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ARTICLE

# Natural history of widespread high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: should we rebiopsy them all?

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**ABSTRACT**

**Objective:** To evaluate the premalignant potential of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP).

**Methods:** Patients diagnosed with monofocal HGPIN (mHGPIN), widespread HGPIN (≥4 cores, wHGPIN) and/or ASAP who underwent at least one rebiopsy during their follow-up, were enrolled. All enrollment biopsies underwent central pathologic revision. Risks for PCa were estimated using Fine and Gray method for competing risk.

**Results:** Pathologic revision changed the original diagnosis in 32.3% of cases. Among 336 cases enrolled, PCa was diagnosed in 164 (48.8%), and more specifically in 20 (30.3%) mHGPIN, 10 (34.5%) wHGPIN, 101 (54.0%) ASAP, and 33 (61.1%) HGPIN + ASAP (mean follow-up 124 months). Most PCa were Gleason score 6(3 + 3) (51.0%) and 7(3 + 4) (34.3%). On multivariate analysis, HGPIN + ASAP (HR 2.76, $p < 0.001$) and ASAP alone (HR 2.41, $p < 0.001$) were the only lesions significantly associated with PCa development. Of all cancers detected, 64.3% were at first rebiopsy. A rebiopsy performed within 3 months after ASAP diagnosis had a 45% chance of finding PCa. At Kaplan–Meier survival curves, median PCa-free survival was 48.1 months for HGPIN + ASAP and 64.9 months for ASAP ($p$ 0.0005 at Log-rank test). At 1 year, 70% of HGPIN + ASAP, 73% of ASAP, 89% of wHGPIN, and 84% of mHGPIN were PCa-free.

**Conclusion:** The diagnosis of ASAP and HGPIN strongly relies on the expertise of dedicated uro-pathologists. Finding of ASAP is a strong risk factor for a subsequent PCa diagnosis, advising a rebiopsy, possibly within 3 months. m/wHGPIN should not be routinely rebiopsied.

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HGPIN; ASAP; prostate biopsy; widespread; prostate cancer

## 1. Introduction

High-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) are common histological findings on prostate biopsy, considered as predictors of prostate cancer (PCa). In the last years, however, the premalignant potential of these lesions has been deeply questioned.

HGPIN is defined as abnormal, proliferative change in pre-existing, architecturally normal prostatic ducts and acini with nuclear atypia similar to that seen in prostatic cancer. Recent studies have estimated that the risk of developing PCa after initial diagnosis of HGPIN is around 22–23%, not different from the same risk after a benign diagnosis [1]. A separate entity is represented by widespread HGPIN (wHGPIN), defined by Netto and Epstein as four or more cores involved by HGPIN, which has shown a higher likelihood of finding PCa on rebiopsy, up to 55% [2]. The situation is completely different for ASAP that indicates a situation of diagnostic uncertainty, highly predictive for concurrent or subsequent PCa. This pathological finding encompasses a variety of lesions including benign mimickers of cancer and small foci of adenocarcinoma which, for a several reasons, cannot be accurately diagnosed [3]. The risk of PCa detection on rebiopsy after ASAP is estimated around 40%, ranging from 17% to 60% [4–6]. A recent study showed that the combination of HGPIN and ASAP in the same biopsy is even more predictive of subsequent cancer (58%) than isolated ASAP (35%) [5]. Given that the natural history of HGPIN and ASAP is not thoroughly known, however, it is difficult to provide reliable estimates of association with PCa. Consequently, there is no consensus whether to repeat a prostate biopsy after such diagnoses, and which is the best timing to do it.

Aim of the current study is to shed light on the natural history of HGPIN and ASAP evaluating a large series of patients with a long follow-up including at least one rebiopsy.

## 2. Methods

This was a retrospective study based on a prospectively maintained database collecting data of patients undergoing

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Supplemental data for this article can be accessed here.

prostate biopsy. All patients diagnosed with HGPIN and/or ASAP on prostate biopsy (negative for PCa) from January 2001 to December 2010, who underwent at least one rebiopsy during their follow-up, were enrolled. In the considered timespan, the prevalence of HGPIN and ASAP in our center was 20% and 13%, respectively. Minimum follow-up allowed was 5 years in absence of PCa detection. Follow-up visits (comprehensive of PSA measurement and digital rectal examination) and rebiopsies were scheduled according to clinical need and urologist decision. Multiparametric prostate MRI (mpMRI) was performed when needed, since its introduction in the clinical practice dating 2015.

