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# Predictors of prostate cancer cetection in MRI PI-RADS 3 lesions – Reality of a terciary center

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**Summary** *Introduction and objectives: The Prostate Imaging Reporting and Data System (PI-RADS) score reports the likelihood of a clinically significant prostate cancer (CsPCa) based on various multiparametric prostate magnetic resonance imaging (mpMRI) characteristics. The PI-RADS category 3 is an intermediate status, with an equivocal risk of malignancy. The PSA density (PSAD) has been proposed as a tool to facilitate biopsy decisions on PI-RADS category 3 lesions. The objective of this study is to determine the frequency of CsPCa, assess the diagnostic value of targeted biopsy and identify clinical predictors to improve the CsPCa detection rate in PI-RADS category 3 lesions.*

*Methods: Between 1st January 2017 and 31st December 2022, a total of 1661 men underwent a prostate biopsy at our institution. Clinical and mpMRI data of men with PI-RADS 3 lesions was reviewed. The study population was divided into two groups: target group, including those submitted to systematic plus targeted biopsy versus non-target group when only systematic or saturation biopsy were performed. Patients with PI-RADS 3 lesions were divided into three categories based on pathological biopsy results: benign, clinically insignificant disease (score Gleason = 6 or International Society of Urologic Pathologic (ISUP) 1) and clinically significant cancer (score Gleason ≥ 7 (3+4) or ISUP ≥ 2) according to target and non-target group. Univariate and multivariate analyses were performed to identify clinical predictors to improve the CsPCa detection rate in PI-RADS category 3 lesions.*

*Results: A total of 130 men with PIRADS 3 index lesions were identified. Pathologic results were benign in 77 lesions (59.2%), 19 (14.6%) were clinically insignificant (Gleason score 6) and 34 (26.2%) were clinically significant (Gleason score 7 or higher). Eighty-seven of the patients were included in the target group (66.9%) and 43 in the non-target group (33.1%). The CsPCa detection was higher in the non-target group (32.6%, n = 14 vs 23.0%, n = 20 respectively). When systematic and target biopsies were jointly performed, if the results of systematic biopsies are not considered and only the results of target biopsies are taken into account, a CsPCa diagnosis would be missed on 9 patients. The differences of insignificant cancer and CsPCa rates among the target or non-target group were not statistically significant (p = 0.50 and p = 0.24, respectively). On multivariate analysis, the abnormal DRE and lesions localized in Peripheral zone (PZ) were significantly associated with a presence of CsPCa in PI-RADS 3 lesions (OR = 3.61, 95% CI [1.22,10.72], p = 0.02 and OR = 3.31, 95% CI [1.35, 8.11], p = 0.01, respectively). A higher median PSAD significantly predisposed for CsPCa on univariate analyses (p = 0.05), however, was not significant in the multivariate analysis (p = 0.76). In our population, using 0.10 ng/ml/ml as a cut-off to perform biopsy, 41 patients would have avoided biopsy (31.5%), but 5 cases of CsPCa would not have been detected (3.4%). We could not identify any statistical significance between other clinical and imagiological variables and CsPCa detection.*

*Conclusions: PI-RADS 3 lesions were associated with a low likelihood of CsPCa detection. A systematic biopsy associated or not with target biopsy is essential in PI-RADS 3 lesions, and targeted biopsy did not demonstrate to be superior in the detection of CsPCa. The presence of abnormal DRE and lesions localized in PZ potentially predict the presence of CsPCa in biopsied PI-RADS 3 lesions.*

KEY WORDS: *Prostate cancer; PI-RADS category 3 lesions; Prostate multiparametric MRI.*

