Prostate adenocarcinoma detected after high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation

José I. López
Department of Anatomic Pathology, Hospital de Basurto, Basque Country University (EHU/UPV), Bilbao, Spain
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INTRODUCTION

High-grade prostatic intraepithelial neoplasia (HGPIN) has been traditionally considered as a precursor of prostate cancer [1,2] and many studies have addressed this issue. However, recent reports showed a varied association between HGPIN and prostate cancer, at 22–100% [3–9]. Apart from the generic recommendation to repeat the biopsy in these patients, there are no unifying criteria about how and when to do so, and urologists do not agree on the best clinical follow-up strategy in these cases. In addition, some contradictory data were reported relating the potential risk of future prostate cancer with the amount of HGPIN found in the core biopsy [3,8,10–12]. The diagnosis of atypical small acinar proliferation (ASAP) has also been correlated with the finding of prostate cancer in subsequent biopsies [13–17]. Indeed, the term was coined to focus attention in cases not completely fulfilling the minimal criteria of prostate cancer [18], thus advising a close follow-up. Also, there are various reported rates and opinions of the association between ASAP and subsequent prostate cancer [13–17].

Despite the relationship of HGPIN and ASAP with prostate cancer, there is no study comparing the histological characteristics of prostate cancer with and without previous diagnoses of HGPIN/ASAP. The aim of the present study was to investigate whether these two groups of prostate cancer are different and if so, in what sense.

PATIENTS AND METHODS

All the transrectal core biopsies of the prostate taken from patients at the author's institution during an 8-year period (1998–2005) were included in the analysis. The author conducted or reviewed the histopathological diagnoses in all patients and assessed the recorded data retrospectively. After local anaesthesia, the patients were biopsied under TRUS guidance, using routine methods. Patients with a diagnosis of cancer were treated by following the Institution's protocol [19] and those with a diagnosis of HGPIN or ASAP were followed with a DRE and serum PSA determinations every 6 months. ASAP was diagnosed by strictly applying the histological criteria; consequently, men with large atypical glands were not included in the study. Following precise clinical criteria, including an abnormal DRE and/or abnormal PSA density (>15 ng/mL per mL) or velocity (>0.75 ng/mL/year or >20%/year), patients were advised to have a repeat biopsy.

Six to eight cores of prostate tissue were obtained in every case in the first biopsy, and 10–12 in the subsequent ones, following previously established protocols [5,8,13,20]. Specimens were fixed in formalin and processed routinely. In all, 24–36 consecutive

RESULTS

HGPIN was followed by prostate cancer on repeat biopsy in 16.8% of patients, and ASAP in 26.7%. The mean age of patients with HGPIN or ASAP was higher than in those with no such diagnoses ($P<0.001$). Similarly, patients with these previous diagnoses had a lower Gleason score ($P=0.017$ and $<0.001$, respectively) and lower tumour volume variables (fewer tumour foci, $P=0.033$ and 0.041, respectively) and shorter cancer ($P=0.048$ and 0.030) in core biopsies than those without.

CONCLUSIONS

Patients with prostate cancer who had previous biopsies with HGPIN or ASAP were older and has lower grade- and volume-cancers than those who had not.

KEYWORDS

prostate cancer, high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation, Gleason score, tumour volume

Study Type – Prognosis (retrospective cohort study)
Level of Evidence 2b
histological sections, stained with haematoxylin and eosin, were assessed in every case. HGPIN and ASAP diagnoses were based on previously described criteria [21,22].

Immunostaining with α-methylacyl CoA racemase (p504S, dilution 1 : 50), p63 (1 : 50), and cytokeratin 5.6 (1 : 50, all from Dako, Carpinteria, CA, USA) was used to differentiate, when needed, the diagnostic dilemma between ASAP and minimal cancer [18], or HGPIN and intraductal carcinoma [23].

The presence of HGPIN/ASAP in core biopsies was correlated with several histological variables of prognostic significance in prostate cancer, e.g. bilateral tumour extension, Gleason score, number of tumour foci, total length of cancer measured, as previously stated [19], perineural invasion, vascular permeation, extraprostatic extension, hyaline micronodules, and glomerulartion. The time elapsed between the diagnosis of HGPIN or ASAP and that of prostate cancer was also quantified in every patient.

In addition, several histological variables were compared between cancers with previous diagnoses of HGPIN/ASAP and those without, to determine whether there was any significant difference among these two groups of prostate cancer.

### RESULTS

Among the 4770 prostate biopsies taken 1450 (30.3%) were diagnosed as prostate adenocarcinoma, 125 (2.6%) as HGPIN and 45 as ASAP (0.9%). Among patients with HGPIN 21 (16.8%) had a diagnosis of cancer in subsequent biopsies, and among ASAP, 12 (26.7%) had so.

The mean (range) age of patients with cancer after HGPIN was 72 (65–81) years, the mean delay between the diagnosis of HGPIN and that of cancer was 12.3 (2–39) months and the number of repeat biopsies needed to diagnose cancer was 1.3 (1–4). Following clinical criteria, no additional biopsies were taken in 29 patients (23.2%). HGPIN continued to be the only finding in repeated biopsies in nine patients (7%).

Table 1 summarizes the pathological findings in prostate cancers diagnosed after HGPIN; notably, 1.4% of prostate cancers diagnosed in this series had one or more previous biopsies in which HGPIN was the unique relevant finding. The Gleason score distribution in these patients was <7 in nine, 3 + 4 in two, 4 + 3 in one and >7 in none. Tumour volume, expressed as the mean (range) number of tumour foci and total length of cancer, was 1.8 (1–4) and 5.5 (1–19) mm, respectively.