All enrollment biopsies underwent central pathologic re-evaluation by three dedicated uropathologists to confirm the diagnosis of HGPIN and/or ASAP. Four entities were considered: monofocal HGPIN (mHGPIN), wHGPIN, ASAP, and contemporary finding of both HGPIN and ASAP (HGPIN + ASAP). wHGPIN was considered as finding of $\geq$4 cores involved by HGPIN [2]. Biopsies were routinely performed taking at 12 cores.

### 2.1. Statistical analyses

Data were expressed with mean and standard deviation (SD) or frequency and proportion for continuous and categorical variables respectively. Comparisons between continuous variables were performed with Wilcoxon–Mann–Whitney test depending on type of distribution; Chi-square test or Fisher exact test were used to compare proportions of categorical variables. Risks for PCa development were estimated in univariate and multivariable analysis using Fine and Gray method for competing risk: results were shown with Hazard Ratio (HR) and confidence interval at 95% level. Cancer-free survival curves were estimated with the Kaplan–Meier method and compared with the log rank test. Statistical significance was considered at two-sided with a significant level of $p < 0.05$. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

## 3. Results

A total of 384 patients with diagnosis of HGPIN and/or ASAP were retrospectively identified at our institution and underwent central pathologic revision.

### 3.1. Central pathologic re-evaluation

All the enrollment biopsies were reviewed by dedicated uropathologists, leading to a change in diagnosis in 32.3% of cases. Figure 1 shows the results of this re-evaluation: 2 patients were excluded as diagnosed as PCa (originally ASAP), 22 as low grade PIN and 6 as atrophy.

### 3.2. Natural history of HGPIN/ASAP

Among the 354 patients with confirmed diagnosis of HGPIN and/or ASAP at pathologic revision, 336 satisfied the enrollment criteria concerning a minimum follow-up of 5 years and remained in study. Mean patient age was 65 (±6) years and mean PSA 7.3 (±4.6). Among these patients, 66 (19.6%) were diagnosed as mHGPIN, 29 (8.6%) as wHGPIN, 187 (55.6%) as ASAP and 54 (16.0%) as ASAP + HGPIN. Biopsy at enrollment was driven by high PSA in 77.7%, suspicious digital rectal examination (DRE) in 4.2%, and both findings in 13.4%.

At an overall mean follow-up of 124 months, PCa was diagnosed in 164 (48.8%) patients, and more specifically in 20 (30.3%) mHGPIN, 10 (34.5%) wHGPIN, 101 (54.0%) ASAP, and 33 (61.1%) HGPIN + ASAP. The great majority of PCa diagnosed were graded as Gleason score 6(3 + 3) (51.0%) and 7(3 + 4) (34.3%). Only 8.7% and 4.5% were Gleason score 7(4 + 3) and 8(4 + 4), respectively. Low- and high grades were evenly distributed among groups (Supplementary Figure 1). 151 (44.9%) patients were alive and disease-free, while 21 (6.2%) died without PCa, for other causes. Only three patients died of PCa.

At Fine and Gray competing risk regression model (Figure 2), the hazard ratio (HR) for PCa development was significantly higher for HGPIN + ASAP (HR 2.594 [1.505, 4.471], $p = 0.0006$ and ASAP alone (HR 2.222, [1.381, 3.573], $p = 0.001$) as compared with mHGPIN. No significant difference was recorded for wHGPIN (HR 1.173, [0.557, 2.470], $p$ 0.67). After adjusting for age, PSA, DRE and number of cores, the multivariate model confirmed a significantly higher HR for HGPIN + ASAP (HR 2.76, $p < 0.001$) and ASAP alone (HR 2.41, $p < 0.001$).

### 3.3. Rebiopsies and timings

Timings and outcomes of each rebiopsy according to the initial histology are shown in Table 1. At follow-up biopsies,

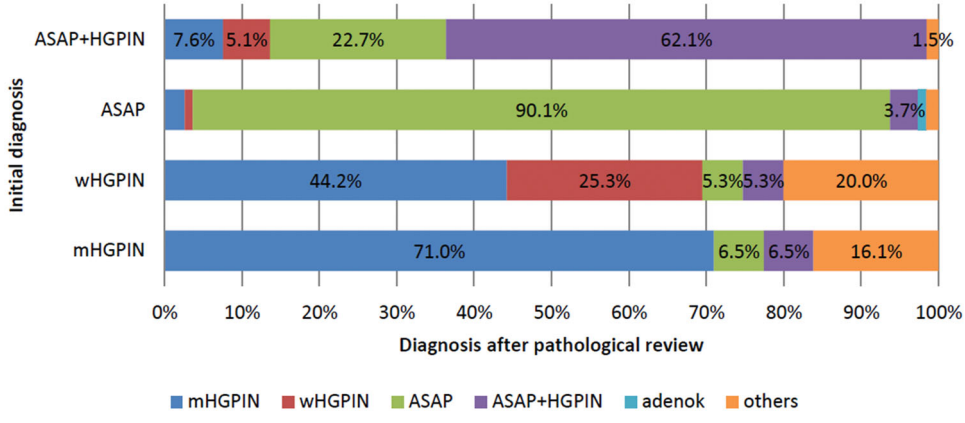


Figure 1. Results of pathologic re-evaluation of enrollment biopsies from initial diagnosis of premalignant lesions.

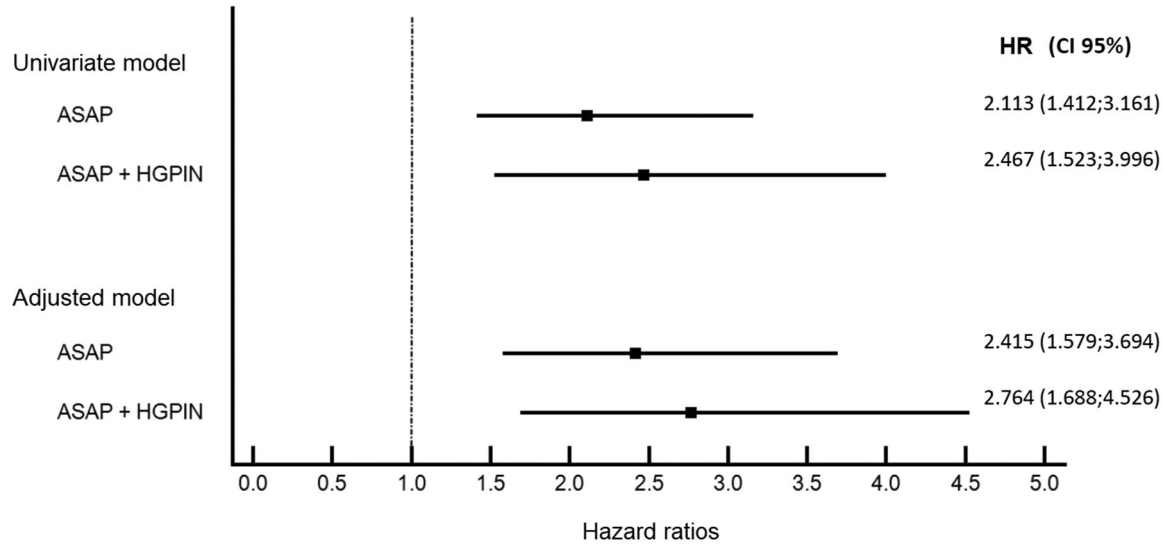


Figure 2. Forest plot showing the risk of PCa development according to Fine and Gray competing risk regression model.

174 PCa diagnoses were obtained (10 patients already diagnosed with low-risk PCa had a confirmation diagnosis at the third or fourth rebiopsy). Of 174 PCa detected, 112 (64.3%) were at first rebiopsy, 54 (31.0%) at second, 7 (4.0%) at third, and 1 (0.005%) at fourth.

Five rebiopsy intervals were chosen to analyze the relationship with PCa detection: 55 patients underwent rebiopsy within 3 months, 60 between 3 and 6 months, 139 between 6 and 12 months, 130 between 1 and 3 years, and 109 over 3 years. As shown in Supplementary Figure 2, the likelihood of finding PCa after ASAP exceeds 45% if a rebiopsy is performed within 3 months. The likelihood remains high also between 1 and 3 years, exceeding 40%, probably also influenced by clinical factors triggering a rebiopsy.

At Kaplan–Meier survival curves (Figure 3), median PCa-free survival was 48.1 months for HGPIN + ASAP and 64.9 months for ASAP ($p$ 0.0005 at Log-rank test). At 1 year, 70% of HGPIN + ASAP, 73% of ASAP, 89% of wHGPIN, and 84% of mHGPIN were PCa-free.

