasivisvanathan V, Grummet J, Nandurkar R, Ploussard G, et al. The Detection of Prostate Cancer with Magnetic Resonance Imaging-Targeted Prostate Biopsies is Superior with the Transperineal vs. the Transrectal Approach. A European Association of Urology-Young Academic Urologists Prostate Cancer Working Group Multi-Institutional Study. *J. Urol.* 2022; 208:830–837.
186. Ahmed HU, Kirkham A, Arya M, Illing R, Freeman A, Emberton M, et al. Is it time to consider a role for MRI before prostate biopsy? *Nat. Rev. Clin. Oncol.* 2009; 6:197–206.
187. Chen M, Zhang Q, Zhang C, Zhao X, Marra G, Gao J, et al. Combination of ⁶⁸Ga-PSMA PET/CT and Multiparametric MRI Improves the Detection of Clinically Significant Prostate Cancer: A Lesion-by-Lesion Analysis. *J. Nucl. Med.* 2019; 60:944–949.
188. Hugosson J, Månsson M, Wallström J, Axcrone U, Carlsson SV, Egevad L, et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. *N. Engl. J. Med.* 2022; 387:2126–2137.
189. Grummet J, Gorin MA, Popert R, Royce P, Murphy D, Woo H, et al. "TREXIT 2020": why the time to abandon transrectal prostate biopsy starts now. *Prostate Cancer Prostatic Dis.* 2020; 23:62-65.
190. Koparal M, Sözen T, Karsıyakalı N, Aslan G, Akdoğan B, Şahin B, et al. Comparison of transperineal and transrectal targeted prostate biopsy using

- Mahalanobis distance matching within propensity score caliper method: A multicenter study of Turkish Urooncology Association. *Prostate* 2022; 82:425–432.
191. Hu JC, Assel M, Allaf ME, Ehdaie B, Vickers A, Cohen AJ, et al. Transperineal Versus Transrectal Magnetic Resonance Imaging-targeted and Systematic Prostate Biopsy to Prevent Infectious Complications: The PREVENT Randomized Trial. *Eur. Urol.* 2024; 86:61–68.
 192. Hoeh B, Wenzel M, Humke C, Cano Garcia C, Siech C, Schneider M, et al. Transition from Transrectal to Transperineal MRI-Fusion Prostate Biopsy Does Not Comprise Detection Rates of Clinically Significant Prostate Cancer at a Tertiary Care Center. *Diagnostics* 2024; 14:1184.
 193. Uleri A, Baboudjian M, Tedde A, Gallioli A, Palou J, Long-Depaquit T, et al. Is There an Impact of Transperineal Versus Transrectal Magnetic Resonance Imaging-targeted Biopsy in Clinically Significant Prostate Cancer Detection Rate? A Systematic Review and Meta-analysis. *Eur. Urol. Oncol.* 2023; 6:621–628.
 194. Tewes S, Peters I, Tiemeyer A, Peperhove M, Hartung D, Pertschy S, et al. Evaluation of MRI/Ultrasound Fusion-Guided Prostate Biopsy Using Transrectal and Transperineal Approaches. *Biomed Res Int.* 2017; 2017:2176471.
 195. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: A Prospective Development Study. *Eur Urol.* 2015; 68:927-936.
 196. Kachanov M, Leyh-Bannurah SR, Roberts MJ, Sauer M, Beyersdorff D, Boiko S, et al. Optimizing Combined Magnetic Resonance Imaging (MRI)- Targeted and Systematic Biopsy Strategies: Sparing the Multiparametric MRI-Negative Transitional Zone in Presence of Exclusively Peripheral Multiparametric MRI-Suspect Lesions. *J Urol.* 2022; 207:333-340.
 197. Tschirdewahn S, Wiesenfarth M, Bonekamp D, Püllen L, Reis H, Panic A, et al. Detection of Significant Prostate Cancer Using Target Saturation in Transperineal Magnetic Resonance Imaging/ Transrectal Ultrasonography-fusion Biopsy. *Eur Urol Focus.* 2021; 7:1300-1307.
 198. Lv Z, Wang J, Wang M, Hou H, Song L, Li H, et al. Is it necessary for all patients with suspicious lesions undergo systematic biopsy in the era of MRI-TRUS fusion targeted biopsy? *Int Braz J Urol.* 2023; 49:359-371.