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## INTRODUCTION

The implementation of *multiparametric prostate magnetic resonance imaging* (mpMRI) prior to prostate biopsy led to an improvement of *clinically significant prostate cancer* (CsPCa) diagnosis, contributing to the reduction of unnecessary biopsies and over-diagnosis of clinically insignificant prostate cancer and resultant overtreatment (1-4). In the setting of primary diagnosis, mpMRI was interpreted according to the *Prostate Imaging Reporting and Data System* (PI-RADS), created by the *European Society of Urogenital Radiology* (ESUR) to standardize radiologic reports and improve the diagnostic quality of prostate mpMRI exams (5). In 2021 a new PI-RADS version 2.1 replaced the previous 2.0 version published in 2015 (6). The PI-RADS score report the likelihood of a CsPCa based on various mpMRI characteristics. Categories PI-RADS 1 or 2 indicate (very) low likelihood of CsPCa, whereas categories 4 or 5 indicate (very) high likelihood of CsPCa. The European Association of Urology recommends performing a prostate biopsy when mpMRI shows lesions with PI-RADS ≥ 3 (7). However, the PI-RADS category 3 is an intermediate status, with an equivocal risk of malignancy (8). A metanalysis with 17 studies reported a cancer detection rate of 16% (7-27%) in patients with PI-RADS category 3 lesions. (9) The *PSA density* (PSAD) has been proposed as a tool to facilitate biopsy decisions on PI-RADS categoric 3 lesions. A recent study on biopsy naive patients with PI-RADS 3 lesions and low PSAD (< 0.10 ng/ml/ml) reported a low risk of sig-

nificant disease (4%) suggesting that biopsies could be avoided. Nevertheless, PI-RADS 3 scores in patients with high PSAD (> 0.20 ng/ml/ml) should be offered targeted and systematic biopsies due to the higher risk of significant disease (29%) (10).
The objective of this study is to determine the frequency of CsPCa, assess the diagnostic value of targeted biopsy and identify clinical predictors to improve the CsPCa detection rate in PI-RADS category 3 lesions.

## *Materials and methods*

Between 1st January 2017 and 31st December 2022, a total of 1661 men underwent a prostate biopsy at our center due to altered *prostate-specific antigen* (PSA) and/or abnormal *digital rectal examination* (DRE). The inclusion criteria were: mpMRI with a PI-RADS 3 lesion followed by prostate biopsy. These patients could be biopsy naive, with previous negative biopsies or in active surveillance protocol. The exclusion criteria were absence of mpMRI before prostate biopsy, mpMRI without PI-RADS classification, having a scored lesion other than PI-RADS 3 or only having performed target biopsy. A flowchart with study inclusion criteria is presented in Figure 1.
A total of 130 patients with PI-RADS 3 index lesions were retrospectively reviewed. All patients were treatment naive and clinical, mpMRI and pathologic data were collected for each patient. Clinical data included age, total PSA, ratio free to total PSA and DRE results (normal and abnormal findings). Abnormal findings were areas of localized or diffuse firmness, induration, irregularity or nodularity suggestive of a cT2 lesion. Prostate volume, number of target lesions, maximum lesion diameter and location (peripheral, transitional, or anterior zone and the base, middle or apex) were examined on mpMRI. PSAD was calculated using pre-biopsy PSA and mpMRI-derived volume.
All patients were submitted to a *transrectal ultrasound* (TRUS)-guided biopsy performed by an urologist (6 urologists, with a median 6.5 years of experience (range, 3-10 years)). Before the prostate biopsy, mpMRI was reviewed and analysed, identifying the presence of any PI-RADS lesion. The mpMRI was performed and reported by different radiologists but every mpMRI protocol included multiplanar T2-weighted imaging, *diffusion weighted imaging* (DWI), and *dynamic contrast-enhanced MRI* (DCE-MRI). The study population was divided into two groups to assess the diagnostic value of targeted biopsy: target group, including those submitted to systematic plus targeted biopsy versus non-target group when only systematic or saturation biopsy were performed. The patients were distributed according to physician's preference, and the two groups' pathological results were compared. The mpMRI-targeted biopsy was performed through cognitive guidance. Three to 5 cores were obtained from each target lesion.
The histopathology of the prostate biopsies was reported as a Gleason score and according to the 2014 *International Society of Urologic Pathologic* (ISUP) guidelines. Patients with PI-RADS 3 lesions were divided into three categories based on pathological biopsy results: benign, clinically insignificant disease (score Gleason = 6 or ISUP 1) and clinically significant cancer (score Gleason ≥ 7 (3+4) or ISUP ≥ 2) according to target and non-target group.