There was a correlation between HGPIN in the first biopsy and several histological findings with prognostic significance in subsequent biopsies. Thus HGPIN correlated (Spearman’s ρ) with bilateral tumour invasion (P = 0.024), Gleason score (P = 0.011), number of tumour foci (P = 0.003), total length of cancer (P < 0.001) and perineural invasion (P = 0.015).

When comparing cancers with and with no previous diagnosis of HGPIN, the mean age was significantly higher in the group with previous HGPIN, at 72 (65–81) vs 64.8 (43–77) years (P < 0.001); the Gleason score was lower (P = 0.017), there were fewer tumour foci, at 1.8 (1–4) vs 2.5 (1–7) (P = 0.033), and the total length of cancer less, at 5.5 (1–19) vs 9.7 (1–58) (P = 0.048) in the group with previous HGPIN.

The mean age of patients with cancer after a diagnosis of ASAP was 68 (54–87) years, with a delay between diagnosis of ASAP and that of cancer of 12.7 (2–30) months, and 0.8 (1–3) repeat biopsies necessary to diagnose cancer. There was no patient with two consecutive diagnoses of ASAP. Table 1 also summarizes the pathological findings in prostate cancers diagnosed after ASAP; 0.8% of prostate cancers diagnosed had a previous diagnosis of ASAP. The Gleason score distribution in these cases was <7 in nine, 3 + 4 in two, 4 + 3 in none and >7 in one. The tumour volume (number of tumour foci and total length of cancer) was 2.1 (1–5) and 5 (1–14) mm, respectively.

There was a correlation between ASAP in the first biopsy and several histological findings with prognostic significance in subsequent biopsies; ASAP correlated (Spearman’s ρ) with Gleason score (P = 0.022), number of tumour foci (P = 0.015) and total length of cancer (P = 0.005).

Comparing patients with cancer with and with no previous ASAP, the mean age was significantly higher in the group with previous ASAP, at 70 (57–79) vs 64.8 (43–77) years (P < 0.001), the Gleason score was lower (P < 0.001), there were fewer tumour foci, at 2.1 (1–5) vs 2.5 (1–7) (P = 0.041) and the total length of cancer lower, at 5 (1–14) vs 9.7 (1–58) mm (P = 0.030) in the group with previous ASAP. Two patients had HGPIN and ASAP in the same core, and both had prostate cancer in the subsequent biopsy.

<table>
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<tr>
<th>Variable</th>
<th>Mean (range)</th>
<th>p value</th>
<th>P</th>
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<tr>
<td>HGPIN</td>
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<tr>
<td>Repeat biopsies</td>
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<td>Gleason score</td>
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<tr>
<td>&gt;7</td>
<td>0</td>
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<tr>
<td>Tumour foci</td>
<td>1.8 (1–4)</td>
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<td>0.003</td>
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<td>Length of cancer, mm</td>
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<tr>
<td>Repeat biopsies</td>
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<tr>
<td>Tumour foci</td>
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<tr>
<td>Length of cancer, mm</td>
<td>5 (1–14)</td>
<td>0.250</td>
<td>0.005</td>
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**Table 1** The histological findings in prostate cancer with a previous diagnosis of HGPIN or ASAP
The influence of the number of HGPIN foci on adding intriguing results to the topic and with low-grade rather than with HGPIN, thus discovering cancer on repeat biopsy in cases of multifocal HGPIN, while Naya et al. [26,27] found it less frequently, in a repeat biopsy in these patients. However, for predicting cancer, and the convenience of the supposed importance of detecting HGPIN, patients with cancer after ASAP were older, and the tumours had a lower Gleason score and fewer tumour foci.

To date there is no published comparison between the histological characteristics of cancers diagnosed after a diagnosis of either HGPIN or ASAP and cancers without this antecedent. As with HGPIN, patients with cancer after ASAP were older, and the tumours had a lower Gleason score and fewer tumour foci.

Obviously, finding prostate cancer in a core biopsy is a combined matter of statistical probabilities and tumour size. There is no definite explanation of why prostate cancer detected after a diagnosis of either HGPIN or ASAP is of lower Gleason score and smaller tumour volume, and there is no previously published reference to this. However, clinically insignificant or small-volume prostate carcinomas have less chance of being sampled in core biopsies than the remaining tumours, and in the particular setting of a ‘no tumour present’ biopsy in a patient with highly suggestive clinical data, the pathologist might unconsciously assess the submitted material more closely to find, if not cancer, at least some cancer-related features like HGPIN or ASAP.

To summarize, the incidence of HGPIN and ASAP in the present series was 2.6% and 0.9%, with a subsequent cancer rate of 16.8% and 26.7%, respectively, in those who had repeat biopsies. These values agree with those reported previously and further support the relationship between both conditions and cancer. As previously reported, ASAP has a closer relation with cancer than HGPIN. Finally, prostate carcinomas detected after HGPIN or ASAP appear in older patients, are of lower grade, and have a smaller tumour volume than cancers without these antecedents. These differences between prostate cancers with and without previous diagnoses of HGPIN or ASAP have not been reported to date.

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CONFLICT OF INTEREST

None declared.

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Correspondence: José I. López, Department of Anatomic Pathology, Hospital de Basurto, Avda. de Montevideo 18, 48013 Bilbao, Spain. e-mail: joseignacio.lopez@ehu.es

Abbreviations: (HG)PIN, (high-grade) prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation.