Follow-up on patients with initial negative mpMRI target and systematic biopsy for PI-RADS ≥ 3 lesions – an EAU-YAU study enhancing prostate cancer detection

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Abstract

Purpose

To investigate the detection and predictors of prostate cancer (PCA) and clinically significant prostate cancer (csPCA) in patients with positive multiparametric MRI (mpMRI) followed by a negative MRI – guided target biopsy (TB) and systematic biopsy (SB).

Materials and methods

This retrospective multicenter study included 694 patients from 10 tertiary referral centers with an initial positive mpMRI (PI-RADS ≥ 3) and negative results on both MRI-TB and SB. Patients were classified into three groups based on follow-up: Group 1 (prostate re-biopsy without new mpMRI), Group 2 (standardized second prostate mpMRI and subsequent re-biopsy), and Group 3 (follow-up with mpMRIs and biopsy based on clinical and radiological triggers). The primary outcomes were the detection of any PCA and csPCA during follow up. Study groups were compared according to their probability of PCA and csPCA assessed with the ERSPC-MRI risk calculator. Statistical analysis included Kaplan – Meier analysis, Cox regression, and multivariable analysis for the detection of (cs)PCa.

Results

The overall detection of PCA and csPCA was 26.8% and 19.3%, respectively, with varying rates in different PI-RADS groups. Group 3 had the highest 2-year and 5-year PCA–free survival (94 and 84%) and csPCA – free survival (96 and 86%). Multivariable analysis revealed a significantly higher risk of PCA and csPCA in Group 1 and 2 compared to Group 3 ($p < 0.01$). Clinical and radiological predictors for PCA and csPCA included higher age, prostate volume, PI-RADS score, the presence of atypical small acinar proliferation (ASAP), and a smaller number of TB and SB performed during the initial biopsy. Study limitations, include the retrospective design and reliance on clinical and radiological triggers for follow–up decisions.

Conclusions

Patients with positive mpMRI but negative TB and SB results exhibit varying rates of PCA and csPCA depending on the follow up scheme. Tailored follow-up strategies are essential for optimal management in this clinical scenario.

Introduction

The detection of prostate cancer (PCA) has significantly changed recently due to the introduction of multiparametric MRI (mpMRI). The integration of artificial intelligence and computer-aided diagnosis with mpMRI has further enhanced lesion characterization by automating detection, reducing variability among radiologists, and increasing diagnostic accuracy [1, 2]. MRI-based risk calculators guide management in patients with positive MRI and negative biopsies by improving the prediction of clinically significant (CS) prostate cancer (PCa) [3]. While they reduce unnecessary biopsies through more accurate patient's selection with MRI and MRI-based risk calculators [4], continuous validation of predictive models is essential for enhancing their clinical utility for different clinical settings and populations [3].

MRI-guided target biopsy (TB) was associated with significantly higher diagnostic accuracy for CSPca reducing at the same time the diagnosis of clinically insignificant (CI) PCA [5] compared to systematic biopsy alone (SB). Further increases in diagnostic accuracy can be achieved by combining TB with SB, although this may come at the cost of increased infection and pain morbidity [6]. Moreover, in patients with negative MRI, its predictive value ranges from 91 to 96% for the detection of csPCA according to the different definitions of csPCA, allowing the possibility of avoiding biopsy in many patients with negative MRI [7, 8].

One of the current unclear clinical scenarios is represented by the patients with positive mpMRI but negative TB and SB. This could either be explained by false positive MRI review or missed positive lesion at prostate biopsy. A recent mini-systematic review identified nine studies [9,10,11,12,13,14] including overall less than 500 patients in this clinical setting. On the whole, the systematic review demonstrated a highly variable detection rate of csPCA, ranging from 7.5 to 80% in PI-RADS 3 lesions, from 17 to 75% in PI-RADS 4 lesions, and over 80% in PI-RADS 5 lesions [15]. Based on those limited and heterogeneous data, the EAU guidelines suggested performing a rereview of the MRI after negative TBx, preferably from a high-volume expert radiologist in a tertiary referral center and, subsequently, clinical follow-up with PSA and repeated mpMRI at 6–12 mo for PI-RADS/Likert 3 lesions; clinical follow-up with PSA, repeated mpMRI, and repeated biopsy at 3–6 mo for PI-RADS/Likert 4 lesions; direct repeated biopsy for PI-RADS/Likert 5 lesions [15].

In the face of such a paucity of data supporting these recommendations, we elected to investigate further the detection of any PCA and csPCA and their clinical and radiological predictors in patients with positive mpMRI and negative MRI-TB and SB in a retrospective, multi-center series of patients with negative TB and SB following initial positive mpMRI, including patients receiving repeated biopsy only, repeated mpMRI and repeated biopsy, only clinical follow-up.

Materials & methods

The present study obtained Internal Review Board approval for retrospective data collection in accordance with the policies of each participating institution. Informed consent was obtained from all subjects included in the study. A total of 694 patients from 10 tertiary referral centers were included. Inclusion criteria were patients with a first positive mpMRI (PI-RADS ≥ 3) along with negative results on both MRI TB and SB (initial biopsy).

During the first 18 months, we classified patient management according to three different types of follow-ups, as decided by treating urologist:

1.
Group 1: Prostate re-biopsy without a new mpMRI.

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Group 2: Standardized second prostate mpMRI and subsequent re-biopsy, including either MRI-TBx and/or SB. Detailed information regarding this population is described elsewhere [12].

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The exclusion criteria included patients who underwent systematic biopsy before the initial MRI-TBx, as well as individuals who were previously diagnosed with PCa.

Prostate biopsy techniques

A mpMRI was performed before the first biopsy, following each institution's protocol. All centers utilized the PI-RADS v2 scoring system to assess MRI findings [16]. Expert genitourinary radiologists reviewed all MRIs in accordance with the ESUR/ESUI consensus for image acquisition, interpretation, and radiologists' training [17]. Transrectal or transperineal targeted biopsies were performed by experienced urologists using their preferred biopsy approach. No changes in biopsy techniques were made at each center during the follow-up period. TBs were performed using dedicated biopsy fusion software or cognitive methods, according to the expertise of each center. Transperineal TB was performed with a brachytherapy grid or freehand technique under general or local anesthesia. The number of SB after TB were performed according to each institution protocol.

Assessing the probability of any PCA and csPCA at the first negative biopsy

The probability of any PCA and csPCA has been calculated for each patient with the ERSPC-MRI risk groups (RC5, and RC6) at the first negative biopsy [18]. To ensure the optimal risk prediction in our cohort, the probability has been recalibrated according to the present cohort PCA and csPCA prevalence.

Statistical analysis

Categorical variables were presented as frequencies, while continuous variables were reported as mean ± standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Differences in baseline characteristics between categorical and continuous variables were assessed using either chi-square, ANOVA or Mann-Whitney U test, as appropriate. Kruskal-Wallis test was used to assess any significant differences on a continuous dependent variable by the three groups.

PCA and csPCA detection-free survival were evaluated using Kaplan-Meier analysis. The multiple log-rank test was used for comparison of the survival curves. Univariable (UVA) and multivariable (MVA) Cox regression analyses were performed to evaluate predictors for PCA and csPCA at the moment of repeat biopsy. CsPCA was defined as any ISUP ≥ 2 cancer. Covariates included in the model were selected based on univariable results with p-values ≤ 0.1. Variables with suspicious interaction terms (PSA and Prostate volume with PSAD as well as PI-RADS with cT stage at MRI) were adjusted accordingly. The analyses were performed in the whole population and in the subgroup with PI-RADS ≥ 4 lesions.

A significance level of $p < 0.05$ was used for all tests. Statistical analyses were performed using SPSS version 28 (IBM, Armonk, NY, USA).

Results

Table 1 describes the characteristics of the initial biopsy and follow-up for the 694 patients in the whole cohort and stratified by study group. Each center contributed with all three follow-up strategies. Figure 1 illustrates the evolution of the diagnostic pathway from the first biopsy to the available follow-up of this selected patient population in a Sankey diagram.

Overall, we identified 174 (27%) any grade PCA and 134 (19%) csPCA at a median follow-up duration of 28 mo (13–51). The median time from the first MRI to PCA diagnosis or last follow-up was 24 (13–40), 28 mo (17–45), and 20 mo (9–51) for groups 1 to 3, respectively ($p < 0.01$). The detection of any PCA and csPCA was 19 and 15% in initial PI-RADS 3 lesions; 27 and 21% in initial PI-RADS 4 lesions; and 60 and 37% in initial PI-RADS 5 lesions.

The three groups differ in most of the clinical and radiological characteristics. However, no differences have been observed among the three groups in the detection of any PCA and csPCA after the first negative biopsy as estimated by the ERSPC-MRI PCA risk calculator.

From the original biopsy, the median number of mpMRI was 0 (0–1) for group 1 and 1 (1–2) for groups 2 and 3 (p value < 0.01). The median number of prostate re-biopsy was 1 (1–2) in groups 1 and 2 and 1 (0–1) in group 3 (p value < 0.01). Overall, 75% of the patients had software-based registration for repeated TB, and 60% of the patients had a transperineal biopsy during repeated biopsies.