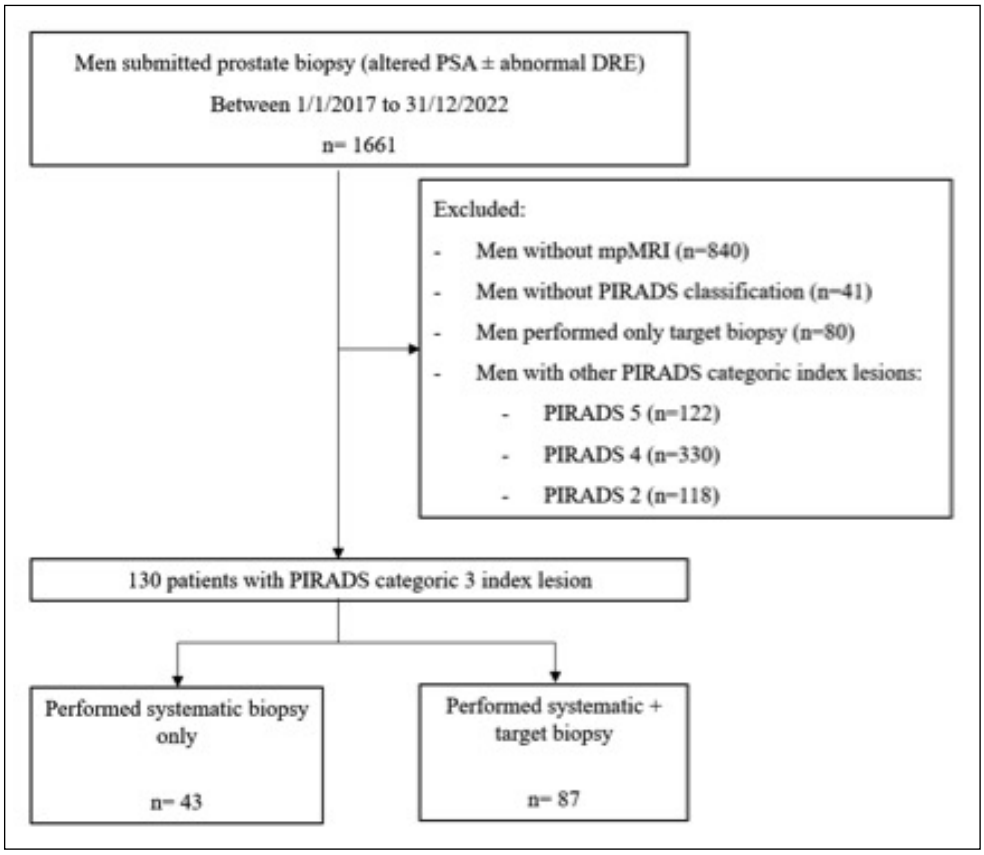


***Figure 1.***
*Flowchart for study inclusion among patients with PI-RADS 3 index lesions with clinical suspicion of prostate cancer.*

*DRE: Digital rectal examination; mpMRI: multiparametric magnetic resonance imaging; PSA: Prostate-specific antigen.*

Statistical analyses were performed using IBM SPSS Statistics software version 25. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Pearson's chi-squared or Fisher's Exact test were used to test for associations in categorical variables. Continuous variables were compared with the T-test student and Mann-Whitney U test. Simple and multiple logistic regression were performed to determine clinical predictors of CsPCa. A p-value ≤ 0.05 was considered statistically significant.

## Results

One thousand six hundred sixty-one men were submitted to prostate biopsy for altered PSA or/and abnormal DRE over the last 6 years. Patients without a pre-biopsy mpMRI (n = 840), without a PI-RADS classification in mpMRI (n = 41) and patients submitted to a target biopsy alone (n = 80) were excluded. One hundred and twenty-two patients with a PI-RADS category 5 lesions (17.4%), 330 with a PI-RADS category 4 lesions (47.1%) and 118 with PI-RADS category 2 lesions (16.9%) were not included in the cohort. The detailed patient inclusion and exclusion flow charts are presented in Figure 1.

