Different clinical significance of ASAP/HGPIN pattern in systematic vs. MRI-US fusion guided prostate biopsy

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Abstract. Atypical small acinar proliferation (ASAP) and high grade intraepithelial neoplasia (HGPIN) patterns identified at prostate biopsy yield an important clinical significance, their presence signaling an increased likelihood of future oncological development or underdiagnosed PCa. MRI and MRI-TRUS fusion prostate biopsy have recently become the standard for the diagnosis of prostate cancer. Thus, we aimed to assess the role of ASAP/HGPIN pattern in the context of these recent developments as compared with the standard systematic biopsy. The present study included 400 patients who underwent MRI-TRUS fusion prostate biopsy. A subgroup of these patients had a history of prior systematic biopsy and their results were also included in the analysis. We observed that ASAP/HGPIN pattern diagnosed at systematic biopsy is suggestive of a high-volume clinically-significant disease, most probably located outside the standard sampling area. On the contrary, ASAP/HGPIN at MRI-TRUS fusion biopsy has clinical features more similar to benign prostate hyperplasia, thus suggesting a more incipient disease, if present. No relation between concurrent ASAP/HGPIN and PCa was observed in our study.

Introduction

Prostate cancer (PCa) represents the second most frequent form of neoplasia diagnosed in men, comprising 13.5% of all cancer diagnoses, ranking as the fifth cause of cancer related mortality in the male population worldwide (after lung, liver, stomach and colorectal malignancies) (1). First-line screening for patients over 50 years of age is done by assessing the prostate through digital rectal examination and measuring the prostate specific antigen (PSA) blood levels. The final diagnosis of PCa is based on the pathological examination of prostate tissue, acquired through an image-guided needle biopsy (2).

However, between normally structured prostatic tissue and typical aspect of PCa, a wide variety of morphological findings occur, called precursor lesions, such as atypical adenomatous hyperplasia, post-atrophic hyperplasia and prostatic intraepithelial neoplasia (PIN) (3). While all of them are susceptible to evolve into prostate adenocarcinoma, the most frequent route of progression that has been suggested is from normal tissue to PIN and to malignant tumors (4).

PIN is divided into low and high grade neoplasia, low grade findings bearing great inter-examiner variability and, therefore, having questionable clinical significance. On the other hand, high grade PIN (HGPIN), found in approximately 7.6% of biopsies (5), is described as the most plausible precursor lesion for prostatic adenocarcinoma (6), being the first accepted stage of the carcinogenesis process (7). HGPIN is an intermediate lesion, composed by ducts and acini of benign structure, lined with cells that borrow the morphological features of malignant phenotype, confined within the basal membrane (8).

Another frequent finding among biopsy results is atypical small acinar proliferation (ASAP). It is defined as prostatic structures presenting morphological or architectural atypia, however not enough to meet the standard requirements in order to be classified as prostatic adenocarcinoma, appearing in about 5% of biopsies (8). Other authors might argue that ASAP is not a stand-alone entity, being just a tumor that has been biopsied tangentially (6) and being encountered only on biopsy cores, but failing to be diagnosed in radical prostatectomy specimens (3).

Both these histopathological results yield an important clinical significance, their presence signaling an increased likelihood of future oncological development or

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nearly-missed/underdiagnosed PCa (9). If multifocal HGPIN (more than 3 biopsy cores identified) or ASAP is found, the patient is considered to be at high risk and repeated biopsy is advised (10). Moreover, the risk of clinically significant cancer at re-biopsy is 22% for HGPIN (5) and 17.3% for ASAP, as compared with less than 10% when these lesions are not present (11).

Systematic biopsy is the standard procedure for the diagnosis of PCa and represents the sampling of the posterior area of the prostate, where PCa most frequently develops. The main drawback of this procedure is that the ultrasound (US) guidance fails to identify PCa, thus the biopsy is performed in a blind manner according to a preestablished scheme (12). The advent of prostate magnetic resonance imaging (MRI) lead to a change in the diagnosis of PCa, allowing for the first time to identify lesions potentially harboring malignant disease (13). Currently, MRI is also used to guide the biopsy. The most widely available systems in this regard are the ones that perform the real time MRI-US fusion of the images. MRI and MRI-targeted biopsy have improved the accuracy of this procedure and have led to an increase in the diagnosis of aggressive PCa and of lesions located outside the peripheral area, which were usually missed by systematic biopsy (14).

