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ARTICLE

Clinical evaluation and disease management of PI-RADS 3 lesions. Analysis from a single tertiary high-volume center

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ABSTRACT

Objective: To evaluate the clinical and pathological implications of Prostate Cancer (PCa) patients with a Prostate Imaging - Reporting and Data System (PI-RADS) 3 lesion at multi parametric magnetic resonance imaging (mpMRI).

Methods: We included 356 patients with a PI-RADS score 3 lesion at mpMRI who underwent prostate biopsy for a suspect of PCa at a single tertiary high-volume centre between 2013 and 2016.
We developed Uni- (UVA) and multi variable (MVA) logistic regression analyses assessing the predictors of three endpoints: 1) diagnosis of PCa, 2) active surveillance (AS) criteria and 3) clinically significant (CS) PCa at final pathology.

Results: PCa was diagnosed in 285 patients (80%), out of these 154 (56%) were eligible for AS according to Prostate Cancer Research International Active Surveillance (PRIAS) criteria. Over the 228 (64%) patients who underwent surgery, 93 (40.8%) had a CS disease at final pathology. Hundred and ninety-three (84.6%) had a pT2 disease and 35 (15.4%) had a pT3 disease. The size of the main lesion, age, PSA and prostate volume efficiently predicted PCa at MVA (all $p < 0.05$). None of our predictors were significantly associated with AS characteristics. Over those patients who underwent surgery, the biopsy Gleason Score ($p = 0.007$) efficiently predicted a CS PCa at final pathology.

Conclusions: mpMRI-detected PI-RADS 3 lesions should be sent to a prostate biopsy if other clinical parameters suggest the presence of a PCa. In case of diagnosis of a PCa, patients should undergo confirmatory biopsy before being included in AS protocols to avoid underestimation of a CS disease.

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Introduction

In the last decade, multiparametric prostatic magnetic resonance imaging (mp-MRI) has gained a primary role in detecting and counselling patients with a suspect of prostate cancer (PCa). It has been recently included in European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines for PCa diagnosis, surveillance and staging [1,2].

While the Prostate Imaging - Reporting and Data System (PI-RADS 4) and 5 lesions are associated with prostate cancer in >90% of cases [3,4], PI-RADS 3 lesions characteristics are still not well described.

On the other hand, patients with PI-RADS ≤2 lesions are often associated to benign lesions or insignificant tumors, a non-negligible number of patients with a mpMRI detected PI-RADS 3 lesions will harbor a significant prostate cancer [3–6].

In this setting, urologists are confined in a sort of '*grey zone*' without clear indications whether to offer this population a prostate biopsy or observation. Additionally, for those patients already diagnosed with a PCa suitable for active surveillance (AS) [7], a PI-RADS 3 lesion could hide a clinically significant disease deserving an active treatment.

For this reason, we explored this class of patients aiming at evaluating clinical and pathological characteristics of a PI-RADS 3 population underwent prostate biopsy and/or radical prostatectomy.

Materials and methods

Study population

We retrospectively evaluated 1,863 consecutive prostatic mp-MRI performed at a single high-volume center between 2013 and 2016 in patients with an increased PSA and a suspect of PCa. Patients without a target lesion (PI-RADS ≤ 2; $n = 412$) were excluded from the database. Additionally, patients with a PI-RADS >3 lesion ($n = 722$), as well as patients with a PI-RADS 3 lesion coexisting with another highly suspicious lesion (namely PI-RADS 4 or 5) were excluded from the cohort ($n = 373$).

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Overall, 356 (19.1%) consecutive patients from the prospectively collected database respected our criteria and were included for further analyses.

All patients signed an informed consent approved by the internal ethical committee authorizing the anonymous disclosure of their health information. Complete demographic, pre-operative and pathologic data were collected.

When a PCa was diagnosed, indication for active surveillance (AS) was given according to the Prostate Cancer Research International Active Surveillance (PRIAS) criteria, namely: clinical stage T1/T2, PSA $\leq$10 ng/ml, PSA density $<$0.2 ng/ml per milliliter, one or two positive biopsy cores, and Gleason score $\leq$6 [7].