A total of 130 men (18.5%) with PI-RADS 3 index lesions were biopsied and included in this study. One hundred fifty-three PI-RADS 3 index lesions were observed. General characteristics of the PI-RADS 3 lesions and patients are summarized in Table 1. The mean age was 65.2 ± 6.9 years. Median total PSA was 7.7 ng/dl (IQR 5.43-9.77), with a median of free/total PSA of 14.6% (IQR 11.0-18.9). Seventeen of 121 patients had an abnormal DRE (14.0%). Mean prostate size on mpMRI was 60.1 ± 22.6 ml. When calculated, median PSAD was 0.12 ng/ml/ml (IQR 0.09-0.18). Median maximum lesion diameter was 10.0 mm (IQR 7.0-13.0). The majority of the lesions were located on the *peripheral zone* (PZ) (64.9%) followed by *transitional* (TZ) and anterior zone (33.1% and 1.9%, respectively). Regarding prostatic location, most were in the middle of prostate (54.3%). One hundred and eight men had prostates with only one targeted lesion (83.1%) and 22 patients had more than one PI-RADS 3 lesion (16.9%). The number of PI-RADS 3 lesions in the prostate ranged from 1 to 4 lesions.

Pathologic results in this cohort were benign in 77 lesions (59.2%), 19 (14.6%) were clinically insignificant (Gleason score 6 or ISUP 1) and 34 (26.2%) were CsPCa (more than Gleason score 7 or above ISUP 2). Of the 34 patients with CsPCa, 30 patients had a Gleason score of 7 (3+4), 3 patients had a Gleason score of 7 (4+3) and one patient had a Gleason score 9 (5+4). Eighty-seven of the patients were included in the target group (66.9%) and 43 in the non-target group (33.1%). The pathologic outcomes of PI-RADS 3 lesions, considering the clinical data and target and non-target group, are described in Figure 2. The presence of benign histology was the most common result in both groups. The CsPCa detection in patients with previous negative biopsy was inferior compared to naive or active surveillance patients. The difference in CsPCa rates among the three clinical scenarios was not statistically significant (p = 0.32). The CsPCa detection was higher in the non-target group (32.6%, n = 14 *vs* 23.0%, n = 20 respectively). Regarding the target group, 11 patients with PI-RADS 3 lesions had CsPCa in both systematic and target biopsy (55.0%). Nine patients had a positive systematic and negative target biopsy. No case of a positive target biopsy and a negative systematic biopsy was identified. In all patients, the presence of positive pathologic findings in systemic and target biopsy, equivalent histological results for both specimens were found. When systematic and target biopsies were jointly performed, if the results of systematic biopsies are not considered and only the results of target biopsies are taken into account, a CsPCa diagnosis would be missed on 9 patients. The difference of insignificant cancer and CsPCa rates among the target or non-target group was not statistically significant (p = 0.50 and p = 0.24, respectively).

PSAD, abnormal DRE and peripheral target lesion location were significantly associated with CsPCa in PI-RADS 3 lesions (p = 0.05, 0.01 and 0.01, respectively). Clinical, mpMRI and pathologic findings on CsPCa lesions are reported in Table 3. On multivariate analysis, the abnormal DRE and lesions localized in *Peripheral zone* (PZ) were significantly associated with a presence of CsPCa in PI-RADS 3 lesions (OR = 3.61, 95% CI [1.22, 10.72], p = 0.02 and OR = 3.31, 95% CI [1.35, 8.11], p= 0.01, respectively). The frequency of abnormal DRE was superior in the group of CsPCa patients (29.0% *vs* 14.0%, respectively). The median PSAD was similar in CsPCa positive patients and the overall PI-RADS 3 lesions group. A higher median PSAD significantly predisposed for CsPCa on