199. Lee AYM, Chen K, Cheng CWS, Ho H, Yuen J, Tay K, et al. Intensive sampling of the umbra and penumbra improves clinically significant prostate cancer detection and reduces risk of grade group upgrading at radical prostatectomy. *World J Urol.* 2023; 41:2265-2271.
200. Porpiglia F, De Luca S, Passera R, De Pascale A, Amparore D, Cattaneo G, et al. Multiparametric Magnetic Resonance/Ultrasound Fusion Prostate Biopsy: Number and Spatial Distribution of Cores for Better Index Tumor Detection and Characterization. *J Urol.* 2017; 198:58-64.
201. Eklund M, Jäderling F, Discacciati A, Bergman M, Carlsson S, Nordström T, et al. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. *N Engl J Med.* 2021; 385:908-920.
202. Rachubinski P, Witt JH, Budäus L, Zinke J, Fangmeyer B, Spieker T, et al. Precision-guidance vs Systematic Sampling: Optimizing Biopsy Assessment of Secondary Prostate Cancer Suspicious Multiparametric Magnetic Resonance Imaging Lesions. *J Urol.* 2022; 208:1203-1213.
203. Petov V, Azilgareeva C, Shpikina A, Morozov A, Krupinov G, Kozlov V, et al. Robot-Assisted Magnetic Resonance Imaging-Targeted versus Systematic Prostate Biopsy; Systematic Review and Meta-Analysis. *Cancers (Basel).* 2023; 15:1181.
204. Marra G, Zhuang J, Beltrami M, Callaris G, Zhao X, Marquis A, et al. Transperineal freehand multiparametric MRI fusion targeted biopsies under local anaesthesia for prostate cancer diagnosis: a multicentre prospective study of 1014 cases. *BJU Int.* 2021; 127:122-130.
205. Porpiglia F, Checcucci E, DE Cillis S, Piramide F, Amparore D, Piana A, et al. A prospective randomized controlled trial comparing target prostate biopsy alone approach vs. target plus standard in naïve patients with positive mpMRI. *Minerva Urol Nephrol.* 2023; 75:31-41.
206. Radtke JP, Schwab C, Wolf MB, Freitag MT, Alt CD, Kesch C, et al. Multiparametric Magnetic Resonance Imaging (MRI) and MRI-Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen. *Eur. Urol.* 2016; 70:846–853.
207. Calio BP, Sidana A, Sugano D, Gaur S, Maruf M, Jain AL, et al. Risk of Upgrading from Prostate Biopsy to Radical Prostatectomy Pathology-Does Saturation Biopsy

- of Index Lesion during Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsy Help. *J. Urol.* 2018; 199:976–982.
208. Hansen NL, Barrett T, Lloyd T, Warren A, Samel C, Bratt O, et al. Optimising the number of cores for magnetic resonance imaging-guided targeted and systematic transperineal prostate biopsy. *BJU Int.* 2020; 125: 260–269.
 209. Cetin S, Huseyinli A, Koparal MY, Bulut EC, Ucar M, Gonul II, et al. How many cores should be taken from each region of interest when performing a targeted transrectal prostate biopsy. *Prostate Int.* 2023; 11:122–126.
 210. Saner YM, Wiesenfarth M, Weru V, Ladyzhensky B, Tschirdewahn S, Püllen L, et al. Detection of Clinically Significant Prostate Cancer Using Targeted Biopsy with Four Cores Versus Target Saturation Biopsy with Nine Cores in Transperineal Prostate Fusion Biopsy: A Prospective Randomized Trial. *Eur. Urol. Oncol.* 2023; 6:49–55.
 211. Fletcher P, De Santis M, Ippoliti S, Orecchia L, Charlesworth P, Barrett T, et al. Vector Prostate Biopsy: A Novel Magnetic Resonance Imaging/Ultrasound Image Fusion Transperineal Biopsy Technique Using Electromagnetic Needle Tracking Under Local Anaesthesia. *Eur. Urol.* 2023; 83:249–256.
 212. Kaneko M, Medina LG, Lenon MSL, Sayegh AS, Lebastchi AH, Cacciamani GE, et al. Transperineal magnetic resonance imaging/transrectal ultrasonography fusion prostate biopsy under local anaesthesia: The ‘double-freehand’ technique. *BJU Int.* 2023; 131:770–774.
 213. Calio B, Sidana A, Sugano D, Gaur S, Jain A, Maruf M, et al. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: Evidence of a learning curve. *Prostate Cancer Prostatic Dis.* 2017; 20:436–441.
 214. Pepe P, Garufi A, Priolo G, Pennisi M. Transperineal versus Transrectal MRI/TRUS Fusion Targeted Biopsy: Detection Rate of Clinically Significant Prostate Cancer. *Clin. Genitourin. Cancer* 2017; 15:e33–e36.
 215. Kim JK, Lee HJ, Hwang SI, Choe G, Kim HJ, Hong SK. The effect of 5 alpha-reductase inhibitor therapy on prostate cancer detection in the era of multiparametric magnetic resonance imaging. *Sci Rep* 2019; 9:17862.
 216. Wang Z, Wang K, Ong HY, Tsang WC, Wu QH, Chiong E (2023) 5-alpha reductase inhibitors and MRI prostates: actively reducing prostate sizes and ambiguity. *BMC Urol.* 2023; 23:61.

217. Falagario UG, Lantz A, Jambor I, Busetto GM, Bettocchi C, Carrieri G, et al. and PROMOD SG. Diagnosis of prostate cancer with magnetic resonance imaging in men treated with 5-alpha-reductase inhibitors. *World J Urol* 2023; 41:2967–2974.
218. Marberger M, Freedland SJ, Andriole GL, Emberton M, Pettaway C, Montorsi F, et al. Usefulness of prostate-specific antigen (PSA) rise as a marker of prostate cancer in men treated with dutasteride: lessons from the REDUCE study. *BJU Int* 2012; 109:1162–1169.
219. Chang LW, Wang SS, Yang CK, Lu K, Chen CS, Cheng CL, et al. Risk analysis of prostate Cancer Development following five-alpha reductase inhibitor treatment for benign prostate Hyperplasia. *Anticancer Res* 2023; 43:485–491.
220. Moore CM, Robertson NL, Jichi F, Damola A, Ambler G, Emberton M, et al. The Effect of Dutasteride on magnetic resonance imaging defined prostate Cancer: MAPPED-A Randomized, Placebo Controlled, double-blind clinical trial. *J Urol* 2017; 197:1006–1013.
221. Starobinets O, Kurhanewicz J, Noworolski SM. Improved multiparametric MRI discrimination between low-risk prostate cancer and benign tissues in a small cohort of 5 α -reductase inhibitor treated individuals as compared with an untreated cohort. *NMR Biomed* 2017; 30:3696.
222. Forte V, Cavallo AU, Bertolo R, de Soccio V, Bove P, Ciccariello M, et al. PI-RADS score v.2 in predicting malignancy in patients undergoing 5 α -reductase inhibitor therapy. *Prostate Cancer Prostatic Dis* 2021; 24:150–155.
223. Morote J, Borque-Fernando Á, Triquell M, Abascal JM, Servian P, Planas J, et al. A risk-organised model for clinically significant prostate cancer early detection. *BJUI Compass*. 2023; 4:420-422.
224. Oerther B, Engel H, Bamberg F, Sigle A, Gratzke C, Benndorf M. Cancer detection rates of the PI-RADSV2.1 assessment categories: Systematic review and meta-analysis on lesion level and patient level. *Prostate Cancer Prostatic Dis*. 2022; 25:256–263.
225. Morote J, Borque-Fernando Á, Triquell M, Esteban LM, Trilla E. The True Utility of Predictive Models Based on Magnetic Resonance Imaging in Selecting Candidates for Prostate Biopsy. *Eur Urol Open Sci*. 2022; 42:40-41.
226. Morote J, Borque-Fernando Á, Triquell M, Campistol M, Celma A, Regis L, et al. A Clinically Significant Prostate Cancer Predictive Model Using Digital Rectal

- Examination Prostate Volume Category to Stratify Initial Prostate Cancer Suspicion and Reduce Magnetic Resonance Imaging Demand. *Cancers (Basel)*. 2022; 14:5100.
227. Morote J, Borque-Fernando Á, Esteban LE, Picola N, Muñoz- Rodríguez J, Paesano N, et al. Reducing the demand for magnetic resonance imaging scans and prostate biopsies during the early detection of clinically significant prostate cancer: Applying the Barcelona risk-stratified pathway in Catalonia. *Urol Oncol*. 2024; 42:115. e1-115.e7.
 228. Remmers S, Kasivisvanathan V, Verbeek JFM, Moore CM, Roobol MJ; ERSPC Rotterdam Study Group PRECISION Investigators Group. Reducing Biopsies and Magnetic Resonance Imaging Scans During the Diagnostic Pathway of Prostate Cancer: Applying the Rotterdam Prostate Cancer Risk Calculator to the PRECISION Trial Data. *Eur Urol Open Sci*. 2021; 36:1-8.
 229. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. 1996. *Clin Orthop Relat Res*. 2007; 455:3-5.

11. ANEXO

INFORME DEL COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS Y COMISIÓN DE PROYECTOS DE INVESTIGACIÓN DEL HOSPITAL UNIVERSITARI VALL D'HEBRON

Sra. Mireia Navarro Sebastián, Secretaria del COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron,

CERTIFICA

Que el Comité de Ética de Investigación con Medicamentos del Hospital Universitario Vall d'Hebron, en el cual la Comisión de proyectos de investigación está integrada, se reunió en sesión ordinaria nº 475 el pasado 12/02/2021 y evaluó el proyecto de investigación **PR(AG)02/2021**, presentado por el promotor VALL D'HEBRON INSTITUT DE RECERCA (VHIR), titulado "*Predicción de la agresividad del cáncer de próstata a través de radiogenómica e inteligencia artificial (FIS PI20/01666)*" que tiene como investigador principal al Dr. Joan Morote Robles del Servicio de Urología de nuestro Centro.

Versión de documentos:

Memoria de Proyecto	versión 1 del 12/02/2020
HIP/CI	versión 1.0 del 08/12/2020
Solicita dispensa CI	versión con fecha 14/12/2020
Solicitud de evaluación CEIm	versión 1 del 04/12/2020

Y que tras evaluar la documentación recibida posteriormente por el promotor en respuesta al informe de dicha reunión, emite la siguiente resolución:

Aprobado

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y su composición actual es la siguiente:

- Presidente:**
- SOLEDAD GALLEGO MELCÓN - Médico
- Vicepresidente:**
- JOAN SEGARRA SARRIES - Abogado
- Secretario:**
- MIREIA NAVARRO SEBASTIAN - Química
- Vocales:**
- LLUIS ARMADANS GIL - Médico
- FERNANDO AZPIROZ VIDAUR - Médico
- VALENTINA BALASSO - Médico
- INES M DE TORRES RAMÍREZ - Médico
- ELADIO FERNÁNDEZ LIZ - Farmacéutico Atención Primaria
- INMACULADA FUENTES CAMPS - Médico Farmacólogo
- JAUME GUARDIA MASSÓ - Médico
- JUAN CARLOS HORTAL IBARRA - Profesor de Universidad
- MARIA LUJAN IAVECCHIA - Médico Farmacólogo
- ALEXIS RODRIGUEZ GALLEGO - Médico Farmacólogo
- JUDITH SANCHEZ RAYA - Médico
- MARTA SOLÉ ORSOLA - Personal de Enfermería
- PILAR SUÑÉ MARTÍN - Farmacéutica Hospital
- VÍCTOR VARGAS BLASCO - Médico
- ESTHER CUCURULL FOLGUERA - Médico Farmacólogo
- GLORIA GÁLVEZ HERNANDO - Personal de Enfermería
- ORIOL ROCA GAS - Médico
- ESPERANZA ZURIGUEL PEREZ - Personal de Enfermería
- ANA BELÉN ESTÉVEZ RODRÍGUEZ - Abogada experta en protección de datos

En dicha reunión del Comité de Ética de Investigación con Medicamentos se cumplió el quórum preceptivo legalmente.

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

MIREIA NAVARRO
SEBASTIAN

Firmado digitalmente por
MIREIA NAVARRO SEBASTIAN
Fecha: 2021.02.19 14:35:36
+01'00'

Sra. Mireia Navarro Sebastián
Secretaria técnica CEIM HUVH