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ORIGINAL RESEARCH

Identifying Risk Factors for MRI-Invisible Prostate Cancer in Patients Undergoing Transperineal Saturation Biopsy

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Purpose: Prostatic multi-parametric magnetic resonance imaging (mpMRI) has markedly improved the assessment of men with suspected prostate cancer (PCa). Nevertheless, as mpMRI exhibits a high negative predictive value, a negative MRI may represent a diagnostic dilemma. The aim of this study was to evaluate the incidence of positive transperineal saturation biopsy in men who have negative mpMRI and to analyse the factors associated with positive biopsy in this scenario.

Patients and Methods: A retrospective study of men with normal mpMRI and suspicion of PCa who underwent saturation biopsy (≥20 cores) was carried out. A total of 580 patients underwent transperineal MRI/transrectal ultrasound fusion targeted biopsies or saturation prostate biopsies from January 2017 to September 2020. Of them, 73 had a pre-biopsy negative mpMRI (with Prostate Imaging – Reporting and Data System, PI-RADS, ≤2) and were included in this study. Demographics, clinical characteristics, data regarding biopsy results and potential predictive factors of positive saturation biopsy were collected. Univariate and multivariate logistic regression analyses were used to identify independent risk factors for MRI-invisible PCa.

Results: The detection rate of PCa with saturation biopsy in patients with negative MRI was 34/73 (46.58%). Out of 34 MRI-invisible prostate cancers detected, 12 (35.29%) were clinically significant PCa (csPCa) forms. Regarding factors of positive biopsy, in univariate analysis, the use of 5-alpha reductase inhibitors and free:total prostate-specific antigen (PSA) ratio were associated with the result of the saturation biopsy. In multivariate analysis, only an unfavourable free:total PSA ratio remained a risk factor (OR 11.03, CI95% 1.93–63.15, p=0.01). Furthermore, multivariate logistic analysis demonstrated that prostate volume >50mL significantly predicts the absence of csPCa on saturation biopsy (OR 0.11, 95% CI 0.01–0.94, p=0.04).

Conclusion: A free:total PSA ratio <20% is a risk factor for MRI-invisible PCa. Saturation biopsy could be considered in patients with suspected PCa, despite having a negative MRI.

Keywords: clinically significant prostate cancer, multi-parametric magnetic resonance imaging, negative MRI, prostate cancer, saturation biopsy

Introduction

Prostatic multi-parametric magnetic resonance imaging (mpMRI) has experienced a great development becoming a cornerstone of the management of prostate cancer (PCa).[1] It is used to better target lesions in biopsy-naïve patients, before repeating biopsy in patients with a growing prostate-specific antigen (PSA) level and previous negative biopsy, in patients on active surveillance (AS) and to improve the prostate cancer staging, mainly in relation to extracapsular extension. Recently, several guidelines have endorsed

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the routine use of mpMRI in biopsy-naïve patients with suspected PCa and there is an ongoing implementation process in clinical practice.[2]

The negative predictive value of a normal mpMRI (nMRI) is high, and many urologists may use a nMRI to avoid prostate biopsies altogether.[3]

A meta-analysis showed that the sensitivity and specificity for mpMRI is 0.87 [95% CI, 0.81–0.91] and 0.68 [95% CI, 0.56–0.79], respectively. It suggests that mpMRI is a sensitive tool to diagnose PCa.[4] However, although we live in the era of mpMRI, the role of saturation biopsy in reducing the false negative rate is a controverted issue.