***Table 1.***
*Clinical and imagiological characteristics of the PI-RADS categoric 3 cohort population.*

| Variables | No. (%) |
|---|---|
| Age (years) [Mean ± SD] | 65.2 ± 6.9 |
| Total PSA (ng/dl) [Median (IQR)] | 7.7 (5.43-9.77) |
| Free/total PSA (%) [Median (IQR)] | 14.6 (11.0-18.9) |
| Prostate volume (mL) [Mean ± SD] | 60.1 ± 22.6 |
| PSA Density (ng/ml/ml) [Median (IQR)] | 0.12 (0.09-0.18) |
| Abnormal DRE (n, %) | 17 (14.0) |
| Clinical scenario (n, %) | |
| - Biopsy naive | 84 (64.6) |
| - Previous negative biopsy | 34 (26.2) |
| - Active surveillance | 12 (9.2) |
| Maximum lesion diameter (ml) [Median (IQR)] | 10.0 (7.0-13.0) |
| Number of PI-RADS 3 index lesions (n, %) | |
| - Single | 108 (83.1) |
| - Multiple | 22 (16.9) |
| Target lesion zonal location (n = 154) (n, %) | |
| - Peripheral zone | 100 (64.9) |
| - Transition/central zone | 51 (33.1) |
| - Anterior fibromuscular stroma | 3 (1.9) |
| Target lesion quadrantal location (n = 140) (n, %) | |
| - Base | 30 (21.4) |
| - Middle | 76 (54.3) |
| - Apex | 34 (24.3) |

*DRE: Digital rectal examination; IQR: interquartile range; SD: Standard deviation; PSA: Prostate-specific antigen.*

univariate analyses (p = 0.05) but was not significant in the multivariate analysis (p = 0.76). In our population, using 0.10 ng/ml/ml as a cut-off to perform biopsy, 41 patients would have avoided biopsy (31.5%), but 5 cases of CsPCa would not have been detected (3.4%). We could not identify statistical significance between others clinical and imagiological variables and CsPCa detection.

## Discussion

The evaluation of PI-RADS 3 lesions does not represent the primary endpoint in most studies of prostate cancer diagnosis, and, currently, the quality of the studies focusing on this PI-RADS subset remains low. PI-RADS classification was designed to reduce the mpMRI inter-reader reproducibility, however, it does not provide a specific management algorithm for each category (11). Concerning the PI-RADS 3 lesions, there is no agreement on the best clinical management - biopsy or clinical surveillance (12, 13). Prostate biopsy is the standard recommendation, however, in some cases a follow-up strategy could be an acceptable option (10, 11).

In our institution, the prevalence of PI-RADS 3 lesions was 18.5%. *Maggi et al.*, in a review of 23 studies, reported a prevalence of PI-RADS 3 cases of 17.3% (range 6.4-45.7%) (11). Given the incidence of these lesions, choosing the best approach is essential. We demonstrated that PI-RADS 3 lesions were associated with a low risk of prostate cancer (40.8%), especially when considering CsPCa. In our study, most PI-RADS 3 lesions were benign (59.2%) and only 26.2% were CsPCa. The most common Gleason scored diagnosed was score 7 (3+4) or ISUP 2 (30/34). Regarding the diagnosis of ISUP 4 or higher, only one case was identified on PI-RADS 3 lesions. The CsPCa rate was significantly variable between published studies. This can be explained based on the population heterogeneity, MRI protocols, type of mpMRI-targeted biopsy (cognitive guidance, ultrasound or MRI fusion software or direct in-bore guidance) and CsPCa definitions. *Oerther et al.* reported a cancer detection rate of 16% (7-27%) in patients with PI-RADS 3 lesions (9). *Schoots et al.* reviewed 3006 biopsy-naive men in five studies and found the percentage of ISUP ≥ 2 detection rate in lesions PIRADS 3 was 16% (10). In a review of thirteen prospective studies of PI-RADS 3 lesions, the overall PCa detection rate was 37%, while for CsPCa it was 21% (14). *Magui et al.*, in a systematic review of 28 studies with a total of 1759 cases of PIRADS 3 lesions, reported a prostate cancer detection rate of 36% (range 10.3-55.8%) and CsPCa rate of 18.5% (range 3.4-46.5%) (11).

