The incidence of high-grade prostatic intraepithelial neoplasia and atypical glands suspicious for carcinoma on first-time saturation needle biopsy, and the subsequent risk of cancer

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OBJECTIVE

To investigate the detection rate and extent of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical glands (AG) suspicious for prostate cancer, and the cancer risk in subsequent biopsies, diagnosed by a first 24-core saturation biopsy, as although the optimum extent of biopsy is controversial there is a trend to increase the number of cores taken, and apart from detecting prostate cancer, identifying HGPIN and AG is associated with a greater risk of finding cancer in subsequent biopsies, thus warranting a closer follow-up.

PATIENTS AND METHODS

The study included 100 men with consecutive first-time saturation biopsies; the indications for biopsy were an abnormal digital rectal examination and/or a serum prostate-specific antigen (PSA) level of >2.5 ng/mL. Each biopsy specimen was reviewed retrospectively by two pathologists to confirm the histological diagnosis. The number and percentage of cores positive for HGPIN, bilateral involvement and multifocality (HGPIN involving two or more cores) were recorded in each case. The presence of AG and cancer was also recorded. An extended (10–12 cores) repeat biopsy was available in 23 patients.

RESULTS

The median (range) age and PSA level of the patients was 63 (41–80) years and 4.9 (1.5–67.0) ng/mL, respectively. Of the 100 patients, 34% had normal findings (benign prostatic tissue, BPT), 39% had cancer, 26% had HGPIN and cancer, 22% had HGPIN alone, and 5% had AG. Repeat biopsies were available in nine of the 22 (41%) patients with HGPIN, four of five with AG, and 10 of the 34 (29%) with BPT. The median (range) interval between the first and second biopsy was 13 (4–36) months. Prostate cancer was detected at the second biopsy in a third of patients with isolated HGPIN on the first biopsy, and one of the four with AG. None of the patients with BPT had cancer on re-biopsy. The cancer detection rate was significantly greater in patients with multifocal than in those with unifocal HGPIN (80% vs none, \( P = 0.010 \)). The median number of cores and percentage of tissue involved by HGPIN was 3.5 (2–5) and 1.0 (0.5–1.2)%, respectively, in patients with cancer detected in repeat biopsies, compared to 1.0 (1–3) and 0.2 (0.2–0.6)% in patients without cancer on repeat biopsy (\( P = 0.023 \) and 0.015, respectively).

CONCLUSION

Identifying multifocal HGPIN on first saturation biopsy is associated with an overall cancer detection rate of 80% on repeat 10–12-core biopsy. Although there were few patients, the detection of multifocal HGPIN warrants additional searches for concurrent invasive carcinoma by repeated biopsy.

KEYWORDS

atypical glands, high-grade prostatic intraepithelial neoplasia, prostate cancer, saturation needle biopsy

INTRODUCTION

Men with elevated serum PSA levels are advised to have needle biopsies of the prostate; the TRUS-guided systematic sampling of the prostate gland introduced by Hodge et al. in 1989 [1] has greatly increased the ability to detect prostate cancer. The sextant biopsy approach has been historically associated with a relatively high false-negative rate, of 15–31% [2–5]. Concerned about the possibility of missing clinically significant tumours, different groups have suggested several different regimens involving more extensive sampling of larger glands, and particularly of the far lateral and more medial aspects of the peripheral zone of the prostate [6–8]. Although the optimal extent of prostate biopsy remains controversial, there is a trend to increase the number of cores taken to increase the cancer detection rate.

Extended biopsies usually involving ≥10 cores have been shown to improve the diagnostic accuracy of clinically significant prostate cancer [8,9]. Extensive prostate biopsy schemes of 14–45 cores, a procedure also referred to as 'saturation biopsy', has in general been reserved for a highly selected group of men with persistently high PSA levels and initial or multiple negative biopsies [10,11].