In group 1, the re-biopsy was performed at a median of 13 (10–14) months after the original biopsy and detected PCA and csPCA in 29 (50%) and 21 patients (36%). Among the patients with negative repeated biopsy, 2 had further mpMRI, and 2 patients had further prostatic biopsy. At a follow-up of 24 (IQR: 13.3. 40.2), no further cancer was diagnosed. Data for group 2 were extensively reported previously [12]. The interval from the initial to repeated mpMRI and from the initial to repeated biopsy were 16 mo (IQR 12–20) and 18 mo (IQR 12–21), respectively. The PI-RADS score at the second MRI was classified as <3 in 25 patients (9%), 3 in 91 patients (31%), 4 in 137 patients (47%), and 5 in 37 patients (13%). One hundred and eight patients (37%) were diagnosed with PCA and 74 (25.5%) with csPCA at re-biopsy. SB and MRI-TBx identified PCA in 28 and 31% of the cases (including 18 and 20% of csPCA).

The median follow-up from second negative biopsy was 20 months (IQR: 5.7–34.7). Further MRI and subsequent biopsy were performed in 19 patients, of whom only 2 patients were diagnosed with PCA.

In group 3, additional mpMRI during follow up was performed in 198 (69%) patients, identifying graded as PI-RADS < 3, 3 and >3 in 24%, 68%, and 8% of patients, respectively. On the whole, 93 patients (27%) received at least one repeated biopsy during follow-up. PCA and csPCA were detected in 35 (12%) and 27 patients (9.3%), however in a “repeat biopsy analysis” PCA and csPCA were detected in a percentage similar to group 1 and 2 ($p = 0.06$).

Predictors of any grade and clinically significant PCA
Figure 2 reports Kaplan-Meier curves for PCA and csPCA free survival in the whole cohort and stratified by study group and PI-RADS score.

Overall, the 2- and 5-year PCA free survival estimates were 99 and 65% respectively; the 2- and 5-year csPCA free survival estimates were 99 and 71%, respectively.

When stratified by study group, PCA-free and csPCA-free survival estimates were similar in groups 1 and 2 (log rank p value 0.4 for PCA and 0.7 for csPCA) but significantly higher in group 3 (log rank p value < 0.01) (Fig. 3). In particular the 2-year and 5 year Pca were respectively 63 and 50% for group 1, 72 and 51% for group 2 and 94 and 84% for group 3 ($p < 0.01$ between group 3 vs. group 1 and group 2).

The 2-year and 5-year csPca were respectively 77 and 60% for group 1, 94 and 61% for group 2 and 96 and 86% for group 3 ($p < 0.01$ between group 3 vs. group 1 and group 2).

When stratified by PI-RADS score, PCA-free and csPCA-free survival estimates were significantly the lowest in PI-RADS 5 lesions and the highest in PI-RADS 3 lesions (log rank p value < 0.01) (Fig. 4).

Table 2 summarizes UVA and MVA Cox regression analyses assessing clinical and radiological predictors of PCA and csPCA after the initial negative biopsy.

In the multivariable analysis, there was no statistically significant difference between group 1 and 2 (HR = 0.8, 95% CI = 0.5–1.3, p = 0.4), see Table 2. However, the hazard on PCa and csPCa (HR = 0.2, 95% CI 0.1–0.4, p = p < 0.01) was lower for Group 3 vs. Group 1.

Furthermore, several clinical and radiological covariates (including patients age, prostate volume, PI-RADS score at the first MRI, presence of ASAP at the initial biopsy, number of TB and SB performed during the initial biopsy) were identified as predictors of PCA diagnosis during further follow-up.

Table 3 summarizes UVA and MVA Cox regression analyses assessing clinical and radiological predictors of PCA and cs-PCA after the initial negative biopsy in cases with PI-RADS > 3 at the first MRI.

Once again, the study group variable, the number of systematic biopsies, and the presence of ASAP at the initial biopsy were identified as predictors of subsequent detection of PCA and csPCA. In addition, PSAD was an independent predictor of PCA (HR: 6.9, p < 0.01).

Treatments
Supplementary Table 1 summarizes the treatment for the patients diagnosed with PCA and radical prostatectomy specimen data for the patients who received surgery.

Among the selected treatment options, active surveillance/watchful waiting, surgery, radiation therapy, and focal therapy were chosen by 36 (21.4%), 109 (64.9%), 19 (11.3%), and 5 (2.4%) patients, respectively (supplementary Table 1).

Among the 109 radical prostatectomies, 53/109 had a pT stage T3 and 63/109 had a ISUP score 3.