The aim of our study was to assess the importance of ASAP/HGPIN pattern diagnosed by standard systematic biopsy in comparison with MRI-transrectal ultrasound (TRUS) fusion guided biopsy, as the latter represents one of the most accurate methods of diagnosis available. A secondary aim was to evaluate their role as concurrent secondary lesions in patients diagnosed with PCa.

Patients and methods

Between October 2017 and February 2020, a total of 400 patients with clinical and biochemical suspicion of PCa underwent MRI-TRUS fusion-guided prostate biopsy in our department. All biopsies were performed by two urologists using Hitachi Arietta 70 system (Hitachi, Japan) with Real-Time Visual Software using transrectal approach. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the 'Iuliu Hatieganu' University of Medicine and Pharmacy (Cluj-Napoca, Romania). All patients provided a signed informed consent.

All patients included in the study harbored at least one suspicious lesion for PCa. The cut-off for biopsy indication was a PIRADS score of 3 or higher. MRI-TRUS fusion biopsy comprised of initial targeted cores, followed by standard 12-core systematic biopsy. One to four biopsy cores were obtained from each MRI-visible lesion.

The pathology assessment was performed by 3 pathologists with significant experience in urologic malignancies, specifically PCa. Clinically significant PCa (csPCa) was defined as any disease with ISUP grade equal to or higher than 2, Gleason score ≥7(3+4).

In order to show an extensive description of ASAP/HGPIN pattern, the study group was assessed in three settings: i) Patients diagnosed with ASAP/HGPIN at previous systematic biopsies: Of the 400 patients included in the study, we selected the ones with a history of at least one systematic biopsy showing ASAP/HGPIN; this subgroup was then compared with patients with previous systematic biopsies showing benign prostate hyperplasia (BPH) and patients without prior biopsies; ii) Patients diagnosed with ASAP/HGPIN at MRI-TRUS fusion biopsy: Of the 400 patients included in the study and who underwent MRI-TRUS fusion biopsy, we selected the ones who currently harbored ASAP/HGPIN, irrespective of their prior biopsy history; these patients were compared with the patients in whom MRI-TRUS fusion biopsy showed the presence of BPH or PCa, and iii) Patients diagnosed with PCa by MRI-TRUS fusion prostate biopsy, harboring ASAP/HGPIN as secondary lesions: Of the 400 patients included in the study, we selected the ones who were diagnosed with PCa; in this subgroup of patients, we assessed the differences between patients who harbored concurrent ASAP/HGPIN and those who did not.

The statistical analysis was performed using Medcalc software (Ostend, Belgium). Categorial variables were presented as absolute numbers and proportions, whereas quantitative data was presented as median and interquartile range. The correlation between categorical data was assessed using Chi-square test and between continuous and categorical data by Kruskal-Wallis test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients diagnosed with ASAP/HGPIN at previous systematic biopsies. Of the total 400 patients included in the current study, 100 had at least one previous biopsy. Of these 100 patients, 27 (6.7% of the whole study group) harbored preneoplasic lesions-ASAP (21)/multifocal HGPIN (6). The remaining 73 patients were diagnosed with BPH. We observed that patients with a history of ASAP/HGPIN in previous biopsy and patients at first biopsy setting or with previous BPH result had similar median age (65 years for ASAP/HGPIN vs. 64 years in first biopsy setting/BPH, P=0.862) and prostate volume (47 g for ASAP/HGPIN vs. 48 g for first biopsy/BPH, P=0.338) (Table I). On the contrary, patients with ASAP/HGPIN had higher PSA (P=0.001), higher percentage of PIRADS 5 lesions (P=0.07), a larger suspicious lesion visible on MRI (P=0.08) and higher percentage of lesions located in the transitional area (P=0.01). The overall and csPCa diagnosis rate was 63 and 44% for ASAP/HGPIN group, as compared with 44.8 and 36.7%, respectively, for first biopsy/BPH group (P=0.12 and P=0.42). Also, patients with ASAP/HGPIN had a higher rate of PCa exclusive diagnosis on both systematic and targeted biopsy cores (P=0.12). Patients who had a history of ASAP/HGPIN and were confirmed with PCa had a lower percentage of cancer positive cores (P=0.01) and PCa tissue on positive cores (P=0.317; Table I).