## 4. Discussion

The clinical management of the so-called precancerous lesions HGPIN and ASAP still represents a dilemma for urologists. Although HGPIN has been historically considered as a precursor of PCa, its risk of evolution into PCa has been reduced to 22–23% in recent series, not being different from the same risk after a benign diagnosis [1]. Things change when multiple cores of HGPIN are detected: in this case, the risk seems to be higher. Kim et al. [7] found that the rate of cancer detection was 16.7% and 30.5% in patients with a single core and more than one core of HGPIN, respectively. These rates were much higher in the recent study by Nakai et al. [8], being 53% in patients with previous monofocal HGPIN and 89% in those with two or more cores of HGPIN. All patients were rebiopsied with transperineal template prostate biopsy (median 37 cores) but sample size was very small, limiting the generalization of these results. In 2007, Schoenfield et al. [9] had already warranted a close follow-up of patient with multifocal HGPIN (two or more cores), reporting a risk of 80% of subsequent PCa on repeat biopsy.

When considering multifocal HGPIN, a pathological entity has been identified by Netto as Epstein, who have defined 'widespread HGPIN' the detection of four or core bioptic cores involved by HGPIN. This entity has been associated to a 39% likelihood of finding PCa on rebiopsy, even higher (55%) in patients older than 70 years [2]. According to these findings, patients with widespread HGPIN would form a subset at higher risk, worthy of repeating prostate biopsy with shorter intervals than isolated HGPIN. Following this lead, in our study we separately analyzed monofocal and widespread HGPIN, therefore intended as four or more cores with HGPIN.

Unlike HGPIN, ASAP indicates the presence of suspicious glands with insufficient cytological or architectural atypia for a definitive diagnosis of prostatic adenocarcinoma. In short, it indicates a situation of diagnostic uncertainty, highly predictive for PCa on subsequent biopsies [10]. PCa detection rate after ASAP has been estimated around 34–60%. Roscigno et al. [5] demonstrated that the combination of HGPIN and ASAP in the same biopsy might be even more predictive of subsequent cancer (58%) than isolated ASAP (35%). According to this evidence, the presence of ASAP warrants a repeat biopsy [11]. Nevertheless, recent studies have questioned the need for a repeat biopsy after ASAP. In 2016, Leone et al. [12] showed that 34% of patients with an initial diagnosis of ASAP were subsequently diagnosed with PCa, but only 22% (8% of the total cohort) were found to have high-grade disease. According to the authors, these findings would suggest that immediate repeat biopsy might be omitted in the majority of men with ASAP. Similar conclusions were drawn by Wiener et al. [13]: the rate of PCa detection at repeat biopsy within 1 year after diagnosis of ASAP was 34%, significantly different from HGPIN (20%) or benign tissue (16%). However, the rates of clinically significant PCa did not differ between groups, being only 8% among the 261 ASAP patients. On the same line, Srirangam et al. [14] did

Table 1. Details and outcomes of rebiopsies (after the enrollment biopsy) for each premalignant lesion.