As a consequence of the interest in defining more accurate prostate biopsy schemes, the concepts of "extended biopsy" (10–12 cores) and "saturation biopsy" (≥20 cores) have emerged.[5] Saturation biopsy can be performed via transrectal or transperineal approaches, with similarly high detection rates. Recently, the transperineal approach has been preferred because of sampling accuracy, particularly for the anterior prostate region. The cancer detection rate of transperineal saturation biopsy is approximately 40–60% in repeated biopsies. Previous studies on saturation repeat biopsy showed higher detection rates than those on TRUS-guided repeat biopsy.[6]

Currently, pre-biopsy multiparametric MRI is recommended by several guidelines, not only for men with persistent suspicion of prostate cancer after prior negative systematic biopsy, but also before the first biopsy.[7] According to the updated European Association of Urology (EAU) guidelines, in patients with prior negative biopsy, when mpMRI is negative (ie, Prostate Imaging – Reporting and Data System, PI-RADS, ≤2), and clinical suspicion of prostate cancer is high, there is strong evidence to perform a systematic biopsy based on shared decision-making with the patient. On the other hand, in biopsy-naïve patients, there is a weak evidence to recommend a systematic biopsy when mpMRI is negative, and clinical suspicion of prostate cancer is low. Furthermore, these guidelines recommend to do not use mpMRI as an initial screening tool.[8]

PI-RADS allows standardization of prostate MRI interpretation. The PI-RADS v2 document was launched in 2014.[9] A considerable variability in PI-RADS score assignment and significant cancer yield across radiologists has been reported.[10] As a result, scepticism against MRI reporting is prevalent among some clinicians. The study of Nassiri et al, involving more than 2000 MRI/ultrasound-fusion biopsies, indicates that if biopsy is indicated on clinical grounds (eg, palpable abnormality, family or racial history, persistent PSA suspicion), a negative mpMRI should not preclude a systematic biopsy.[11]

With the advent of prostatic mpMRI studies, considered as a reliable diagnostic tool of prostate cancer, it is necessary to identify the predictive factors for positive saturation biopsy in patients with negative mpMRI. Several parameters, especially increased PSA density, may help to select patients who need a rebiopsy after a negative MRI.

MRI-invisible prostate cancer is relatively common. A series of 1042 men undergoing template biopsy regardless of MRI findings, the incidence of csPCa in men with no MRI-suspicious lesions (biopsy-naïve subgroup) was 12%. Furthermore, that percentage increased to 28% after carefully review of prostatectomy specimens.[12]

The scope of the current study was to assess the incidence of positive transperineal saturation biopsy in men who have a negative mpMRI and to determine the factors associated with positive biopsy in this scenario.

Patients and Methods

We conducted a retrospective study of men with normal mpMRI and suspected prostate cancer, who underwent saturation biopsy. A total of 580 patients underwent transperineal MRI/TRUS fusion targeted biopsies or saturation prostate biopsies from January 2017 to September 2020 in our centre. Of them, 73 had a pre-biopsy negative mpMRI (with PI-RADS≤2) and were included in this study.

All MRI studies were interpreted by experienced radiologists using the Prostate Imaging Reporting and Data System (PI-RADS version 2) and they were re-read before biopsy. Saturation biopsy consisted of at least 20 biopsy cores taken from the prostate and it was performed using the transperineal approach. All biopsies were performed by one urologist with extensive experience in prostate cancer diagnosis.

Patient records were reviewed, and demographic and clinical data were collected. Additionally, we investigated the potential predictive factors of positive saturation biopsy in MRI-negative men: Body mass index (BMI), prostate cancer family history of first-degree relatives, PSA level, PSA-density and PSA-velocity, abnormal findings on digital rectal examination (DRE), previous biopsy showing high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP), prostate volume measured by MRI, number of previous biopsies, number of biopsy cores,

and indicators of systemic inflammation, such as neutrophil–lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and neutrophil-to-monocyte ratio (NMR). Systemic immune response index (SII) was calculated as follows: SII = platelet × neutrophil-to-lymphocyte ratio. Clinically insignificant prostate cancer was defined as Gleason score <7, ≤3 positive cores and ≤50% core involvement.

Continuous variables were expressed as mean and standard deviation (SD), and categorical variables were expressed as frequency counts and percentages. The Shapiro–Wilk test was used to assess the normality of the distribution of continuous variables. Statistical tests used to determine the association between some factors and positive saturation biopsy included chi-square test or Fisher's exact test for categorical variables and Student's t-test or Wilcoxon's rank sum test for continuous variables. Multivariate logistic regression analyses were also conducted to assess the factors associated with the positive saturation biopsy. A two-tailed p-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using STATA 14 (StataCorp, College Station, Texas, USA).

Results

Seventy-three saturation biopsies were performed during the study period. The incidence of prostate cancer was 34/73 (46.58%) in men with nMRI who underwent a saturation biopsy. Twenty-two out of 34 (64.71%) had a clinically insignificant prostate cancer. Seven patients enrolled in AS (19.44%) with prior negative mpMRI were upgraded after saturation biopsy. Table 1 shows the tumour characteristics of patients with positive saturation biopsy and negative MRI.

Mean age was similar in both groups (62.89 years – SD 6.47 – in the positive saturation biopsy vs 65.08 years – SD 6.78 – in the normal biopsy group, p= 0.16). 84.62% of patients with both no prior negative biopsy and free:total PSA<20% had a positive saturation biopsy (11/13).

Table 2 contains the baseline characteristics of MRI-negative patients with positive and negative saturation biopsy. Regarding baseline characteristics, we found statistically significant differences in the use of 5-alpha reductase inhibitors, prostate volume, PSA range and free:total PSA ratio. In univariate analysis (see Table 3), the use of 5-alpha reductase inhibitors and free:total PSA ratio were associated with the result of saturation biopsy. In the multivariate analysis, only an unfavourable free:

Table 1 Tumour Characteristics in Patients with Positive Saturation Biopsy and Prior Negative MRI (n=34)

Variable	Value
Grade	
Gleason 6 (3+3) (ISUP 1)	22 (64.71%)
Gleason 7 (3+4) (ISUP 2)	8 (23.52%)
Gleason 7 (4+3) (ISUP 3)	1 (2.94%)
Gleason 8 (4+4) (ISUP 4)	2 (5.88%)
Gleason 9 (4+5) (ISUP 5)	1 (2.94%)
Percentage of positive cores	12.89 (SD 11.38)
Extent of involvement of needle cores	10.41 (SD 9.41)
Bilateral tumor	11 (33.33%)
csPCa	12 (35.29%)
Gleason score in active surveillance patients (n=36)	
Gleason 6	11 (30.55%)
Gleason 7 or greater	7 (19.44%)

Abbreviation: csPCa, clinically significant prostate cancer.

total PSA ratio remained significant independent predictor of a positive saturation biopsy (OR 11.03, CI95% 1.93–63.15, p=0.01).

Out of 34 MRI-invisible cancers detected, 12 (35.29%) patients had a clinically significant prostate cancer (csPCa). For the purpose of determining the factors associated with a csPCa on saturation biopsy, patients were divided into 2 groups according to the result of saturation biopsy: The csPCa patients group (n=12) and the group composed of patients with normal saturation biopsy or with an insignificant PCa (n=61) (Table 4). With regard to the baseline characteristics of patients diagnosed with csPCa, a statistically significant difference between groups was found in prostate volume and PSA density. On univariate analysis of risk factors for csPCa, only prostate volumen >50mL was associated with the presence of csPCa on core biopsy samples. Finally, multivariate analysis showed that prostate volume >50mL significantly predicts absence of csPCa on saturation biopsy (OR 0.11, 95% CI 0.01–0.94, p=0.04) (Table 5).

Discussion

Prostate mpMRI has become a promising tool used to improve the accuracy of prostate cancer detection. Until recently, saturation biopsy was considered the method of choice to improve prostate cancer-detection rate after previous negative biopsy series.[13] It is important to define the role of the saturation biopsy in the era of mpMRI.