Patients diagnosed with ASAP/HGPIN at MRI-TRUS fusion biopsy. Of the 400 patients who underwent MRI-TRUS fusion prostate biopsy, 184 were diagnosed with PCa. Fifty-four patients were identified as harboring ASAP/multifocal HGPIN, whereas the remaining 162 had benign pathology (BPH) (Table II). Patients diagnosed with ASAP/HGPIN by MRI-TRUS fusion prostate biopsy had similar characteristics with BPH in terms of age, PSA, maximum dimension of the lesion and site of the

Table I. Characteristics of patients with ASAP/HGPIN in previous biopsies, as compared with patients in first biopsy setting or with benign result at previous biopsies.

Characteristics	Prior biopsy-ASAP/HGPIN	No prior biopsy/prior biopsy with BPH	P-value
No. of patients [n (%)]	27 (6.75)	373 (93.25)	
Age [years; median (IQR)]	65 (60.25-67)	64 (59-69)	0.862
PSA [ng/ml; median (IQR)]	9.46 (7.1-17.75)	6.8 (5-9.9)	**0.001**
Prostate volume [g; median (IQR)]	47 (35.96-55.35)	48 (38-72)	0.338
PIRADS score [n (%)]	3-5 (18.51) 4-5 (18.51) 5-9 (33.33) Not reported 8 (29.62)	3-75 (20.1) 4-118 (31.63) 5-63 (16.89) Not reported 117 (31.36)	0.07
Maximum diameter of lesion [mm; median (IQR)]	16 (12-19)	13 (10-17)	0.08
Location of lesion [n (%)]	Anterior 2 (7.4) Peripheral 8 (29.62) Transitional 15 (55.55) Diffuse 2 (7.4)	Anterior 8 (2.14) Peripheral 227 (60.85) Transitional 119 (31.9) Diffuse 19 (5.09)	**0.01**
Site of lesion [n (%)]	Apex 3 (11.11) Mid-gland 10 (37.03) Base 10 (37.03) Diffuse 4 (14.81)	Apex 73 (19.57) Mid-gland 131 (35.12) Base 141 (37.8) Diffuse 28 (7.5)	0.639
Overall PCa [n (%)]	17 (63)	167 (44.8)	0.12
csPCa [n (%)]	12 (44)	137 (36.7)	0.42
Exclusive PCa diagnosis on systematic cores [n (%)]	6 (22.2)	42 (11.2)	0.12
Exclusive PCa diagnosis on targeted cores [n (%)]	2 (7.4)	11 (2.94)	0.12
Percentage of positive biopsy cores for patients diagnosed with PCa [median (IQR)]	21.43 (13.12-29.76)	37.5 (20-50)	**0.01**
Percentage of PCa tissue on positive cores [median (IQR)]	21 (8.75-5.97)	35.5 (16.5-72)	0.317

The values in bold are statistically significant. ASAP, atypical small acinar proliferation; BPH, benign prostate hyperplasia; cs, clinically significant; HGPIN, high grade intraepithelial neoplasia; PCa, prostate cancer; PSA, prostate specific antigen.

lesion. On the contrary, when comparing ASAP/HGPIN patients with those diagnosed with PCa, we observed that the first group had significantly lower age (63.5 years for ASAP/HGPIN vs. 66 years for PCa, P<0.05), lower PSA (6.68 ng/ml for ASAP/HGPIN vs. 8.2 ng/ml for PCa, P<0.05) and higher prostate volume (52 g for ASAP/HGPIN vs. 41 g for PCa, P<0.05). Furthermore, patients with ASAP/HGPIN had a higher percentage of PIRADS 3 lesions, lower percentage of PIRADS 5 (P<0.0001) and harbored smaller lesions than patients with PCa (P=0.006). Also, they had a significantly higher percentage of lesions located in the transitional area as compared with patients diagnosed with PCa (P=0.0001; Table II).

A secondary analysis was performed, comparing the patients diagnosed with ASAP/HGPIN at MRI-TRUS fusion biopsy with the ones diagnosed at systematic biopsy (setting 1). It was observed that patients with ASAP/HGPIN at MRI-TRUS fusion biopsy had a lower age (P=0.463), lower PSA (P=0.002), higher prostate volume (P=0.313), lower percentage of PIRADS 5 lesions (P=0.02), smaller diameter of lesions (P=0.02) and lower percentage of lesions located in the transitional area (P=0.121).