Discussion

The presented study investigates the characteristics, follow-up outcomes, treatment decisions, and predictors of PCA and csPCA in a cohort of 694 patients with an initial positive mpMRI and negative prostate biopsies followed up according to different protocols. Overall, about 25% of the patients were diagnosed with PCA, more than 75% of which were identified as csPCA. This underscores the critical importance of establishing an accurate follow-up schedule for these patients, as the presence of csPCA cannot be definitively ruled out in a significant number of patients. Notably, about 16% of those patients with Pca underwent radical prostatectomy during the available follow-up. Among these patients, more than 50% exhibited a pT stage T3 and about the same percentage had a ISUP score 3.

We conducted a comprehensive comparative analysis of three distinct follow-up schedules, revealing outcomes disparities. Patients who underwent a second biopsy without a new MRI exhibited similar results to those who received a new MRI before the second biopsy. Conversely, individuals who underwent a second biopsy triggered by specific clinical and radiological factors demonstrated a low detection of PCA and csPCA. This underscores the need for a risk-based strategy to mitigate overdiagnosis on one hand and, on the other, a more rigorous follow-up approach to prevent the omission of caPCA diagnosis. In particular, the potential limitations of the first TB emphasize the need for further investigations and follow-up in cases with inconsistent results between MRI images and MRI-guided biopsy findings. In addition to MRI, a possible role of PET/CT has been explored in recent studies [19, 20]. The implementation of PSMA PET/CT with MRI results would help the selection of men who would benefit the most of screening or further biopsies [21].

The significance of second MRI within the initial 18 months after the first biopsy has been assessed in our prior publication [22]. In cases where lesions were initially described in the first MRI, downgrading occurred in only 19% of instances, while upgrading was observed in 39%, and stability was maintained in 42% of cases. The approach of combining SB and TB yielded elevated detection rates. For patients with lesions detected at the first MRI, the positivity rates were 16%, and for those with new lesions detected at the second MRI, the rate was 17.2% [22]. Conversely, the data of the present analysis suggested very similar diagnostic performance with group 1, i.e. the group of patients who repeated prostate biopsy without a new mpMRI. That was shown in the whole cohort and the subgroup of patients with initial PI-RADS lesions graded as 4 or 5. Unfortunately, even in a large multicenter series, the limited number of cases did not allow to further stratify the analyses.

This finding suggests that an additional MRI within one year may not always be necessary before repeat biopsies in this setting of patients, potentially reducing the overall cost and burden of prostate cancer diagnosis, streamlining protocols, particularly in regions with limited access to advanced imaging. Since in a recent mini-systematic review by Grivas [15] only nine studies, including less than 500 patients in this clinical setting, strong recommendations cannot be done by international guidelines. Overall, the systematic review demonstrated that the detection of csPCA was highly variable among the few available studies. Specifically, csPCA was detected in 7.5 to 80% of the patients with PI-RADS 3 lesions, 17 to 75% with PI-RADS 4 lesions, and over 80% with PI-RADS 5 lesions [15].

Different factors, including heterogeneity in mpMRI quality and accuracy, inaccuracy/errors in TB or SB, and discrepancies in the follow-up protocols can explain such large differences. In the present analysis, we identified csPCA in about 20% of the whole population and 36%, 30%, and 8% of groups 1 to 3, respectively. Notably, those patients who were followed up less strictly, with repeated biopsy triggered by PSA increase, DRE changes and radiological progression in repeated MRIs, had a significantly lower chance of being diagnosed with PCA and csPCA. Although several differences in the patients' characteristics are evident among the different study groups, the detection of PCA and csPCA estimated by the ERSPC-MRI PCA risk calculator was similar. The data is constant in all our analyses and might allow us to hypothesize a certain level of underdetection of csPCA in this subgroup of patients.

We identified several predictors of PCA and csPCA during the initial biopsy that warrant thorough evaluation when considering the decision for a second biopsy during patient consultation. Specifically, the presence of a high PI-RADS score, advanced age, smaller prostate volume, adequate prostate biopsy sampling with >3 fusion cores and >12 systematic biopsies, along with the presence of ASAP at the first biopsy, can serve as indicators for the likelihood of PCA and csPCA presence.

ASAP is regarded as a precursor lesion, often indicating that the prostate tissue is undergoing changes that are more likely to progress to cancer over time. While not all instances of ASAP will inevitably develop into cancer, its presence prompts clinicians to engage in closer patient monitoring. However, there is an ongoing debate regarding the role of ASAP in the MRI era [23, 24]. In our study, we observed a robust correlation between the presence of ASAP on the initial biopsy and the likelihood of PCA and csPCA occurrence. This supports the growing interest in investigating glandular-stromal alterations, along with acute or chronic inflammation and vascular changes.