| Rebiopsy, number | First | Second | Third | Fourth |
|---|---|---|---|---|
| Number of patients undergoing rebiopsy | | | | |
| Overall | 336 | 132 | 23 | 2 |
| mHGPIN | 66 | 25 | 5 | 0 |
| wHGPIN | 29 | 14 | 2 | 1 |
| ASAP | 187 | 67 | 8 | 0 |
| ASAP + HGPIN | 54 | 26 | 8 | 1 |
| Months from enrollment to rebiopsy, mean (SD) | | | | |
| Overall | 12.6 (15.5) | 48.0 (35.7) | 66.8 (31.5) | 54.3 (0.3) |
| mHGPIN | 14.1 (15.4) | 51.4 (34.7) | 85.1 (20.3) | – |
| wHGPIN | 8.8 (6.6) | 36.9 (29.7) | 16.0 (5.3) | 54.5 (–) |
| ASAP | 13.7 (17.8) | 51.3 (37.1) | 68.4 (29.0) | – |
| ASAP + HGPIN | 9.3 (7.6) | 41.7 (35.6) | 66.4 (32.7) | 54.0 (–) |
| *p* value[#] | 0.1527 | 0.2110 | 0.0930 | – |
| PCa detected (%)[a] | | | | |
| Overall | 112/336 (33) | 54/132 (41) | 7/23 (30) | 1/2 (50) |
| mHGPIN | 12/66 (18) | 9/25 (36) | 2/5 (40) | 0/0 (0) |
| wHGPIN | 4/29 (14) | 4/14 (29) | 1/2 (50) | 1/1 (100) |
| ASAP | 75/187 (40) | 29/67 (43) | 3/8 (37) | 0/0 (0) |
| ASAP + HGPIN | 21/54 (39) | 12/26 (46) | 1/8 (12) | 0/1 (0) |
| *p* value[##] | 0.0009 | 0.58 | 0.85 | 0.014 |
| Months from enrollment to tumor detection, mean (SD) | | | | |
| Overall | 14.6 (17.6) | 53.2 (39.3) | 56.2 (30.4) | 54.5 (–) |
| mHGPIN | 18.0 (17.7) | 49.8 (42.8) | 93.8 (18.5) | – |
| wHGPIN | 12.4 (9.8) | 39.2 (30.9) | 12.2 (–) | 54.5 (–) |
| ASAP | 15.0 (19.4) | 55.1 (39.1) | 48.4 (9.8) | – |
| ASAP + HGPIN | 11.8 (10.9) | 55.8 (43.0) | 48.2 (–) | – |
| *p* value[#] | 0.5801 | 0.8728 | 0.1798 | – |
| Prostate cancer features[b] | | | | |
| Gleason score ≤6 (%) | | | | |
| Overall | 42/112 (37.5%) | 25/54 (46.3%) | 3/7 (42.9%) | 0/1 (0%) |
| mHGPIN | 6/12 (50.0%) | 5/9 (55.6%) | 1/2 (50.0%) | – |
| wHGPIN | 1/4 (25.0%) | 2/4 (50.0%) | 0/1 (0%) | – |
| ASAP | 30/75 (40.0%) | 14/29 (48.3%) | 2/3 (66.7%) | – |
| ASAP + HGPIN | 5/21 (23.8%) | 4/12 (33.3%) | 0/1 (0%) | – |
| Gleason score 7 (3 + 4) (%) | | | | |
| Overall | 33/112 (29.5%) | 12/54 (22.2%) | 2/7 (28.6%) | 0/1 (0%) |
| mHGPIN | 2/12 (16.7%) | 2/9 (22.2%) | 1/2 (50.0%) | – |
| wHGPIN | 3/4 (75.0%) | 1/4 (25.0%) | 0/1 (0%) | – |
| ASAP | 20/75 (26.7%) | 7/29 (24.1%) | 0/3 (0%) | – |
| ASAP + HGPIN | 8/21 (38.1%) | 2/12 (16.7%) | 1/1 (100.0%) | – |
| Gleason score 7 (4 + 3) (%) | | | | |
| Overall | 6/112 (5.4%) | 5/54 (9.3%) | 0/7 (0%) | 1/1 (100.0%) |
| mHGPIN | 2/12 (16.7%) | 0/9 (0%) | 0/2 (0%) | – |
| wHGPIN | 0/4 (0%) | 1/4 (25.0%) | 0/1 (0%) | 1/1 (100.0%) |
| ASAP | 3/75 (4.0%) | 2/29 (6.9%) | 0/3 (0%) | – |
| ASAP + HGPIN | 1/21 (4.8%) | 2/12 (16.7%) | 0/1 (0%) | – |
| Gleason score 8–10 (%) | | | | |
| Overall | 5/112 (4.5%) | 3/54 (5.5%) | 0/7 (0%) | 0/1 (0%) |
| mHGPIN | 1/12 (8.3%) | 1/9 (11.1%) | 0/2 (0%) | – |
| wHGPIN | 0/4 (0%) | 0/4 (0%) | 0/1 (0%) | – |
| ASAP | 3/75 (4.0%) | 1/29 (3.4%) | 0/3 (0%) | – |
| ASAP + HGPIN | 1/21 (4.8%) | 1/12 (8.3%) | 0/1 (0%) | – |
| *p* value[##] | 0.5316 | 0.8849 | 0.2326 | – |

[a]10 patients already diagnosed with cancer had a confirmation diagnosis at the third or fourth rebiopsy.
[b]37 patients had missing data for prostate cancer features.
[#]Wilcoxon–Mann–Whitney test.
[##]Chi-square test.