For patients who underwent robot assisted radical prostatectomy (RARP), the neurovascular bundle preservation was performed if an organ confined disease was depicted at the mp-MRI, regardless of the preoperative functional status. When performed, the nerve-sparing surgical technique was carried out as previously described [8–10]. None received preoperative hormonal treatment.

Imaging

All mpMRIs were performed with a 1.5 Tesla device. T2w, DWI, and DCE sequences were obtained according to PI-RADS version 2 guidelines [11]. The *b* values used for the DWI acquisition were 0, 500 and 1000 till 2014; from 2015 the *b* values used were 0, 500, 1000 and a value calculated at 1500.

All MRIs performed before 2015 were reviewed by a dedicated genitourinary radiologist (GP) according to PI-RADS version 2 [11].

In case the exam was performed in another institution, images were recorded in our telematic software (Telemis-Medical PACS version 4) and reviewed, by our expert radiologist (GP) with eight-year experience on mpMRI and more than 1000 exams performed.

Finally, data on size, location, T2 score, DWI and DCE scores, PI-RADS score and EPE (extraprostatic extension) score were recorded.

A PI-RADS 3 score was assigned to those areas in which the presence of a clinically significant PCa was suspected according to PI-RADS version 2, namely, DWI score of 3, negative DCE score and any T2 score for lesion located in the peripheral zone and a T2 score of 3; $\leq$4 DWI score and any DCE score for lesions located in the transitional zone [11].

The MRI was described in a standardized internal report depicting the prostatic area where the cancer was located as suggested by the European Society of Urogenital Radiology (ESUR) [11]. This drove our uro-pathologists for the prostatic sampling and the detection of the tumor.

Biopsy protocol

Sampling of PI-RADS 3 lesions was obtained according to an internal validated biopsy protocol, according to clinician preference and/or lesion dimension and location.

For IL $<$10 mm and/or located in the anterior/cranial aspect of the gland, an in-bore MRI guided approach was suggested. All the in-bore biopsies were performed by a single dedicated radiologist with several years of experience (GP), using one commercially available transrectal biopsy device (DynaTRIM, Invivo, Gainesville, FL, USA). From two to five cores were obtained from each lesion.

All other patients underwent transperineal US MRI fusion guided targeted biopsies. The BKTM MRI/US fusion system (BK Medical Aps, Herlev, Denmark) was used. First, 3–5 cores were taken from each target lesion. Then, patients underwent a 12 cores systematic sampling of the remaining part of the gland [12]. All fusion biopsies procedures were performed by full-trained urologists in an outpatient setting under local anesthesia.

Patient's follow up

A specific informed consent was signed by all the patients included in our internal AS protocol.

Then, while mpMRI was repeated every year, prostate biopsies were repeated 12 months after their inclusion in the program and afterwards only in case of mpMRI progression, defined according to the PRECISE criteria [13,14].

Patients willing or experiencing a progression of the disease confirmed by prostate biopsy were addressed to active treatment.

Statistical analysis

Statistical analyses reporting and interpretation of the results were conducted according to established guidelines [15] and consisted of three main steps (per person level).

First, a multivariable (MVA) logistic-regression analysis testing predictors of PCa at biopsy.

Second, a MVA logistic-regression analysis testing predictors of PCa eligible for AS [7].

Third, a MVA logistic-regression analysis evaluating predictors of clinically significant prostate cancer (defined as GS $\geq$ 7 and/or non-organ confined and/or tumor volume $>$5%) at final pathology [16].

Covariates consisted of: age at biopsy, PSA, prostate volume, presence of a palpable lesion, the presence of a second lesion at MRI, previous negative biopsies and Gleason score at biopsy.

Statistical analyses were performed using SPSS software v.21.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline patient characteristics

Table 1 summarizes the overall population's characteristics.

Over the entire cohort, the mean age was 63 years old (median 63; IQR 58–68), the mean prostate volume 58 cc (median 50 cc; IQR 34–70), mean PSA was 8.81 (median 6.06, IQR 4.62–8.3).

Among those patients who underwent prostate biopsy, PCa was found in 80% (285 patients). Of patients diagnosed with PCa, 154 (56%) were eligible for AS.