Interestingly, the TR vs. TP route was not found to be an independent predictor of PCa and csPCa this unique population, supporting recent evidence from prospective studies [25].

The present study is relevant for several reasons. It includes more patients than the only available systematic review on the topic. Consequently, the study provides more reliable data on the detection of PCA and, above all, csPCA in such an interesting patients population. Moreover, the series collected data from different tertiary referral

centers, indicating a potentiality for good validity of the data in real life practice. Third, we provided data on PCA and csPCA predictors. Several limitations should be acknowledged. First of all, despite the present retrospective series being large, the number of patients with initial PI-RADS 4 or 5 lesions at MRI and subsequently negative TB/SB is limited. That might have made some of our analyses underpowered and limited our ability to perform more accurate subgroup analyses. Secondly, the study is retrospective, which introduces a significant risk of selection bias for follow-up, and patients were followed with different protocols. In other words, it is possible that patients with a higher risk of cancers, in the opinion of the attending urologists, might have been followed more strictly than those with a potentially lower risk. Although our statistical analyses tried to correct for the differences in covariate distributions, we cannot be sure that a selection bias might explain at least partially our findings. However, the finding that the detection of PCA and csPCA estimated by the ERSPC-MR PCA risk calculator was similar in the 3 groups suggest that such selection bias should not play a major role. The dataset includes both transperineal and transrectal prostate biopsies which may have different detection rate [26, 27] and the results could have been different including one procedure only. The present study is preliminary, and randomized controlled trials evaluating various follow-up protocols in patients with positive MRI and negative TB/SB results would be valuable for standardizing the follow-up procedures for these patients. Finally, at the current follow- up, we are not able to understand the prognostic implications related to the diagnosis of such csPCA, which could arguably have lower volume and reduced clinical aggressively compared to those diagnosed in the first prostatic biopsy.

Conclusions

Prostate cancer diagnostics should be regarded as a longitudinal process, instead of a cross-sectional one-time approach. Overall, our findings contribute to a better understanding of patient characteristics, follow-up trajectories, treatment preferences, and predictive factors for PCA and csPCA, offering valuable insights for clinical decision-making and management strategies in these men with abnormal MRI but negative biopsy. Less aggressive re-imaging and re-biopsy may lead to more csPCa being missed. Improved knowledge on follow-up findings aids in primary biopsy decisions.

Data availability

The data that support the findings of this study are available for sharing but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of authors.

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Materials and methods

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Results

The overall detection of PCA and csPCA was 26.8% and 19.3%, respectively, with varying rates in different PI-RADS groups. Group 3 had the highest 2-year and 5-year PCA–free survival (94 and 84%) and csPCA – free survival (96 and 86%). Multivariable analysis revealed a significantly higher risk of PCA and csPCA in Group 1 and 2 compared to Group 3 ($p < 0.01$). Clinical and radiological predictors for PCA and csPCA included higher age, prostate volume, PI-RADS score, the presence of atypical small acinar proliferation (ASAP), and a smaller number of TB and SB performed during the initial biopsy. Study limitations, include the retrospective design and reliance on clinical and radiological triggers for follow–up decisions.

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The probability of any PCA and csPCA has been calculated for each patient with the ERSPC-MRI risk groups (RC5, and RC6) at the first negative biopsy [18]. To ensure the optimal risk prediction in our cohort, the probability has been recalibrated according to the present cohort PCA and csPCA prevalence.

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Categorical variables were presented as frequencies, while continuous variables were reported as mean ± standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Differences in baseline characteristics between categorical and continuous variables were assessed using either chi-square, ANOVA or Mann-Whitney U test, as appropriate. Kruskal-Wallis test was used to assess any significant differences on a continuous dependent variable by the three groups.

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Table 1 characteristics of the 694 patients with positive mpMRI and initial negative biopsy.
Full size table

Fig. 1: Sankey Diagram: Patient Progression from Initial MRI to Final Diagnosis.
figure 1

This diagram illustrates the clinical pathway across three study groups, starting with their initial MRI results categorized as PI-RADS 3, 4, or 5 lesions. It shows the proportion of patients in each group who had a negative result, clinically significant prostate cancer (csPCA), or prostate cancer (PCA) after undergoing a second biopsy and follow-up evaluation.

Full size image

Overall, we identified 174 (27%) any grade PCA and 134 (19%) csPCA at a median follow-up duration of 28 mo (13–51). The median time from the first MRI to PCA diagnosis or last follow-up was 24 (13–40), 28 mo (17–45), and 20 mo (9–51) for groups 1 to 3, respectively ($p < 0.01$). The detection of any PCA and csPCA was 19 and 15% in initial PI-RADS 3 lesions; 27 and 21% in initial PI-RADS 4 lesions; and 60 and 37% in initial PI-RADS 5 lesions.