Patients diagnosed with PCa by MRI-TRUS fusion prostate biopsy, harboring ASAP/HGPIN as secondary lesions. We assessed whether concurrent presence of ASAP/HGPIN pattern in patients diagnosed with PCa was correlated with a more aggressive or extensive disease. Of the 164 patients with PCa, 41 harbored ASAP/HGPIN as concurrent secondary pattern, whereas 143 patients did not (Table III). We did not identify any differences between patients with PCa who harbored ASAP/HGPIN as secondary lesions and patients without secondary lesions in terms of age (P=0.567), PSA (P=0.697), prostate volume (P=0.705), PIRADS score (P=0.17) and location of the lesion (P=0.393; Table III). A higher rate of csPCa was identified in patients without secondary lesions (79.72% vs. 68.29% for patients with concurrent ASAP/HGPIN), albeit not statistically significant (P=0.125). The percentage of positive biopsy cores was similar between the two groups.

Table II. Characteristics of the patients who underwent MRI-TRUS fusion prostate biopsy.

Characteristics	ASAP/HGPIN	BPH	PCa	P-value
No. of patients [n (%)]	54 (13.5)	162 (40.5)	184 (46)	-
Age [years; median (IQR)]	63.5 (57-67)	62.5 (57-68)	66 (62-70)	**<0.05**[a]
PSA [ng/ml; median (IQR)]	6.68 (5.7-9.15)	6 (4.7-8.43)	8.2 (5.42-13)	**<0.05**[a]
Prostate volume [g, median (IQR)]	52 (37.75-73.75)	60.96 (44.3-87.26)	41 (33.16-52)	**<0.05**
PIRADS score [n (%)]	3-14 (25.92)	3-48 (29.62)	3-18 (9.78)	**<0.0001**[a]
	4-14 (25.92)	4-46 (28.39)	4-63 (34.23)	
	5-5 (9.25)	5-18 (11.11)	5-49 (26.63)	
	Not reported-21 (38.88)	Not reported 50 (30.86)	Not reported 54 (29.34)	
Maximum diameter of lesion [mm; median (IQR)]	12.5 (10-15)	12 (9-15)	14 (11-19)	**0.006**[a]
Location of lesion [n (%)]	Anterior-0 (0)	Anterior 2 (1.23)	Anterior 8 (4.34)	**0.0001**
	Transitional-23 (42.59)	Transitional 73 (45.06)	Transitional 38 (20.65)	
	Peripheral-28 (51.85)	Peripheral 80 (49.38)	Peripheral 127 (69.02)	
	Diffuse-3 patients (5.55)	Diffuse 7 (4.32)	Diffuse 11 (5.97)	
Site of lesion [n (%)]	Apex-8 (14.81)	Apex 33 (20.37)	Apex 35 (19.02)	0.54
	Mid-gland-16 (29.62)	Mid-gland 59 (36.41)	Mid-gland 66 (35.86)	
	Base-26 (48.14)	Base 62 (38.27)	Base 63 (34.23)	
	Diffuse-4 (7.4)	Diffuse 8 (4.93)	Diffuse 20 (10.86)	

[a]Statistical significance was achieved when comparing either of the first two groups with PCa group. The values in bold are statistically significant. ASAP, atypical small acinar proliferation; BPH, benign prostate hyperplasia; HGPIN, high grade intraepithelial neoplasia; MRI, magnetic resonance imaging; PCa, prostate cancer; PSA, prostate specific antigen; TRUS, transrectal ultrasound.

Table III. Characteristics of PCa patients diagnosed by MRI-TRUS fusion prostate biopsy with and without ASAP/HGPIN as concurrent secondary pattern.