Table 2 Baseline Characteristics of MRI-Negative Patients with Positive and Negative Saturation Biopsy

Variable	Biopsy Outcome		p
	Negative (n = 39)	Positive (Gleason≥6) (n = 34)	
Age	62.89 (SD 6.47)	65.08 (SD 6.78)	0.16
BMI	27.57 (SD 3.38)	27.93 (SD 4.39)	0.81
Suspicious DRE	2 (5.26%)	2 (5.88%)	1
Family history of prostate cancer	1 (2.63%)	0	1
Use of 5-alpha reductase inhibitors	7 (23.33%)	1 (2.94%)	0.02*
Prior ASAP	2 (5.13%)	3 (8.82%)	0.66
Prior HG-PIN	1 (2.63%)	0	1
Active surveillance program	18 (47.37%)	18 (52.94%)	0.64
Prostate volume	69.45 (SD 33.63)	54.49 (SD 30.14)	0.03*
Prior negative biopsy (at least one)	18 (51.43%)	10 (31.25%)	0.09
Number of prior negative biopsies	0.88 (SD 1.05)	0.46 (SD 0.80)	0.07
PSA range			0.03*
<10	24 (64.86%)	29 (87.88%)	
≥10	13 (35.14%)	4 (12.12%)	
PSA level	10.34 (SD 9.37)	7.55 (SD 3.20)	0.53
PSA density	0.15 (SD 0.13)	0.16 (SD 0.09)	0.32
Free:total PSA ratio	0.22 (SD 0.08)	0.16 (SD 0.07)	0.01*
Intervals of free:total PSA ratio			0.02*
<20%	6 (37.50%)	17 (80.95%)	
≥20%	10 (62.50%)	4 (19.05%)	
PSA velocity	4.31 (SD 6.24)	1.72 (SD 0.95)	0.45
Total biopsy cores	23.18 (SD 4.41)	21.38 (SD 4.04)	0.10
NLR	1.90 (SD 0.79)	1.92 (SD 0.70)	0.74
PLR	94.31 (SD 29.34)	102.84 (SD 27.25)	0.18
NMR	7.43 (SD 1.94)	7.22 (SD 2.29)	0.42
SII	400593.6 (SD 161906.2)	397579.9 (SD 147953)	0.93

Note: Asterisks (*) represent statistical significance.
Abbreviations: BMI, body mass index; DRE, digital rectal examination; HG-PIN, high-grade prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; NLR, neutrophil–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; SII, systemic immune response index.

Men with a persistent suspicion of PCa with nMRI represents a diagnostic dilemma for urologists because of the high negative predictive value (NPV) of MRI for significant prostate cancer.[14] The overall estimated false negative rate of mpMRI is around 10–20%.[15] The reported false-negative rates of csPCa for targeted fusion prostate biopsy of PI-RADS≥3 and ≥4 lesions are 16.2% and 39.7%, respectively.[16] Therefore, it is important to address the need for biopsy in these patients and to evaluate different predictive factors of positive saturation biopsy in this scenario.

The concept of "mpMRI-invisible disease" has been introduced. MRI-visible tumors are associated with under-expression of cellular organization genes. Mutations in known cancer-associated genes, for example *PTEN*, could explain the phenomenon of mpMRI-invisible cancer.[17]

Buisset et al analysed the risk of csPCa in a nMRI biopsy-naïve population (503 patients) at baseline and during long-term follow-up. They reported that the risk of csPCa of this population was 6–9% at baseline (systematic 12-core biopsy) and 7–13% at long-term follow-up depending on csPCa definitions. Furthermore, they found that PSA density (PSAd) ≥0.15 ng/mL/mL, clinical stage ≥T2a and PCa-family-history were predictors of csPCa risk.[18] Our study confirms the importance of performing a biopsy in negative-MRI men suspected of having prostate cancer. In our study, the rate of csPCa is 12/73 (16.4%). Overall, prostate cancer was detected in 34/73 (46.58%) patients. Although we always brought into focus the clinically significant cancer, some Gleason 6 cancers may have the biological potential for de-differentiation and so they require follow-up.[12]

Table 3 Univariate and Multivariate Analysis of Factors Related to the Positive Saturation Biopsy

Variable	Univariate		Multivariate	
	Odds Ratio (CI)	p	Odds Ratio (CI)	p
Age	1.05 (0.98–1.13)	0.16	–	–
BMI	1.02 (0.90–1.16)	0.71	–	–
Suspicious DRE	1.12 (0.15–8.45)	0.91	–	–
Family history of prostate cancer	–	–	–	–
Use of 5–alpha reductase inhibitors	0.09 (0.01–0.86)	0.03*	–	–
Prior ASAP	1.79 (0.28–11.4)	0.54	–	–
Prior HG–PIN	–	–	–	–
Active surveillance program	1.25 (0.49–3.16)	0.64	–	–
Prostate volumen >50mL	0.49 (0.19–1.28)	0.15	1.71 (0.29–10.07)	0.55
Prior negative biopsy (at least one)	0.43 (0.16–1.16)	0.09	4.48 (0.39–50.39)	0.22
PSA level	0.93 (0.85–1.02)	0.13	0.70 (0.41–1.21)	0.20
PSA density	1.57 (0.03–84.81)	0.82	–	–
Free:total PSA ratio <20%	9.35 (2.04–42.65)	0.00*	11.03 (1.93–63.15)	0.01*
PSA velocity	0.77 (0.49–1.19)	0.24	–	–
Total biopsy cores	0.90 (0.80–1.01)	0.08	–	–
NLR	1.02 (0.55–1.93)	0.93	–	–
PLR	1.01 (0.99–1.03)	0.21	–	–
NMR	0.95 (0.76–1.19)	0.68	–	–
SII	0.99 (0.99–1.00)	0.93	–	–

Note: Asterisks (*) represent statistical significance.
Abbreviations: BMI, body mass index; DRE, digital rectal examination; HG-PIN, high-grade prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; NLR, neutrophil–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; SII, systemic immune response index.

The influence of the number of cores obtained in the detection rate of PCa has been extensively addressed in the literature. An increase of PCa detection rate of 5–20% has been reported when more than six cores are taken at prostate biopsy.[19] Pepe et al analysed the number of needle cores combined with mpMRI needed to diagnose all csPCa in men who undergo transperineal saturation biopsy. They concluded that a maximum of 20 systematic transperineal needle cores could detect all cases of csPCa and reduce the diagnosis of insignificant PCa.[20] In our study, we collected data about total number of biopsy cores. However, the number of biopsy cores was similar between both groups.

As many authors have pointed out, a negative MRI does not guarantee the absence of significant prostate cancer. Some reports have shown alarming rates of PCa among patients with nMRI. For example, Branger et al retrospectively analysed patients who underwent radical prostatectomy and who had a preoperative negative mpMRI. Final pathology showed that 16.9% had extraprostatic extension, 13.8% had primary Gleason pattern 4 (4 + 3 and above), and 47.5% had secondary Gleason pattern 4 or 5. Furthermore, they indicated that data are especially sensitive to radiologist experience.[21] Similarly, Kim et al have reported that among a total of 196 negative

preoperative mpMRI patients who underwent radical prostatectomy, 59.7% had Gleason score 3 + 4 and 22.4% had Gleason score ≥ 4 + 3.[22] A previous report of Sokhi indicates that ISUP ≥2 cancer detection rates were 8% (5/61) for PI-RADS 1–2.[23]

Recently, a systematic review including a total of sixteen studies was carried out by Pagniez et al. The aim was to determine the predictive ability of some factors (age, prostate specific antigen, prostate specific antigen isoforms, prostate specific antigen density, PCA3, prostate volume, family history, ethnicity and risk calculators) for clinically significant prostate cancer diagnosis after prebiopsy negative magnetic resonance imaging in prostate cancer naïve patients. PSA density was the best studied and the strongest predictor of csPCa in patients with prebiopsy nMRI. Furthermore, they conclude that the use of PSA density less than 0.15 ng/mL/mL in patients with prebiopsy nMRI was the most useful factor to identify men without csPCa, in whom biopsy could be precluded.[24] Similarly, in our study we investigated different potential predictors of positive biopsy in patients with nMRI and who underwent saturation biopsy. We observed that an unfavourable free:total PSA ratio was a significant independent predictor of a positive saturation biopsy and

Table 4 Baseline Characteristics of Patients Diagnosed with csPCa

Variable	Biopsy Outcome		p
	Gleason 6 or Negative Biopsy (n = 61)	Clinically Significant Prostate Cancer (n = 12)	
Age	63.40 (SD 6.56)	66.5 (SD 6.88)	0.14
BMI	27.63 (SD 4.00)	28.23 (SD 3.41)	0.58
Suspicious DRE	4 (6.67%)	0	1
Family history of prostate cancer	1 (1.69%)	0	1
Use of 5-alpha reductase inhibitors	8 (15.38%)	0	0.33
Prior ASAP	4 (6.56%)	1 (8.33%)	1
Prior HG-PIN	1 (1.67%)	0	1
Active surveillance program	29 (48.33%)	7 (58.33%)	0.53
Prostate volume	66.26 (SD 33.96)	41.72 (SD 10.95)	0.02*
Prior negative biopsy (at least one)	26 (46.43%)	2 (18.18%)	0.10
Number of prior negative biopsies	0.73 (SD 0.94)	0.45 (SD 1.03)	0.18
PSA range			0.49
<10	44 (75.86%)	8 (66.67%)	
≥10	14 (24.14%)	4 (33.33%)	
PSA level	9.13 (SD 7.70)	8.52 (SD 4.62)	0.94
PSA density	0.15 (SD 0.11)	0.21 (SD 0.11)	0.02*
Free:total PSA ratio	0.20 (SD 0.08)	0.14 (SD 0.05)	0.12
Intervals of free:total PSA ratio			0.07
<20%	17 (53.12%)	5 (100%)	
≥20%	15 (46.88%)	0	
PSA velocity	3.28 (SD 5.02)	1.77 (SD 0.81)	0.96
Total biopsy cores	22.25 (SD 4.57)	22.75 (SD 2.66)	0.66
NLR	1.90 (SD 0.79)	1.96 (SD 0.49)	0.43
PLR	96.70 (SD 27.67)	105.29 (SD 32.86)	0.37
NMR	7.33 (SD 2.09)	7.12 (SD 2.08)	0.97
SII	396970.6 (SD 159665)	410369.9 (SD 132969.6)	0.62

Note: Asterisks (*) represent statistical significance.
Abbreviations: BMI, body mass index; DRE, digital rectal examination; HG-PIN, high-grade prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; NLR, neutrophil–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; SII, systemic immune response index.

a large prostate volume (>50mL) can predict the absence of csPCa. However, we focused on saturation biopsy technique.

PSAd has been shown to be a predictor of csPCa and disease progression on AS for men with low-risk PCa. The combination of saturation biopsy and mpMRI at confirmatory and repeated evaluation can reduce the reclassification rate during AS follow-up (only 5.4% at 3 years).[25] According to Roscigno et al, PSAd ≥0.20 ng/mL^2 is a valuable tool for improving the accuracy of mpMRI results for reclassification of patients in AS.[26]

In the present study we sought to define a group with lower risk for PCa among patients with nMRI. Likewise, Oishi et al proposed that a subset of men with negative MRI, density of PSA less than 0.15 ng/mL/cc and prior

negative biopsy may safely avoid rebiopsy. Stonier et al state that the sensitivity and NPV of transrectal and transperineal biopsy increased to 96.6% and 90.6%, respectively, when a PSA density threshold of 0.15ng/mL/mL was used in nMRI (scores 1–2).[27] Furthermore, Kuhlmann et al identified black race and PSA density as risk factors for the presence of nMRI prostate cancer.[15] Our work indicates that an independent risk factor for csPCa is a smaller prostate gland volume.