The three groups differ in most of the clinical and radiological characteristics. However, no differences have been observed among the three groups in the detection of any PCA and csPCA after the first negative biopsy as estimated by the ERSPC-MRI PCA risk calculator.

From the original biopsy, the median number of mpMRI was 0 (0–1) for group 1 and 1 (1–2) for groups 2 and 3 (p value < 0.01). The median number of prostate re-biopsy was 1 (1–2) in groups 1 and 2 and 1 (0–1) in group 3 (p value < 0.01). Overall, 75% of the patients had software-based registration for repeated TB, and 60% of the patients had a transperineal biopsy during repeated biopsies.

In group 1, the re-biopsy was performed at a median of 13 (10–14) months after the original biopsy and detected PCA and csPCA in 29 (50%) and 21 patients (36%). Among the patients with negative repeated biopsy, 2 had further mpMRI, and 2 patients had further prostatic biopsy. At a follow-up of 24 (IQR: 13.3. 40.2), no further cancer was diagnosed. Data for group 2 were extensively reported previously [12]. The interval from the initial to repeated mpMRI and from the initial to repeated biopsy were 16 mo (IQR 12–20) and 18 mo (IQR 12–21), respectively. The PI-RADS score at the second MRI was classified as <3 in 25 patients (9%), 3 in 91 patients (31%), 4 in 137 patients (47%), and 5 in 37 patients (13%). One hundred and eight patients (37%) were diagnosed with PCA and 74 (25.5%) with csPCA at re-biopsy. SB and MRI-TBx identified PCA in 28 and 31% of the cases (including 18 and 20% of csPCA).

The median follow-up from second negative biopsy was 20 months (IQR: 5.7–34.7). Further MRI and subsequent biopsy were performed in 19 patients, of whom only 2 patients were diagnosed with PCA.

In group 3, additional mpMRI during follow up was performed in 198 (69%) patients, identifying graded as PI-RADS < 3, 3 and >3 in 24%, 68%, and 8% of patients, respectively. On the whole, 93 patients (27%) received at least one repeated biopsy during follow-up. PCA and csPCA were detected in 35 (12%) and 27 patients (9.3%),

however in a “repeat biopsy analysis” PCA and csPCA were detected in a percentage similar to group 1 and 2 ($p = 0.06$).

Predictors of any grade and clinically significant PCA
Figure 2 reports Kaplan-Meier curves for PCA and csPCA free survival in the whole cohort and stratified by study group and PI-RADS score.

Fig. 2: Prostate cancer-free survival in the whole cohort.
figure 2
a Shows PCA-free survival estimates in the cohort, with 2- and 5-year survival rates of 99% and 65%, respectively. b Presents csPCA-free survival estimates, with 2- and 5-year survival at 99% and 71%, respectively.

Full size image

Overall, the 2- and 5-year PCA free survival estimates were 99 and 65% respectively; the 2- and 5-year csPCA free survival estimates were 99 and 71%, respectively.

When stratified by study group, PCA-free and csPCA-free survival estimates were similar in groups 1 and 2 (log rank p value 0.4 for PCA and 0.7 for csPCA) but significantly higher in group 3 (log rank p value < 0.01) (Fig. 3). In particular the 2-year and 5 year Pca were respectively 63 and 50% for group 1, 72 and 51% for group 2 and 94 and 84% for group 3 ($p < 0.01$ between group 3 vs. group 1 and group 2).

Fig. 3: Survival estimates by study groups.
figure 3
a Displays PCA-free survival by study group. Survival rates were similar in groups 1 and 2 ($p = 0.4$) but significantly higher in group 3 ($p < 0.01$). For group 1, 2-, and 5-year survival was 63% and 50%, respectively; for group 2, 72% and 51%; and for group 3, 94% and 84%. b Shows csPCA-free survival, with 2- and 5-year rates of 77% and 60% (group 1), 94% and 61% (group 2), and 96% and 86% (group 3), with $p < 0.01$ between group 3 and groups 1 and 2.

Full size image

The 2-year and 5-year csPca were respectively 77 and 60% for group 1, 94 and 61% for group 2 and 96 and 86% for group 3 ($p < 0.01$ between group 3 vs. group 1 and group 2).

When stratified by PI-RADS score, PCA-free and csPCA-free survival estimates were significantly the lowest in PI-RADS 5 lesions and the highest in PI-RADS 3 lesions (log rank p value < 0.01) (Fig. 4).

Fig. 4: Survival estimates by PI-RADS score.
figure 4
a Illustrates PCA-free survival by initial PI-RADS score, with lowest survival in PI-RADS 5 lesions and highest in PI-RADS 3 ($p < 0.01$). b Shows csPCA-free survival following a similar trend, with the lowest survival in PI-RADS 5 and highest in PI-RADS 3 ($p < 0.01$).