Characteristics	Patients with ASAP/HGPIN as secondary lesions	Patients without secondary lesions	P-value
No. of patients	41	143	
Age [years; median (IQR)]	65 (61.75-69.5)	66 (62-70)	0.567
PSA [ng/ml; median (IQR)]	8.15 (5.64-11.3)	8.27 (5.4-13.9)	0.697
Prostate volume [g, median (IQR)]	41 (36-53.3)	41.93 (32.445-52)	0.705
PIRADS score [n (%)]	3-3 (7.31)	3-15 (10.48)	0.17
	4-15 (36.58)	4-48 (33.56)	
	5-5 (12.19)	5-44 (30.76)	
	Not reported 18 (43.9)	Not reported 36 (25.17)	
Maximum diameter of lesion [mm; median (IQR)]	13.5 (10-17)	14 (11-20)	0.418
Location of lesion [n (%)]	Anterior 1 (2.43)	Anterior 7 (4.89)	0.393
	Peripheral 33 (80.48)	Peripheral 94 (65.73)	
	Transitional 5 (12.19)	Transitional 33 (23.07)	
	Diffuse 2 (4.87)	Diffuse 9 (6.29)	
Site of lesion [n (%)]	Apex 4 (9.75)	Apex 31 (21.67)	0.08
	Mid-gland 13 (31.7)	Mid-gland 53 (37.06)	
	Base 19 (46.34)	Base 44 (30.76)	
	Diffuse 5 (12.19)	Diffuse 15 (10.48)	
csPCa [n (%)]	28 (68.29)	114 (79.72)	0.125
Percentage of positive PCa cores of the total no. of cores [median (IQR)]	33.33 (17.39-47.79)	34.31 (20-50)	0.378

ASAP, atypical small acinar proliferation; HGPIN, high grade intraepithelial neoplasia; MRI, magnetic resonance imaging; PCa, prostate cancer; PSA, prostate specific antigen; TRUS, transrectal ultrasound.

Discussion

HGPIN yields a high predictive value for future development of adenocarcinoma (7) and ASAP has the potential significance of synchronic malignant disease located near the origin of the biopsy (11), both being of great clinical importance regarding early diagnosis of PCa. We aimed to assess the importance of these lesions in three settings: In patients with previous systematic biopsy, patients who underwent MRI-TRUS fusion biopsy and patients who were diagnosed with PCa.

Taking into consideration the first setting, the findings in our study were consistent with the data available in literature for patients previously diagnosed with ASAP. An incidence of 5.25% (n=21) was found in our group, while the mean incidence is approximated to be 5% (8). Only 1.5% of the patients (n=6) harbored previous evidence of HGPIN pattern. Even though this result is below the reported average of 7.4% (5), the available data describes a wide variation, ranging from as low as 0.7 up to 20% (6). The comparison of PSA levels between the patients presenting ASAP/HGPIN on prior biopsies and those without preexisting biopsies or with BPH showed a statistically significant increase for the first group (9.46 ng/ml vs. 6.8 ng/ml, P=0.001). Similar results were reported by Adamczyk *et al* (9), who conducted a study on 1010 men, concerning the mean PSA levels between these categories of patients. Furthermore, we found an increased rate of lesions located in the transitional zone for ASAP/HGPIN group, increased percentage of lesions with PIRADS 5, larger diameter of the lesions and higher rate of overall and csPCa diagnosis as compared with patients without prior biopsies or with BPH. Summarizing our findings for patients with history of previous systematic biopsy positive for ASAP/HGPIN pattern, it was observed that these patients seem to harbor clinically significant disease located outside the peripheral area, that could be missed by systematic biopsy. Exclusive diagnosis, lower percentage of positive biopsy cores and lower PCa tissue on positive cores could suggest that these lesions are not easily accessible.