Table 1. Descriptive characteristics of 356 patients with PI-RADS 3 lesions that underwent prostate biopsy between 2013 and 2016 at our institution.

Variables (356 patients)	
Age, years	
Mean (median, IQR)	63 (63, 58–68)
Prostate volume, cc	
Mean (median, IQR)	58 (50, 34–70)
PSA, ng/ml	
Mean (median, IQR)	8.81 (6.06, 4.62–8.30)
Size of the main lesion, mm	
Mean (median, IQR)	12.41 (11, 9–15)
Presence of a second lesion, n(%)	
Yes	213 (59.8)
No	143 (40.2)
PCa at biopsy, n (%)	
Yes	285 (80)
No	71 (20)
Previous negative biopsy, n (%)	
Yes	84 (23.6)
No	272 (76.4)
GS at biopsy, n (%)	
3 + 3	244 (85.6)
3 + 4	25 (8.8)
4 + 3	11 (3.9)
≥4 + 4	5 (1.8)
PRIAS criteria, n (%)	
Yes	154 (56)
No	125 (44)
missing	1
RARP, n (%)	
Yes	228 (64)
No	128 (36)
CS Disease at final pathology (228 pts), n (%)	
Yes	104 (45.6)
No	124 (54.4)
GS at final pathology, n (%)	
6	135 (59.2)
7	88 (38.6)
≥8	5 (2.2)
pT stage, n (%)	
2	193 (84.6)
3	35 (15.4)

Results are presented as medians (IQR: interquartile range) for continuously coded variables and numbers and percentages for categorical variables.
PCa: prostate cancer; GS: Gleason Score; RARP: Robotic Assisted Radical Prostatectomy; CS: Clinically Significant; PI-RADS: Prostate Imaging - Reporting and Data System; PSA: prostate specific antigen; PRIAS: Prostate Cancer Research International Active Surveillance.

Overall, 228 patients (64%) underwent RARP showing a clinically significant PCa (defined as GS ≥7 and/or non-organ confined and/or tumor volume >5%) in 45.6% (104 patients) of the cases (Supplementary Figure 1) [16].

Among the patients who experienced surgery, a Gleason score ≥7 PCa was found in 40.8% (93 patients) at final pathology, while the rate of a pT2 and pT3 disease was 84.6 and 15.4% respectively.

Finally, we evaluated the concordance between the MRI reports and the final pathology, finding a PCa matching to the site highlighted at MRI in 42.2% of the cases, irrespectively of the Gleason score (Supplementary Table 4). Out of these, only the 23% had a GS > 7 at final pathology.

Per type of biopsy and per site of the lesion's analyses are reported in Supplementary Table 4.

On the other hand, we recorded the 57.6% of non-concordant MRI-final pathology diseases. Namely, PCa was found also in different site from the one suggested by the MRI or in other sites but the highlighted PI-RADS 3 lesion.

Table 2. Multivariable logistic regression analysis predicting Prostate cancer at biopsy ($n = 285$) in patients with PI-RADS 3 lesions.

Variables	OR (95% CI)	p Value
Age (years)	1.03 (1–1.05)	0.027
PSA (ng/ml)	0.88 (0.8–0.97)	<0.01
Prostate Volume (cc)	0.98 (0.97–0.99)	0.02
Size of the main lesion (mm)	1.09 (1–1.2)	0.036
Presence of second lesion (Yes vs. no)	0.8 (0.35–1.83)	0.61
cT		
1 (ref)		
2	14.2 (1.5–28.6)	0.9

OR: Odds ratio; CI: confidence interval; PI-RADS: Prostate Imaging – Reporting and Data System; PSA: prostate specific antigen.

Table 3. Multivariable logistic regression analysis predicting active surveillance criteria ($n = 153$) at biopsy in patients with PI-RADS 3 lesions.