Although showing a significantly greater detection rate for repeat biopsy, the systematic saturation biopsy technique as the initial biopsy strategy does not seem to improve the cancer detection rate when
incidence of HGPIN and atypical glands on needle biopsy and risk of cancer

TABLE 1 HGPIN architectural patterns and extent

<table>
<thead>
<tr>
<th>Variable</th>
<th>HGPIN</th>
<th>+ cancer</th>
<th>+ AG</th>
<th>only</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>3</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Architectural pattern</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>Tufted</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Micropapillary</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Flat</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cribriform</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt; one pattern*</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Extent</td>
<td>21</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>bilateral involvement</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>no. of cores, median</td>
<td>2.5</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>% tissue, median</td>
<td>0.8</td>
<td>0.2</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>multifocality, n (%)</td>
<td>19</td>
<td>1</td>
<td>11</td>
<td>50</td>
</tr>
</tbody>
</table>

The term AG, or atypical small acinar proliferation, denotes the presence of a small focus of atypical glands suspicious for adenocarcinoma, but with insufficient cytological and/or architectural atypia to establish a definitive diagnosis. The median (range) incidence of AG on prostate needle biopsies is 4.4 (0.7–23.4)%, the variability depending on the expertise and skill of the pathologist. The likelihood of finding cancer on repeat biopsy is ≈40%, higher than that with a diagnosis of HGPIN [15].

While many studies have documented that taking more biopsy cores can improve the cancer detection rate, the influence of increased biopsy sampling on the detection rate of HGPIN and AG, and the subsequent risk, has not been determined. The objective of the present study was to determine the detection rate and extent of HGPIN and AG diagnosed by a first 24-core saturation biopsy, and the subsequent cancer risk associated with these diagnoses.

PATIENTS AND METHODS

Between February 2003 and May 2004, 100 consecutive patients were referred for prostate needle biopsy and had a first saturation biopsy; these patients were a subset of a cohort previously reported for cancer detection with a saturation biopsy protocol [16]. The indications for biopsy were an abnormal DRE and/or a serum PSA level of >2.5 ng/mL. None of the patients had an abnormal DRE and/or a serum PSA level of >4.9 (1.5–67.0) ng/mL, respectively. Benign prostatic tissue (BPT) was the only diagnosis in 34 of the 100 patients; cancer was detected in 39, and HGPIN was present as an isolated finding in 22, together with cancer in 26, and with AG in three, and AG as an isolated finding or together with HGPIN was identified in five.

Of the 61 patients, whose diagnosis was other than prostate cancer on the first saturation biopsy, 23 (38%) had a repeat extended (10–12-core) biopsy after a median (range) follow-up of 13 (4–36) months.

RESULTS

The median (range) age and PSA level of the patients was 63 (41–80) years and 4.9 (1.5–67.0) ng/mL, respectively. Benign prostatic tissue (BPT) was the only diagnosis in 34 of the 100 patients; cancer was detected in 39, and HGPIN was present as an isolated finding in 22, together with cancer in 26, and with AG in three, and AG as an isolated finding or together with HGPIN was identified in five.

The most common architectural pattern of HGPIN was tufted (47/51 cases), followed by micropapillary (11), and flat (8); cribriform HGPIN was not identified in this series. In 15 of the 51 cases (29%) more than one architectural pattern of HGPIN was present. Micropapillary HGPIN was never present as the only pattern (Table 1).

HGPIN as an isolated finding was present bilaterally in six of 22 cases (27%), the median number of cores involved being 1.5 (1–7) and the median percentage of tissue involved being 0.5 (0.1–14.3)%. In half of the cases (11) HGPIN was multifocal. In the 26 cases associated with cancer, HGPIN was present bilaterally in 10 (38%), the median number of cores with HGPIN being 2.5 (1–8) and the median percentage of tissue involved being 0.8 (0.2–3.3)% in 19 cases (73%) HGPIN was multifocal.

AG was identified in five cases, three of which were with HGPIN; in two cases the two lesions (HGPIN and AG) coexisted in the same high-power microscopic field and HGPIN was unifocal. In one case HGPIN was multifocal and present in several cores in addition to that with AG (Table 1).

The 23 patients who had a second biopsy included nine with HGPIN, four with AG and 10 with BPT (Table 2); 22 had extended biopsies after a follow-up of 8–36 months, and one had a transurethral biopsy after 4 months.
Of the nine patients with isolated HGPIN on the first saturation biopsy, prostate cancer was detected on the repeat biopsy in three. HGPIN was confirmed in one and BPT in two (Table 2). The median follow-up for the HGPIN group was 15 (8–33) months (Table 3).

Of the four patients with AG on initial biopsy, cancer was detected on repeat biopsy in one (who also had associated multifocal HGPIN), AG in one and BPT in two (Table 2). The median follow-up for the AG group was 12.5 (8–16) months.

Of the 34 patients with benign findings, 10 (29%) had a repeat biopsy with HGPIN detected in three and BPT in seven (Table 2). None of the patients with BPT had cancer on repeat biopsy. The median follow-up for the BPT group was 9 (4–36) months.

The risk of finding cancer on repeat biopsy was not statistically different when considering HGPIN vs AG vs BPT, or HGPIN/AG vs BPT, on initial biopsy (P = 0.14 and 0.10, respectively, Fisher’s exact test).

All the patients with cancer detected on repeat biopsy had multifocal HGPIN on the first saturation biopsy (Table 3). The cancer detection rate on repeat biopsy was significantly greater in patients with multifocal HGPIN (80%) than in those with unifocal HGPIN (none; P = 0.01, Fisher’s exact test).

The number of cores and percentage of tissue involved by HGPIN significantly correlated with the rate of cancer detection on repeat biopsy. Of three patients with HGPIN who were found to have cancer in subsequent biopsies, all had multifocal HGPIN involving 1.2% (median) of tissue in the initial biopsy. By contrast, in six patients with HGPIN in whom cancer was not found in the subsequent biopsy, only one had multifocal HGPIN involving 0.6% of the tissue in the initial biopsy (P = 0.023 and 0.015, respectively; Mann–Whitney test; Table 3). The architectural type of HGPIN present in the initial biopsy did not correlate with the detection of cancer on repeat biopsy (P = 0.06, Fisher’s exact test).

DISCUSSION

Routine screening has increased the importance of prostate biopsy in urological practice and the detection of prostate cancer. Systematic transrectal biopsy is the reference standard to detect the local clinical stage and grade of prostate cancer, but controversy persists about the number of cores and the prognostic significance of HGPIN and AG.

Several studies showed that sextant prostate biopsy might miss a significant percentage of cancers, and additional sampling of the lateral, transitional or anterior zone (extended biopsies) might increase the diagnostic yield by 19–35% [8,17–21]. Presti [22] reviewed several studies evaluating various biopsy schemes, and suggested that a 10–12-core scheme is optimal in most patients having an initial biopsy. Saturation biopsy improves the prostate cancer detection rate in patients with findings suspicious for cancer after a previously negative biopsy, but does not seem to improve the cancer detection rate as an initial biopsy strategy [12].

While many studies documented that taking more biopsy cores can improve the cancer detection rate, few reports have addressed the influence of increased biopsy sampling on the detection rate of HGPIN and AG, and the cancer risk associated with these two diagnoses in subsequent biopsies. In a recent review, Epstein and Herawi [15] reported no relationship between the number of cores (6–16) sampled and the incidence of HGPIN on needle biopsy.

Several studies reported on the positive predictive value of HGPIN as a single finding for cancer on subsequent prostate biopsies, and the detection rate reported was 2.3–100% [23,24]. The positive predictive value of AG as a single finding for cancer on repeat prostate biopsies is 21–51%.

We determined the detection rate, extent, and architectural pattern of HGPIN and AG diagnosed by a first saturation needle biopsy (24 cores) and the subsequent cancer risk associated with these diagnoses. By using strict histological criteria [14], the incidence of isolated HGPIN (22%) found on the first saturation biopsy in the present study was among the highest of those reported previously (0.6–24.6%) despite a high cancer detection rate (39%) [11,15,21,25–27]. The median age and PSA level of the present patients was 63 years and 4.9 ng/mL, respectively, and similar to the values in the cited studies. The incidence of AG (6%) in the present patients was similar to those reported in other studies (0.5–23%, mean 5.5%).

**Corrected Table 3:** Repeat biopsy data for patients with HGPIN on the first biopsy

<table>
<thead>
<tr>
<th>Case</th>
<th>First saturation biopsy</th>
<th>Repeat biopsy</th>
<th>Interval months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HGPIN type*</td>
<td>% HGPIN/ tissue</td>
<td>no. cores</td>
</tr>
<tr>
<td>1</td>
<td>1, 3</td>
<td>0.6</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1, 2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1, 2</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
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</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
</tr>
</tbody>
</table>

*1, tufted; 2, micropapillary; 3, flat.
It was suggested that the greater accuracy of the 10–12-core biopsy scheme could negate the predictive value of HGPIN by simply finding cancer that would have been missed by less extended techniques. According to some contemporary studies, HGPIN found in extended biopsy does not warrant repeat biopsy, but the diagnosis of AG continues to be associated with a high risk of cancer and requires at least one repeat biopsy [27,28].

The present study offers a unique understanding of men who had negative cancer results for an initial saturation biopsy, and a repeat biopsy using an extended biopsy technique. We found an overall positive repeat biopsy rate of 17% in this group of men; a third of patients with HGPIN and one of four with AG were diagnosed as having prostate cancer on repeat biopsy. None of the patients with BPT on initial biopsy was found to have cancer on repeat biopsy. Although the incidence of cancer in the HGPIN or HGPIN/AG groups was greater than in the control group (BPT), the difference was not statistically significant as there were too few patients assessed. We will continue to follow these patients to collect more data.

The positive repeat biopsy rate in the present patients is clearly lower than that previously reported for patients having sextant biopsies, but similar to that reported in repeat extended prostate biopsy [29]. Our finding that none of the patients with BPT on initial biopsy had cancer on repeat biopsy, albeit based on very few men, is probably a result of the increased accuracy of the initial saturation biopsy technique.

In the present patients the cancer detection rate was significantly greater in patients with multifocal HGPIN than in those with unifocal HGPIN (80% vs none, P = 0.010). The number of biopsy cores involved by HGPIN (P = 0.023) and the percentage of core tissue involved by HGPIN (P = 0.015) also differed significantly between patients with and without cancer on repeat biopsy. The cancer detection rate in unifocal HGPIN was similar (none) to that in patients with BPT.

These data suggest that the detection of multifocal or extensive HGPIN is associated with a greater risk of subsequent prostatic adenocarcinoma, and warrants follow-up with repeated needle biopsy. Our findings are in agreement with other studies where multifocality and the number of cores with HGPIN were independent predictors of cancer [30]. However, as suggested by Roscigno et al. [30], it might be presumed that the presence of unifocal HGPIN on first saturation biopsy is associated with a limited extent of HGPIN in the entire prostate gland, and with a low risk of concurrent cancer, and repeat biopsy might not be necessary with this finding.

Several architectural patterns of PIN have been described, including flat, tufted, micropapillary and cribriform, and attempts made to correlate different patterns with predictive value [23]. In the present study, as in others, tufted HGPIN was the most common pattern, although in most cases several patterns coexisted [23]. Our data showed, in agreement with others, no significant association of HGPIN architectural pattern with the presence of cancer on repeat biopsy [29].

Patients with HGPIN and AG are at greater risk of being found to have cancer than those with benign findings on prostate biopsies. Although additional data and analyses are needed to better understand the risk associated with HGPIN and AG, in the present study the presence of multifocal HGPIN was the only significant predictor of prostatic adenocarcinoma in repeat biopsy, and warrants a close follow-up of these patients.

CONFLICT OF INTEREST

None declared.

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Abbreviations: HGPIN, high-grade intraprostatic neoplasia; AG, atypical glands suspicious for prostate cancer; BPT, benign prostatic tissue.