Full size image

Table 2 summarizes UVA and MVA Cox regression analyses assessing clinical and radiological predictors of PCA and csPCA after the initial negative biopsy.

Table 2 Univariable and multivariable analysis assessing predictors of any prostate cancer and clinically-significant prostate cancer.
Full size table

In the multivariable analysis, there was no statistically significant difference between group 1 and 2 (HR = 0.8, 95% CI = 0.5–1.3, p = 0.4), see Table 2. However, the hazard on PCa and csPCa (HR = 0.2, 95% CI 0.1–0.4, p = p < 0.01) was lower for Group 3 vs. Group 1.

Furthermore, several clinical and radiological covariates (including patients age, prostate volume, PI-RADS score at the first MRI, presence of ASAP at the initial biopsy, number of TB and SB performed during the initial biopsy) were identified as predictors of PCA diagnosis during further follow-up.

Table 3 summarizes UVA and MVA Cox regression analyses assessing clinical and radiological predictors of PCA and cs-PCA after the initial negative biopsy in cases with PI-RADS > 3 at the first MRI.

Table 3 Univariable and multivariable analysis assessing predictors of any prostate cancer and clinically – significant prostate cancer during follow-up for PI-RADS > 3 lesions.
Full size table

Once again, the study group variable, the number of systematic biopsies, and the presence of ASAP at the initial biopsy were identified as predictors of subsequent detection of PCA and csPCA. In addition, PSAD was an independent predictor of PCA (HR: 6.9, p < 0.01).

Treatments
Supplementary Table 1 summarizes the treatment for the patients diagnosed with PCA and radical prostatectomy specimen data for the patients who received surgery.

Among the selected treatment options, active surveillance/watchful waiting, surgery, radiation therapy, and focal therapy were chosen by 36 (21.4%), 109 (64.9%), 19 (11.3%), and 5 (2.4%) patients, respectively (supplementary Table 1).

Among the 109 radical prostatectomies, 53/109 had a pT stage T3 and 63/109 had a ISUP score 3.

Discussion

The presented study investigates the characteristics, follow-up outcomes, treatment decisions, and predictors of PCA and csPCA in a cohort of 694 patients with an initial positive mpMRI and negative prostate biopsies followed up according to different protocols. Overall, about 25% of the patients were diagnosed with PCA, more than 75% of which were identified as csPCA. This underscores the critical importance of establishing an accurate follow-up schedule for these patients, as the presence of csPCA cannot be definitively ruled out in a significant number of patients. Notably, about 16% of those patients with Pca underwent radical prostatectomy during the available follow-up. Among these patients, more than 50% exhibited a pT stage T3 and about the same percentage had a ISUP score 3.

We conducted a comprehensive comparative analysis of three distinct follow-up schedules, revealing outcomes disparities. Patients who underwent a second biopsy without a new MRI exhibited similar results to those who received a new MRI before the second biopsy. Conversely, individuals who underwent a second biopsy triggered by specific clinical and radiological factors demonstrated a low detection of PCA and csPCA. This underscores the need for a risk-based strategy to mitigate overdiagnosis on one hand and, on the other, a more rigorous follow-up approach to prevent the omission of caPCA diagnosis. In particular, the potential limitations of the first TB emphasize the need for further investigations and follow-up in cases with inconsistent results between MRI images and MRI-guided biopsy findings. In addition to MRI, a possible role of PET/CT has been explored in recent studies [19, 20]. The implementation of PSMA PET/CT with MRI results would help the selection of men who would benefit the most of screening or further biopsies [21].

The significance of second MRI within the initial 18 months after the first biopsy has been assessed in our prior publication [22]. In cases where lesions were initially described in the first MRI, downgrading occurred in only 19% of instances, while upgrading was observed in 39%, and stability was maintained in 42% of cases. The approach of combining SB and TB yielded elevated detection rates. For patients with lesions detected at the first MRI, the positivity rates were 16%, and for those with new lesions detected at the second MRI, the rate was 17.2% [22]. Conversely, the data of the present analysis suggested very similar diagnostic performance with group 1, i.e. the group of patients who repeated prostate biopsy without a new mpMRI. That was shown in the whole cohort and the subgroup of patients with initial PI-RADS lesions graded as 4 or 5. Unfortunately, even in a large multicenter series, the limited number of cases did not allow to further stratify the analyses.