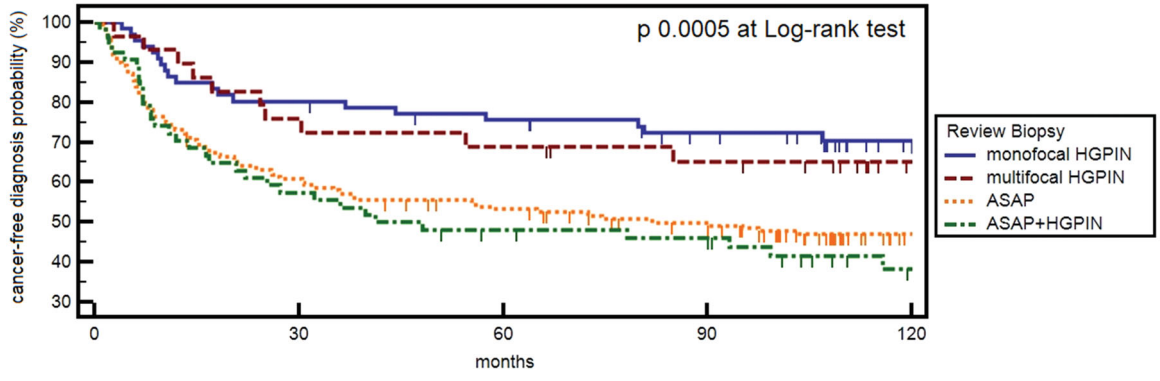


Figure 3. Kaplan–Meier survival curves for PCa-free survival according to the initial diagnosis of premalignancy after biopsy re-evaluation.

not find HGPIN or ASAP to be predictive of adenocarcinoma, but the sample size was very small, considering that only 7 patients with ASAP undergo repeat biopsy. In 2017, Nakai showed that ASAP was predictor of PCa on repeat transperineal template saturation biopsy, with a 83% PCa detection rate. However, only 12 patients with ASAP were enrolled in study [8].

Our study aimed to shed light on the controversies about HGPIN and ASAP, backed by an ample sample size and an adequate follow-up. Our patients underwent at least one rebiopsy during their follow-up: the choice to rebiopsy was taken by the urologist on the basis of clinical parameters and literature recommendations that suggest a rebiopsy after detection of HGPIN or ASAP. We believe that several findings of our study are of relevance and might impact on the clinical practice.

First, we showed the importance of pathological revision, which led to 32% change in diagnosis at enrollment. A significant proportion of HGPIN and ASAP were not correctly attributed, with some of them being low grade PIN or atrophy, and two patients already harboring PCa. This finding shows that the diagnosis of HGPIN and ASAP strongly relies on the expertise of dedicated uro-pathologist who follow strict criteria for the identification of these lesions, evaluating their architecture, cytology, basal cell layer, cytokeratins, and basal membrane features.

Second, we demonstrated that there is a significant risk of PCa on rebiopsy after diagnosis of ASAP or HGPIN + ASAP. On the other hand, there is no such risk after HGPIN alone, being it monofocal or widespread. Similarly to previous findings by Leone [12] and Wiener [13], the majority of cancers detected was graded as Gleason score 6(3 + 3) and 7(3 + 4), identifying a condition of low- to intermediate-risk. Not all these tumours, however, are to be considered as clinically insignificant, as proposed by some authors: following the histological criteria of the PRIAS study [15], Gleason score 7 or more, or more than two cores of Gleason score 6 are already considered as clinically significant, therefore not addressable to active surveillance.

Third, it seems wise to schedule a rebiopsy after diagnosis of ASAP, considering that we found that the likelihood of finding PCa after ASAP exceeds 45% if a rebiopsy is performed within 3 months. It is very difficult to recommend a precise window for the execution of a rebiopsy, considering that our patients did not undergo rebiopsy at the same time. However, the analysis of positive biopsy rates stratified per different time intervals provides interesting data. On the other hand, it is very likely that the results of a rebiopsy performed after a long time since the first one are affected by other factors beyond the finding of ASAP alone.

This study is not devoid of limitation, mainly residing in its retrospective nature and the impossibility of scheduling for all patients periodic rebiopsies at precise time intervals. The use of mpMRI was implemented since 2015, at discretion of physician. mpMRI has surely an important role in increasing the detection rate of PCa at biopsy, therefore a proportion of cancers could have been missed on rebiopsies for this reason. However, when mpMRI was not performed an updated clinical follow-up of at least 5 years supported the status of PCa-free.

## 5. Conclusions

The diagnosis of ASAP and HGPIN strongly relies on the expertise of dedicated uro-pathologists. Finding of ASAP and HGPIN + ASAP are strong risk factors for a subsequent PCa diagnosis; on the other hand, there is no such risk after HGPIN alone, being it monofocal or widespread. After diagnosis of ASAP, a considerable number of PCa is diagnosed if a rebiopsy is performed within 3 months.

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