Previous work has focused on the value of indicators of cancer-related inflammation, such as PLR and NLR, in PCa detection. Adhyatma et al evaluated pre-biopsy values of PLR and NLR in predicting PCa and concluded that NLR could be useful.[28] Furthermore, SII and SII combination with PI-RADS score have been reported as

Table 5 Univariate and Multivariate Analysis of Factors for the Detection of Clinically Significant Prostate Cancer

Variable	Univariate		Multivariate	
	Odds Ratio (CI)	**p**	**Odds Ratio (CI)**	**p**
Age	1.07 (0.97–1.17)	0.14	–	–
BMI	1.04 (0.88–1.22)	0.62	–	–
Suspicious DRE	–	–	–	–
Family history of prostate cancer	–	–	–	–
Use of 5–alpha reductase inhibitors	–	–	–	–
Prior ASAP	1.29 (0.13–12.72)	0.82	–	–
Prior HG–PIN	–	–	–	–
Active surveillance program	1.49 (0.43–5.24)	0.53	–	–
Prostate volumen >50mL	0.18 (0.04–0.94)	0.04*	0.11 (0.01–0.94)	0.04*
Prior negative biopsy (at least one)	0.25 (0.05–1.29)	0.10	0.48 (0.08–2.73)	0.41
PSA level	0.98 (0.89–1.08)	0.79	–	–
PSA density	38.21 (0.36–4023.70)	0.12	–	–
Free:total PSA ratio	$2.72e^{-06}$ (1.20^{e-13}–61.62)	0.14	–	–
PSA velocity	0.85 (0.52–1.39)	0.52	–	–
Total biopsy cores	1.03 (0.88–1.19)	0.71	–	–
NLR	1.12 (0.49–2.52)	0.78	–	–
PLR	1.01 (0.99–1.03)	0.34	–	–
NMR	0.94 (0.69–1.28)	0.69	–	–
SII	1.00 (0.99–1.00)	0.78	–	–

Note: Asterisks (*) represent statistical significance.
Abbreviations: BMI, body mass index; DRE, digital rectal examination; HG-PIN, high-grade prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; NLR, neutrophil–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; SII, systemic immune response index.

a significant diagnostic marker in patients with high-grade PCa (ISUP grade 3–5).[29] In contrast to these earlier findings, we did not find association between these parameters and the result of saturation biopsy.

Some controversy remains as to whether patients with prostate cancer suspicion and negative MRI can safely omit biopsy. Regis et al have stated categorically that PI-RADS 2 should not be considered as a negative MRI because its NPV in biopsy-naïve patients was 84%.[30] In consonance with this author, Ma et al considered that only PI-RADS 1 has a high NPV.[31]

To sum up, there is no consensus on which patients with a negative prostate MRI should forego biopsy. According to the majority of guidelines, including those published from American Urological Association (AUA), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN), men with an elevated PSA and a negative MRI are referred for biopsy. Some authors defend that biopsy could be avoided in the absence of high-risk features, such as clinical suspicion, family history, low PSA density, and those with low scores on the 4K or Prostate Health Index (PHI), and PCA3 assays.[32]

A nMRI does not necessarily exclude the possibility of a csPCa. Our findings highlight the need for biopsy in men with negative MRI and a free:total PSA ratio <0.2, and indicate that saturation biopsy can play a relevant role in detecting prostate cancer in this context. Furthermore, a large prostate volume (>50mL) can predict the absence of csPCa on saturation biopsy sample in MRI-negative patients. The most important limitations of our work lie in the small sample size and in the retrospective study design. Furthermore, in this study we did not include some parameters which could be potentially useful, such as proPSA (included in the PHI) or PCA3.

Abbreviations

AS, active surveillance; ASAP, atypical small acinar proliferation; BMI, body mass index; csPCa, clinically significant prostate cancer; DRE, digital rectal examination; HG-PIN, high-grade prostatic intraepithelial neoplasia; mpMRI, multi-parametric magnetic resonance imaging; NLR, neutrophil–lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; nMRI, normal mpMRI; PCa, prostate cancer; PLR, platelet-to-lymphocyte ratio; SII, systemic immune response index; TRUS, transrectal ultrasound.

Ethics Approval and Informed Consent

This research is retrospective and involving the collection of existing data and records. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration. The ethical committee of Hospital Ramón y Cajal of Madrid approved all procedures of the study and also provided the waiver for the written informed consent.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no conflicts of interest in this work.

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