Variables	OR (95% CI)	p Value
Age (years)	0.99 (0.98–1.01)	0.76
PSA (ng/ml)	0.96 (0.87–1.06)	0.48
Prostate Volume (cc)	1.01 (0.99–1.02)	0.12
cT		
1 (ref)		
2	0.65 (0.22–2.85)	0.42
Previous negative biopsy (yes vs. no)	2.24 (0.94–5.35)	0.06

OR: Odds ratio; CI: confidence interval; PI-RADS: Prostate Imaging – Reporting and Data System; PSA: prostate specific antigen.

Table 4. Multivariable logistic regression analysis predicting clinically significant prostate cancer at final pathology ($n = 228$) in patients with PI-RADS 3 lesions.

Variables	OR (95% CI)	p Value
Age (years)	0.99 (0.96–1.02)	0.51
PSA (ng/ml)	1.05 (0.88–1.24)	0.6
Prostate Volume (cc)	0.98 (0.97–1)	0.22
cT		
1 (ref)		
2	1.97 (0.53–7.24)	0.31
Previous negative biopsy (yes vs. no)	0.81 (0.18–3.56)	0.78
N° of positive cores	1.12 (0.86–1.45)	0.40
Gleason Score biopsy		
6 (ref)		
≥7	5.79 (1.63–20.54)	0.007

OR: Odds ratio; CI: confidence interval; PI-RADS: Prostate Imaging - Reporting and Data System; PSA: prostate specific antigen.

Logistic regression analyses

Uni-variable (UVA) analysis is reported in Supplementary Tables 1–3.

At the multivariable logistic regression analysis, the size of the main lesion, the age, the PSA and the smaller prostate volume showed a significant association in predicting the presence of PCa (all $p < 0.05$, Table 2).

Considering patients who had a diagnosis of PCa, no one of the factors evaluated were able to predict a disease fit for AS accounting PRIAS criteria (all $p > 0.05$, Table 3).

Finally, Gleason score at biopsy was the only proxy of clinically significant PCa, among patients who underwent surgery ($p = 0.007$, Table 4).

Discussion

The ESUR developed PI-RADS reporting system for a reproducible and coherent detection of clinically significant prostate cancer at mpMRI. This technique has rapidly been employed in clinical practice, but some concerns still remain. While PI-

RADS 4 or 5 lesions are normally considered likely to be a PCa and patients are sent to further analyses such as prostate sampling, PI-RADS 3 lesions are considered doubtful. In these cases, urologists have to decide whether to observe the patient or to offer a prostate biopsy. Such variability can lead to late diagnosis or, in some cases, to overdiagnosis of PCa.

We tried to define the clinical significance of these specific subgroup of MRI lesions for the diagnosis of PCa in order to help clinicians in the management of patients.

Significant variability exists in the available literature. Histologically confirmed prostate adenocarcinoma are reported in 15–29% of the PI-RADS 3 lesions [3,17,18]. Liddell and colleagues rated the 6.5% of PCa in a larger series of PI-RADS 3 that underwent target biopsy [6].

In our study, we included all patients who were find with a PI-RADS 3 area and who underwent prostate biopsies. Overall, 285 patients (80%) had a diagnosis of PCa. Moreover, our MVA model demonstrated a significant correlation between age, PSA, prostate volume and PCa. Our finding is consistent with those of the previously cited studies [3,6,17,18]. Our results showed a higher detection of PCa. It can be probably explained with two main reasons.

First, we are a fully oncological institute receiving patients with a diagnosis of PCa or selecting patients without a diagnosis but with a high clinical risk of harbor PCa (such as increased PSA etc.). Second, we usually perform targeted MRI-guided biopsies when a target lesion is found. This can lead with a higher rate of PCa diagnosis even in patients with a previous negative sampling.

Despite Liddell *et al* already demonstrated the association between PI-RADS 3 and low risk PCa [6], our MVA failed to demonstrate any predictor of PCa respecting PRIAS criteria. Clearly, previous negative biopsies can lead to a small PCa volume, but we cannot affirm this with the data shown ($p = 0.069$). For this reason, at our institution all the PI-RADS 3 lesions undergo a targeted confirmatory biopsy before being included in our AS protocol.

According to the available literature [19], we tried to improve our predictive model adding PSA density (cut-off 0.15 ng/ml/cc) in our analyses. Unfortunately, PSA density was not associated with PCa in UVA analysis and, in consequence, it was not included in the MVA model.

