Prostate biopsies containing prostate intraepithelial neoplasia and atypical small acinar proliferation: what to do?
Biópsias prostáticas contendo neoplasia intraepitelial e proliferação acinar atípica: o que fazer?

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ABSTRACT
Objective: The aim of the study was to assess the frequency of high-grade prostate intraepithelial neoplasia and atypical small acinar proliferations on a contemporary series, and their relation to posterior diagnosis of prostate cancer. Methods: A retrospective study was conducted with 6,490 consecutive men submitted to extended prostate biopsies between 2000 and 2005 at a single institution. Of these, 400 men (6.16%) had atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia, and 43 had at least one follow-up biopsy. Results: The overall incidence of high-grade prostatic intraepithelial neoplasia was 4.6% and 1.4% for atypical small acinar proliferation. High-grade prostatic intraepithelial neoplasia plus atypical small acinar proliferation occurred in 0.11% of men. The detection rates of prostate cancer on repeated biopsies were of 38.5 and 53.6% for high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation, respectively. All patients with high-grade prostatic intraepithelial neoplasia plus atypical small acinar proliferation who had a repeated biopsy were diagnosed with prostate cancer. There was a higher risk of diagnosing prostate cancer in a site close to previous atypical small acinar proliferation (OR = 5.93; p = 0.015). Conclusions: After high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation finding on extended biopsies, close follow-up is recommended, and repeated biopsies should be done according to clinical data as well. Rebiopsies should be strongly recommended when the association high-grade prostatic intraepithelial neoplasia plus atypical small acinar proliferation is present, or when atypical small acinar proliferation is found only after the second biopsy. Repeated biopsies after an atypical small acinar proliferation finding should be always randomized, but sites of atypical small acinar proliferation should be more extensively sampled.

Keywords: Prostate; Biopsy, needle; Prostatic intraepithelial neoplasia; Prostatic neoplasms

RESUMO
Objetivo: O objetivo do estudo foi avaliar a frequência de neoplasia intraepitelial prostática de alto grau e de proliferações atípicas de pequenos ácinos em uma série atual, e sua relação com o diagnóstico de câncer de próstata. Métodos: Foi realizado estudo retrospectivo com 6.490 homens submetidos consecutivamente a biópsia estendida de próstata entre 2000 e 2005. Destes, 400 (6,16%) apresentaram proliferações atípicas de pequenos ácinos ou neoplasia intraepitelial prostática de alto grau, e 43 foram submetidos a rebiópsias. Resultados: A incidência de neoplasia intraepitelial prostática de alto grau foi de 4,6% e, de proliferações atípicas de pequenos ácinos, 1,4%. Neoplasia intraepitelial prostática de alto grau mais proliferações atípicas de pequenos ácinos ocorreu em 0,11% dos homens. Detecção de câncer de próstata em rebiópsias ocorreu em 38,5 e 53,6% dos homens com neoplasia intraepitelial prostática de alto grau e proliferações atípicas de pequenos ácinos, respectivamente. Todos os homens com neoplasia intraepitelial prostática de alto grau mais proliferações atípicas de pequenos ácinos apresentaram câncer de próstata em rebiópsias. Observou-se um risco elevado de detecção de câncer de próstata próximo ao local onde ocorreram proliferações atípicas de pequenos ácinos previamente (OR = 5,93; p = 0,015). Conclusões: Após o achado de neoplasia intraepitelial prostática de alto grau ou proliferações atípicas de pequenos ácinos em biópsias estendidas, seguimento cauteloso é recomendado, e rebiópsias devem ser realizadas de acordo com dados clínicos. Rebiópsias são fortemente recomendadas quando há associação da neoplasia intraepitelial prostática de alto grau mais proliferações atípicas de pequenos ácinos, ou quando proliferações atípicas de pequenos ácinos são encontradas a partir da segunda biópsia repetida. Rebiópsias após proliferações atípicas de pequenos ácinos devem ser randomizadas, porém locais onde ocorreu o achado de proliferações atípicas de pequenos ácinos devem ser mais extensivamente representados.

Descritores: Próstata; Biópsia por agulha; Neoplasia prostática intraepitelial; Neoplasias da próstata
INTRODUCTION

High-grade prostate intraepithelial neoplasia (HGPIN) and small acinar proliferations (ASAP) are thought to have important prognostic significance due to their potential as markers for concurrent or future prostate adenocarcinoma (PCa)(1-3). HGPIN was defined as abnormal proliferative change in preexisting, architecturally normal prostatic ducts and acini with nuclear atypia similar to that seen in PCa. However, HGPIN lacks invasion of the basement membrane of the prostatic glands. Recent 12-core biopsies studies have demonstrated that the risk of finding PCa after the diagnosis of HGPIN is lower than previous studies with sextant biopsies advocated (20 to 30%)(3-4).

ASAP includes a number of atypical lesions that are suspicious for but not diagnostic of PCa. Near 50% of cases of ASAP end with clinically detected PCa(1,3).

OBJECTIVE

The aim of this study was to evaluate the current frequency of (HGPIN) and ASAP on extended prostate needle biopsies, as well as their relation to posterior diagnosis of PCa.

METHODS

A retrospective study was conducted with 6,490 consecutive men submitted to extended prostate needle core biopsies between January 2000 and December 2005, at a single service.

All men had undergone extended biopsies (minimum of 12 cores), and all cases were examined by a genitourinary pathologist (MGC). The slides were examined for the presence of HGPIN and ASAP. HGPIN is defined as abnormal proliferative change in preexisting architecturally normal prostatic acini and ducts with nuclear atypia similar to that seen in prostate cancer(6). ASAP is not a specific diagnosis, it includes a number of atypical lesions that are suspicious for but not diagnostic of cancer. This group of lesions includes cancer mimickers and many cases of focal carcinoma(6). We identified 400 men (6.16%) with ASAP or HGPIN diagnoses on prostate needle biopsies. Of these 400 men, 43 had undergone at least one follow-up biopsy, and they represent our study group. The remaining either did not accept a second biopsy or were lost to follow-up.

Medical records were reviewed to determine: the number of repeat biopsies; the site of initial diagnosis as well as that of subsequent tumors; patient age; and biopsy technique. Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS 13.0 for Mac OS X, SPSS Inc., Chicago, Illinois). Pearson’s χ² test was used to compare data. Statistical significance was determined at p < 0.05. The institutional review board approved the present study.

RESULTS

Overall incidence of HGPIN was 4.65% (n = 302), while the incidence of ASAP was 1.40% (n = 91). HGPIN + ASAP at the same biopsy occurred in 0.11% (n = 7) of men. As the repeat biopsy population, 43 men were analyzed and underwent a total of 96 biopsies (average 2.2 each, range 2 to 4); 13 men with an initial diagnosis of HGPIN had a total of 25 biopsies (average 2.1, range 2 to 3); 28 men with an initial diagnosis of ASAP had a total of 63 biopsies (average 2.3, range 2 to 4); and two men with initial diagnosis of HGPIN + ASAP had 4 biopsies.

PCa detection rates on repeated biopsies were of 38.5 and 53.6% for HGPIN and ASAP, respectively. All patients with HGPIN + ASAP who had a repeated biopsy were diagnosed with PCa (Table 1). Mean time between biopsies was nine months.

Table 1. Prostate cancer diagnosis following finding of high-grade prostate intraepithelial neoplasia, atypical small acinar proliferations and high-grade prostate intraepithelial neoplasia plus atypical small acinar proliferations in extended biopsies

<table>
<thead>
<tr>
<th>Biopsies</th>
<th>HGPIN</th>
<th>ASAP</th>
<th>ASAP + HGPIN</th>
<th>p-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 13)</td>
<td>(n = 28)</td>
<td>(n = 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCa at repeated biopsy</td>
<td>38.5 (5)</td>
<td>53.6 (15)</td>
<td>100.0 (2)</td>
<td>0.245</td>
<td>2.81</td>
</tr>
<tr>
<td>PCa - 2nd biopsy</td>
<td>80.0 (4)</td>
<td>86.6 (13)</td>
<td>100.0 (2)</td>
<td>0.171</td>
<td>3.53</td>
</tr>
<tr>
<td>PCa - 3rd biopsy</td>
<td>0</td>
<td>6.7 (1)</td>
<td>-</td>
<td>0.760</td>
<td>0.548</td>
</tr>
<tr>
<td>PCa - 4th biopsy</td>
<td>20.0 (1)</td>
<td>6.7 (1)</td>
<td>-</td>
<td>0.802</td>
<td>0.442</td>
</tr>
</tbody>
</table>

HGPIN: high-grade prostate intraepithelial neoplasia; ASAP: atypical small acinar proliferations; ASAP + HGPIN: high-grade prostate intraepithelial neoplasia plus atypical small acinar proliferations; PCa: prostate cancer.

Regarding topographic diagnosis of PCa, we observed a significant higher risk of diagnosing PCa close to where ASAP was detected, in comparison to patients with initial finding of HGPIN (OR = 10.1; p = 0.036; Table 2). If considered only the cases in which cancer was detected exactly in the same place, this difference was even clearer for ASAP versus HGPIN (OR = 5.93; p = 0.015).

Table 2. Topography of prostate cancer in comparison to initial findings in repeated biopsies

<table>
<thead>
<tr>
<th>Topography</th>
<th>HGPIN</th>
<th>ASAP</th>
<th>ASAP + HGPIN</th>
<th>p-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 5)</td>
<td>(n = 15)</td>
<td>(n = 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same quadrant</td>
<td>20.0 (1)</td>
<td>80.0 (12)</td>
<td>0.0 (0)</td>
<td>0.036</td>
<td>10.3</td>
</tr>
<tr>
<td>Same side, different quadrant</td>
<td>60.0 (3)</td>
<td>13.3 (2)</td>
<td>100.0 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opposite side</td>
<td>20.0 (1)</td>
<td>6.7 (1)</td>
<td>0.0 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HGPIN: high-grade prostate intraepithelial neoplasia; ASAP: atypical small acinar proliferations; ASAP + HGPIN: high-grade prostate intraepithelial neoplasia plus atypical small acinar proliferations.
DISCUSSION

Most epidemiologic studies evaluating HGPIN and ASAP as risk factors for PCa were from a time when sextant biopsies (six samples) were routinely performed\(^{(1,7)}\). Nowadays, the minimum number considered for a proper PCa screening is 12 samples (extended biopsy). In this context, recent studies have demonstrated that the incidence of HGPIN and ASAP is different from the previously stated, as well as the risk of a subsequent diagnosis of PCa\(^{\text{(3,5-8,10)}}\).

Our study has some important findings. First, the incidence of HGPIN on prostate biopsy was of 4.6%, reproducing the results of recent studies on extended biopsies\(^{(5)}\). HGPIN was associated with a 38.5% chance of PCa detection in repeated biopsies, and there was a significant lower risk of detecting cancer in the topography of previous HGPIN versus ASAP (20 versus 80%; \(p = 0.036\)). However, this risk must also be compared to the risk of finding cancer in a repeated biopsy after a benign diagnosis, which ranges from 10.0 to 30.0%\(^{\text{(11-13)}}\). Other series diagnosed PCa in 10 to 57%\(^{\text{(14-15)}}\) of repeated biopsies after HGPIN\(^{\text{(11-13,16-17)}}\). In the present series with extended biopsies, the diagnosis of PCa was made in 13.2 to 30.5%\(^{\text{(3-5,12)}}\). We found a higher rate of PCa than these authors, and a higher rate than after benign diagnosis, but still lower than observed for ASAP. Therefore, further studies evaluating other factors, such as the number of involved cores and morphologic patterns, might help to determine which of the men with HGPIN are at significantly higher risk of harboring carcinoma and would benefit from rebiopsies\(^{(15)}\).

Second, ASAP occurred in 1.4% of the extended prostate biopsies, what is also similar to larger series\(^{\text{(1,5,14-15)}}\). The risk of diagnosing PCa on repeated biopsies was of 53.6%, comparable to recent series (range from 37.0 to 51.0%)\(^{\text{(3-5,19)}}\). There was also a significant higher risk of detecting the PCa close to the site of ASAP (\(p = 0.001; \text{OR} = 10.8\)). Therefore, patients with ASAP at prostate biopsies are at increased risk of future PCa detection, and it is recommended that ASAP foci should be more extensively sampled on repeated biopsies. As the risk of PCa is higher in patients with ASAP, it is generally recommended that rebiopsies are taken after three to six months\(^{(6)}\).

Third, for patients who had ASAP in the first biopsy, the risk of detecting PCa was 50.0%. However, in all cases (\(n = 3\)) in which ASAP was found only after the second biopsy, a subsequent biopsy diagnosed PCa. Although there were few cases of association HGPIN + ASAP, this finding seems to be related to an even higher rate of future detection of PCa than isolated HGPIN or ASAP, as previously reported\(^{\text{(9)}}\).

Our study has several limitations. Even though a large number of biopsies were evaluated (6,490), the number of patients with HGPIN and ASAP was much lower. Therefore, the relatively small number of men for subsequent analysis limits the power of the study. Also, it is important to note that a high subset of patients were lost to follow-up and did not undertake rebiopsy after HGPIN or ASAP, which can raise a concern of follow-up bias. However, the strength of our study is that a large number of patients in a contemporary extended biopsy series could be evaluated.

CONCLUSION

In conclusion, following the finding of HGPIN or ASAP on extended prostate biopsies, close follow-up is recommended, and repeated biopsies should be performed according to clinical data. Rebiopsies should be strongly recommended when the association HGPIN + ASAP is present or when ASAP is found only after the second biopsy. Repeated biopsies after an ASAP finding should be always randomized, but foci of ASAP finding should be more extensively sampled.

REFERENCES

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