This finding suggests that an additional MRI within one year may not always be necessary before repeat biopsies in this setting of patients, potentially reducing the overall cost and burden of prostate cancer diagnosis, streamlining protocols, particularly in regions with limited access to advanced imaging. Since in a recent mini-systematic review by Grivas [15] only nine studies, including less than 500 patients in this clinical setting, strong recommendations cannot be done by international guidelines. Overall, the systematic review demonstrated that the detection of csPCA was highly variable among the few available studies. Specifically, csPCA was detected

in 7.5 to 80% of the patients with PI-RADS 3 lesions, 17 to 75% with PI-RADS 4 lesions, and over 80% with PI-RADS 5 lesions [15].

Different factors, including heterogeneity in mpMRI quality and accuracy, inaccuracy/errors in TB or SB, and discrepancies in the follow-up protocols can explain such large differences. In the present analysis, we identified csPCA in about 20% of the whole population and 36%, 30%, and 8% of groups 1 to 3, respectively. Notably, those patients who were followed up less strictly, with repeated biopsy triggered by PSA increase, DRE changes and radiological progression in repeated MRIs, had a significantly lower chance of being diagnosed with PCA and csPCA. Although several differences in the patients' characteristics are evident among the different study groups, the detection of PCA and csPCA estimated by the ERSPC-MRI PCA risk calculator was similar. The data is constant in all our analyses and might allow us to hypothesize a certain level of underdectection of csPCA in this subgroup of patients.

We identified several predictors of PCA and csPCA during the initial biopsy that warrant thorough evaluation when considering the decision for a second biopsy during patient consultation. Specifically, the presence of a high PI-RADS score, advanced age, smaller prostate volume, adequate prostate biopsy sampling with >3 fusion cores and >12 systematic biopsies, along with the presence of ASAP at the first biopsy, can serve as indicators for the likelihood of PCA and csPCA presence.

ASAP is regarded as a precursor lesion, often indicating that the prostate tissue is undergoing changes that are more likely to progress to cancer over time. While not all instances of ASAP will inevitably develop into cancer, its presence prompts clinicians to engage in closer patient monitoring. However, there is an ongoing debate regarding the role of ASAP in the MRI era [23, 24]. In our study, we observed a robust correlation between the presence of ASAP on the initial biopsy and the likelihood of PCA and csPCA occurrence. This supports the growing interest in investigating glandular-stromal alterations, along with acute or chronic inflammation and vascular changes.

Interestingly, the TR vs. TP route was not found to be an independent predictor of PCa and csPCa this unique population, supporting recent evidence from prospective studies [25].

The present study is relevant for several reasons. It includes more patients than the only available systematic review on the topic. Consequently, the study provides more reliable data on the detection of PCA and, above all, csPCA in such an interesting patients population. Moreover, the series collected data from different tertiary referral centers, indicating a potentiality for good validity of the data in real life practice. Third, we provided data on PCA and csPCA predictors. Several limitations should be acknowledged. First of all, despite the present retrospective series being large, the number of patients with initial PI-RADS 4 or 5 lesions at MRI and subsequently negative TB/SB is limited. That might have made some of our analyses underpowered and limited our ability to perform more accurate subgroup analyses. Secondly, the study is retrospective, which introduces a significant risk of selection bias for follow-up, and patients were followed with different protocols. In other words, it is possible that

patients with a higher risk of cancers, in the opinion of the attending urologists, might have been followed more strictly than those with a potentially lower risk. Although our statistical analyses tried to correct for the differences in covariate distributions, we cannot be sure that a selection bias might explain at least partially our findings. However, the finding that the detection of PCA and csPCA estimated by the ERSPC-MR PCA risk calculator was similar in the 3 groups suggest that such selection bias should not play a major role. The dataset includes both transperineal and transrectal prostate biopsies which may have different detection rate [26, 27] and the results could have been different including one procedure only. The present study is preliminary, and randomized controlled trials evaluating various follow-up protocols in patients with positive MRI and negative TB/SB results would be valuable for standardizing the follow-up procedures for these patients. Finally, at the current follow- up, we are not able to understand the prognostic implications related to the diagnosis of such csPCA, which could arguably have lower volume and reduced clinical aggressively compared to those diagnosed in the first prostatic biopsy.

Conclusions

Prostate cancer diagnostics should be regarded as a longitudinal process, instead of a cross-sectional one-time approach. Overall, our findings contribute to a better understanding of patient characteristics, follow-up trajectories, treatment preferences, and predictive factors for PCA and csPCA, offering valuable insights for clinical decision-making and management strategies in these men with abnormal MRI but negative biopsy. Less aggressive re-imaging and re-biopsy may lead to more csPCa being missed. Improved knowledge on follow-up findings aids in primary biopsy decisions.

Data availability

The data that support the findings of this study are available for sharing but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of authors.

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