The best biopsy strategy also remains controversial. The inclusion of the MRI previously to prostate biopsy increased the number of CsPCa detected and reduced the number of insignificant cancer. However, omitting systematic biopsy would miss approximately 16% and 10% of all detected ISUP grade ≥ 2 in biopsy-naive and repeat-biopsy patients, respectively (1-4) In our population, the CsPCa rate was slightly higher in non-target group (32.6 *vs*. 23%, respectively); and paradoxically, insignificantly cancer rate was slightly higher in the target group (16.1 *vs*. 11.6%, respectively). However, both results were not statistically significant (p = 0.50 and p = 0.24, respectively). Nevertheless, a CsPCa diagnosis would be missed in 9 patients if targeted biopsy was performed alone, confirming the importance of not omitting the systematic biopsy in this setting. In our cohort, the value of the systematic biopsy was demonstrated. No case of histological upgrading or only positive pathological results on target biopsies were reported. In our opinion, the target biopsy could be omitted in PI-RADS 3 lesions, however the systematic biopsy should always be performed if CsPCA is suspected. The importance of the systematic biopsies in CsPCa detection in PI-RADS 3 lesions can be explained due to MRI interpretation and mistargeting issues (i.e., the lesion has been correctly identified by mpMRI but missed by mpMRI-targeted biopsy and detected by systematic sampling), especially in non-peripheral zones and smaller lesions. Some authors advocate a saturation targeted approach or increasing the number of cores taken by target to raise the CsPCa detection (15, 16). We believe that in reference centers with large number of patients, experienced teams with dedicated radiologists and urologists, well-defined protocols and newer technologies or softwares, the target biopsy may be crucial in PI-RADS 3 lesions. However, in tertiary centers like ours, there are some disadvantages - smaller number of patients, interpretation of mpMRI by different radiologists and different urologists with different levels of experience. Our targeted biopsies were obtained by cognitive guidance. The current literature does not show superiority or inferiority of the cognitive technique compared with US/MR fusion software or direct in-bore guidance (17).

Regarding the pathology analyses, the most common result was benign histology in both groups. The CsPCa detection in patients with previous negative biopsy was lower comparative to naive or active surveillance patients. The difference of CsPCa rates among the three groups was not statistically significant (p = 0.32). Given the high variability of the published studies, it is difficult to decide to perform prostate biopsy in case of PI-RADS 3 lesions independently of clinical scenario (naive patient, or with previous negative biopsy, or active surveillance) (11).

Many studies tried to identify clinical and imagiological findings that can help to identify which patients can be selected for surveillance. PSAD is the most frequently investigated clinical predictor. Recently, a risk-adapted biopsy decision was proposed, based on PSAD and mpMRI report. Concerning the PI-RADS 3 lesions, patients with high-risk PSAD (> 0.20 ng/ml/ml) should be offered targeted and systematic biopsies as they have a higher risk for significant disease (29%). On the other hand, patients with low risk PSAD (< 0.10 ng/ml/ml) have a low risk of significant disease (4%) and biopsies could be avoided (10). In our study, the median PSAD was similar in CsPCa positive patients and the general PI-RADS 3 lesions cases. A higher median PSAD significantly predisposed for CsPCa on univariate analyses (p = 0.05) but not significant in the multivariate analysis (p = 0.76). In our population, using 0.10 ng/ml/ml as a cut-off to perform biopsy, 41 patients would have avoided biopsy (31.5%), but 5 cases of CsPCa would not have been detected (3.4%). *Venderink et al.* demonstrated that biopsying only PI-RADS 3 cases with a PSAD of ≥ 0.15 ng/ml/ml resulted in 42% of cases who would avoid biopsy, thus missing 6%