As expected, our third MVA showed that Gleason score at biopsy was the major predictor of clinically significant disease at final pathology. As previously described, roughly 30% of the patients experience a disease reclassification at final pathology with respect to prostate biopsy [20]. When a previous MRI is performed the reclassification decreased to 12.5% [20]. We can argue this is the reason why the GS detected at targeted biopsy strongly predicted clinically significant PCa at final pathology in our series.

On the other hand, a non-negligible part of RARP had a GS ≥ 7 (93 patients, 40.8%) and a T3 (35 patients, 15.4%) disease at final pathology.

Due to the low correspondence between PI-RADS 3 lesion at MRI and PCa at final pathology (42.2%) we routinely ask for frozen sections during RARPs. As previously described by our group this allows to better nerve-spare reducing positive margins [21]. Several possible explanations could justify the observed lower concordance rates between mpMRI lesion location and final pathology. Specifically, mpMRI could miss very small foci of PCa (tumor volume ≤ 0.4 ml in RARP specimens), as previously reported [22]. Moreover, cribriform pattern of PCa could be frequently missed by mpMRI scans [23].

Last, the performance of the MRI in the detection in CS PCa is influenced by several factors. First, the PIRADS category cut-off that is considered for performing a targeted biopsy. Specifically, while some authors recommend performing a targeted biopsy only in case of highly suspicious lesion (PIRADS 4–5), others suggested that also PIRADS 3 lesions need to be biopsied.

Second, the number of previous negative biopsies could influence the detection rates of MRI + targeted biopsies.

Specifically, patients with previous negative biopsies are at lower risk of harboring a CS PCa, compared to their biopsy naïve counterparts.

Third, MRI readers experience cloud affect cancer detection rates. Indeed, experienced radiologists are less prone to score a lesion as PIRADS 3, compared to less experienced readers [20].

Fourth, the prevalence of CS PCa changes according to the definition of CS PCa used as outcome (Gleason score $\geq 3+4$ vs $\geq 4+3$) [13,14,24].

Taken together it appears difficult to estimate the exact diagnostic performances of the MRI. However, previous authors reported a sensitivity of 77% and a specificity of 68% [25].

Moreover, data are scarce regarding the real rates of clinically significant prostate cancers in patients with PIRADS 3 lesions. In consequence, no convincing data are available today for estimating the performance of MRI in this category of patients.

Despite these strengths, our work is not free from limitations due to its retrospective nature.

As mentioned above, some of the patients coming to our attention already had a PCa diagnosis. This means that part of our cohort performed prostate biopsy elsewhere (except for target biopsies because they were all performed at our institution). For this reason, we do not have a homogeneous population in terms of number of cores taken and technique (transrectal vs transperineal) and this can be a misleading parameter.

Second, including only patients who underwent prostate biopsies we missed all those men who avoided a prostate biopsy, despite the presence of a PI-RADS 3 lesion (i.e. selection bias).

We are conscious that our reported rate of PCa is quite high for a PIRADS 3 population.

Third, we started a standardized and shared AS protocol just 3 years ago. Before this date, any decision on observation or indication to surgery for PCa was related to each single surgeon of our group. This may lead with the relatively high number of low-risk patients underwent RARP.

Finally, we did not test the inter-reader agreement between mpMRI reports. However, recent studies

demonstrated that PI-RADS scoring system has moderate/high vs. fair reproducibility in academic vs. peripheral centers [26,27].

To our knowledge this is the largest study assessing PI-RADS 3 lesions confirmed by biopsies and verifying their nature even at final pathology. Anyway, further studies are needed to better define the 'grey zone' of the PI-RADS 3 lesions to properly counsel our patients.

Our study highlighted how a PI-RADS 3 lesion at mp MRI is not itself appropriate to rise a suspect of PCa in an outpatient setting but it should always be supplemented by other clinical data.

On the other hand, when a PCa is found, it did not safely predict a low risk disease fitted for AS and it must be explored.

Despite this, more than 40% of the patients surgically treated showed a clinically significant PCa at final pathology.

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