Analyzing the patients who underwent MRI-TRUS fusion biopsy, it was observed that the age of the patients and the PSA were lower in ASAP/HGPIN group when compared with patients diagnosed with PCa. Regarding age, a possible explanation, as stated by Chrisofos *et al* (3) is that, by definition, a precursor PCa lesion should meet the epidemiological requirement of being encountered in men below the mean age at which PCa usually is diagnosed. Furthermore, Adamczyk *et al* (9) showed that PSA may be increased in ASAP/HGPIN compared with benign pathology, but it is inferior to those diagnosed with PCa, conclusion that is also proven in our study (6.68 ng/ml vs. 8.2 ng/ml, P<0.05). When comparing ASAP/HGPIN group with BPH group, we observed that the mean prostate volume was significantly lower (52 g vs. 60.96 g, P<0.05), but higher than in the PCa study arm (52 g vs. 41 g, P<0.05). Similar results have been described by Ryu *et al* (15). While age was not found to be significantly lower in patients with precursor lesions, total prostate volume was indeed larger for those mentioned above (41.6 g vs. 35.7 g, P=0.035). As stated by multiple studies (3,5,7), precursor lesions are predominantly located at the peripheral zone of the prostate, only 10-15% being found in the transitional area and 5% in the central zone, this linking them even stronger with the theory that supports them as being the first step of the carcinogenesis process. On the contrary, a different pattern was observed in patients diagnosed at MRI-TRUS fusion biopsy with ASAP/HGPIN vs. PCa: 42.59% transitional and 51.85% peripheral lesions in ASAP/HGPIN vs. 20.65% transitional and 69.02% peripheral lesions in PCa, P=0.0001. This discrepancy between our findings and the literature may be attributed to using the MRI-TRUS fusion biopsy system, which targets with higher accuracy the anterior and transitional zone of the prostate, leading to higher detection rates in these areas (16,17). The average maximum diameter of ASAP/HGPIN lesions was 12.5 mm, in contrast to 14 mm calculated in PCa cases (P=0.006). Regarding PIRADS score, a higher percentage of PIRADS 3 lesions have been identified in the ASAP/HGPIN group compared with csPCa (25.92% vs. 9.78%, P<0.0001), PIRADS 5 lesions following the expected, reverted curve (9.25% vs. 26.63%, P<0.0001). While the correspondence between high PIRADS index lesions and ASAP or HGPIN histopathological results is understandably low, our study revealed an increased percentage of precursor lesions classified as PIRADS 3, compared with the literature. A study comprising of 118 patients and 92 PIRADS 3 lesions had a detection rate for csPCa of 6.5% (similar to our results), but only 1.2% for HGPIN and 2.4% for ASAP lesions (18). The same study concluded consistent evidences with ours regarding the location of precursor and malignant lesions inside the prostate, with neoplasia being more likely to occur in the peripheral zone, while benign results (ASAP, HGPIN and inflammation) prevailed in the transitional area. To conclude our findings in the second setting, we observed that ASAP/HGPIN diagnosis at MRI-TRUS fusion biopsy resembles more a benign pathology than confirmed PCa, suggesting the potential presence of an incipient PCa. These data were also supported by the secondary analysis showing the comparison between ASAP/HGPIN pattern in MRI-TRUS fusion and systematic biopsy.

The patients in our study were further divided into a third pair of groups, one with ASAP/HGPIN coexisting with PCa and one with PCa alone. The parameters set for analysis were the same as for the previous comparisons (age, PSA level, prostate volume, PIRADS score, lesion diameter, location and site) plus the proportion of csPCa. We did not observe significant differences between any of these criteria. Eminaga *et al* (19), lead a study on 1374 radical prostatectomy specimens, in order to assess the distribution of PCa and HGPIN inside the prostate, and the correlation between these two. The authors found lower levels of PSA in patients with PCa alone than in those with combined histological entities, while the latter category had a lower relative tumor volume (13.3% vs. 17.8, P<0.001). The topography of the lesions was predominantly abundant in the peripheral zone, a conclusion that was similar to ours for these subgroups, despite being statistically insignificant.

One of the main limitations of our study consists in the lack of follow-up for the patients diagnosed with ASAP/HGPIN at MRI-TRUS fusion biopsy. The data could be useful to have an unequivocal comparison between ASAP/HGPIN pattern at systematic and targeted biopsy, thus we aim to focus further studies on this setting.

In conclusion, ASAP/HGPIN pattern diagnosed at systematic biopsy is suggestive of a high-volume clinically-significant

disease, most probably located outside the standard sampling area. On the contrary, ASAP/HGPIN at MRI-TRUS fusion biopsy has clinical features more similar to BPH, thus suggesting a more incipient disease, if present. No relation between concurrent ASAP/HGPIN and PCa was observed in our study.

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Availability of data and materials

The dataset analyzed during the present study is available from the corresponding author on reasonable request.

Authors' contributions

IA performed prostate biopsies, analyzed and interpreted the patient data and contributed to the writing of the manuscript. TT was involved in the conception of the study and was a major contributor in the writing of the manuscript. DC analyzed and interpreted the patient data and contributed to the writing of the manuscript. EC performed prostate biopsies and acquired the patient data. PK and DA were involved in the conception of the study and acquired the patient data. MB performed the histological examination of the biopsy samples and assisted with the analysis of the data. IC interpreted the patient data and critically revised the manuscript. NC designed the study and critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the 'Iuliu Hatieganu' University of Medicine and Pharmacy (Cluj-Napoca, Romania) (approval no. 313/27.09.2019). All patients provided a signed informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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