of CsPCa cases. Lowering the cut-off value to 0.12 ng/ml/ml resulted in 26% of cases that would have avoided biopsy without missing any CsPCa (18).
An abnormal DRE (p = 0.02) and a peripheral target lesion (p = 0.01) significantly predisposed for CsPCa in multivariate logistic regression. The frequency of abnormal DRE was higher in the CsPCa patients group comparatively to general PI-RADS 3 cases (29.0% *vs* 14.0%, respectively). *Sheridan et al.* calculated risks factors of CsPCa in PI-RADS 3 lesions in their multivariate analyses and demonstrated that an abnormal DRE was a significant predictor of CsPCa (OR.3.92, p = 0.03), as was advanced age (≥ 70 years) and smaller prostates (≤ 36cc) (19). *Radtle et al.* showed that a higher PSA level (OR, 2.08), a smaller gland size (OR, 0.81), abnormal DRE findings (cT2 or more lesion, OR, 4.09) and advanced age (OR, 1.09) were independently associated with CsPCa in PI-RADS 3 lesions. (20) Abnormal DRE is a strong predictor of advanced PCa that is associated with an increasing risk of higher ISUP and, despite being a subjective test, is an important tool in our population to decide who should underwent biopsy.
Most of the PI-RADs 3 lesions in our cohort were located in the peripheral zone, independently of CsPCa results. *Liddell et al.* showed that PI-RADS 3 lesions within the PZ were more likely to be associated with malignant disease compared with lesions identified within TZ (10.8% *vs.* 3.8%) (21). *Yang et al.* demonstrated in his study that PI-RADS 3 lesions were most frequent in TZ than PZ (n = 67 and n = 54, respectively), however the CsPCa rate was superior in PZ (18.5% *vs*. 6.0%, respectively) (22). *Galosi et al.* defended a low risk of cancer in PI-RADS 3 lesions located in TZ; they concluded that biopsy could be omitted in same patients considering a nomogram with PCa risk, PSAD, and lesion location (23). A systematic review and meta-analyses of a total of 17 articles showed no systematic difference of cancer detection rate between PZ lesions and TZ lesions in different PI-RADS classifications (24). *Schoots et al.* explain that mpMRI interpretation of TZ is more challenging comparative to PZ because the TZ shows heterogeneous signal intensities due to presence of nodules of benign prostatic hyperplasia while a normal PZ is brightly hyperintense on T2 images and hypointense abnormalities can be easily identified. In case of PI-RADS 3 lesions, the overlapping with benign situations often interpreted as false-positive mpMRI findings (benign prostate hyperplasia, inflammation or fibrosis) are more common (25). This can explain the higher frequency of PI-RADS 3 lesions on TZ, however, it was not observed in our cohort.
Our study has several limitations. It is a retrospective study, from a single institution and with limited PI-RADS 3 lesions enrolled which may have resulted in possible risk of selection bias. It included patients from 2017 to 2022 and some lesions were classified as intermediate probability using criteria from version 2 and others with version 2.1. Therefore, the possibility of a bias of interpretation is higher given that the mpMRI reports are reviewed by multiple readers, with an interobserver variability of identification and classification of the lesions. Biopsies were also performed by different urologists with different experience and biopsy specimens were evaluated by multiple pathologists. It was not possible to compare the results with other approaches, namely transperineal biopsy or fusion guided software, to analyse differences in CsPCa detection. Our definition of CsPCa considered only the Gleason/ISUP score without any interpretation on basis in lesion volume. Larger studies, prospective and randomized, are required to evaluate the reproducibility of our results.

## Conclusions

We have demonstrated in our cohort that prostate lesions characterized as PI-RADS 3 lesions, according to the current prevalent scoring systems, were associated with a low likelihood of the CsPCa detection. A systematic biopsy associated or not with a target biopsy is essential in PI-RADS 3 lesions, and targeted biopsy did not demonstrate to be superior in the detection of CsPCa. The presence of abnormal DRE and lesions localized in PZ potentially predict the presence of CsPCa in biopsied PI-RADS 3 lesions.

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