Criteria for Biopsy Diagnosis of Minimal Volume Prostatic Adenocarcinoma

Analytic Comparison With Nondiagnostic but Suspicious Atypical Small Acinar Proliferation

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Prostate cancer screening with prostate-specific antigen (PSA), digital rectal examination, and multiple needle biopsies1 has identified specimens with decreasing volumes of adenocarcinoma. Random systematic biopsy specimens not directed at a mass are obtained with narrow 18-gauge needles, challenging the pathologist to diagnose cancer with limited amounts of tumor, often with little or no clinical evidence of malignancy.2 Biopsy specimens occasionally contain proliferative foci of small atypical acini that display some but not all features diagnostic of adenocarcinoma, referred to as atypical small acinar proliferation (ASAP) suspicious for but not diagnostic of malignancy.3

Context.—Minimal volume prostatic adenocarcinoma (defined as involving less than 5% of biopsy tissue) is diagnosed increasingly today because of successful cancer screening. We previously described the diagnostic category called atypical small acinar proliferation (ASAP), suspicious for but not diagnostic of malignancy, present in about 2.5% of routine prostatic needle biopsy specimens.

Objective.—To establish the criteria enabling a distinction between ASAP and cancer.

Design.—We prospectively evaluated clinical and histologic findings from all 319 patients consecutively diagnosed as having ASAP or minimal cancer by prostatic needle biopsy in a consultation service. Seventeen histopathologic features were assessed.

Results.—Fifty-six patients (18%) had ASAP, and 100 (31%) had minimal cancer; the remaining 163 (51%) had benign diagnoses, high-grade prostatic intraepithelial neoplasia, or larger amounts of cancer. The mean age of patients with ASAP did not differ from that of patients with minimal cancer (64.2 years vs 63.3 years; P = .65). In 10 of 17 histopathologic findings, ASAP differed significantly from minimal cancer. Among architectural findings, ASAP foci averaged 0.4 vs 0.8 mm (P < .0001) and comprised a mean of 11 vs 17 acini (P < .0001). Infiltrative growth occurred in 75% of ASAP foci and 100% of minimal cancers (P < .0001). Among cytologic findings, ASAP was significantly less likely than cancer to have mitotic figures (0% vs 10%, respectively; P < .01) or prominent nucleoli in at least 10% of cells (55% vs 100%, respectively; P < .0001) and showed more frequent nuclear hyperchromasia (44% vs 9%, respectively; P < .0001) and less nuclear enlargement (P = .0002). Luminal blue mucin secretions were less common in ASAP than cancer (6% vs 33%, respectively; P < .0001), but eosinophilic granular secretions and crystalloids were about equally frequent. Concomitant high-grade prostatic intraepithelial neoplasia was present in 23% of ASAP cases and 57% of cancers (P < .0001). Moderate-to-severe atrophy confounded 59% of cases with ASAP and 35% of cancers (P = .003); both ASAP foci and cancer were associated with inflammation in about a quarter of cases. In each case with ASAP, we stratified our level of suspicion among 3 categories (favor benign, uncertain, and favor carcinoma). As suspicion increased so did the mean nuclear enlargement and percentage of cases with infiltrative growth and nuclear hyperchromasia (all P < .05).

Conclusions.—These criteria, which differ significantly between ASAP and minimal volume cancer, can help to separate patients for whom a second biopsy is recommended from candidates for prostatectomy or other therapy.

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were the small size of the focus (70% of cases), disappearance on step levels (61%), lack of significant cytologic atypia such as nucleolomegaly (55%), and associated inflammation that suggests possible reactive atypia (9%). However, to assess the relative importance of each histologic feature, a prospective comparative analysis of ASAP and cancer is needed. We and others who have studied ASAP have yet to isolate the most salient histologic findings that support its distinction from cancer. In this report, we draw on a series of consecutive biopsies diagnosed in a busy consultation service to accomplish the latter goal.

MATERIALS AND METHODS

The study group was chosen prospectively from consecutive prostatic needle biopsy specimens of 319 patients shared with one of us (D.G.B.) in consultation at the Mayo Clinic from January 30 to April 2, 1998. During this period, we identified 100 patients (31%) with minimal volume adenocarcinoma (<5% of the specimen in aggregate area) and 56 (18%) with ASAP. Patients were included in the study only if they had no prior diagnosis of prostate cancer. Age was recorded for all patients; PSA level was not available since it was not provided in most cases. Biopsy specimens originated from numerous colleague pathologists in the United States, Europe, South America, and Asia. Hence, there was considerable variation in the number of sites that underwent biopsy (single, bilateral, sextant, other), the volume and length of specimens, and the number of cores per biopsy specimen. In addition, clinical estimates of prostate volume were unavailable. Consequently, we could not control for volume, length, or number of cores of biopsy material, sampling sites, prostatic volume, or serum PSA. Rare specimens fixed in Bouin solution rather than formalin were excluded.

Histologic features listed in Table 1 were assessed prospectively by 2 pathologists (D.G.B., K.A.I.) immediately after diagnosis. Biopsy specimens were excluded if there was cancer in a core from a different biopsy site in the specimen. In 13 patients, ASAP or cancer was present in 2 separate biopsy sites; we counted these separately. Basal cell immunohistochemistry was performed in a few ASAP cases but did not alter the diagnosis. We stratified suspicion in each ASAP case among 3 levels, namely ASAPB (atypical small acinar proliferation suspicious for but not diagnostic of malignancy), ASAP (atypical small acinar proliferation suspicious for but not diagnostic of malignancy), and ASAPH (atypical small acinar proliferation highly suspicious for but not diagnostic of malignancy). We used ASAP for cases in which we deemed the focus of concern unlikely to be cancer but could not with absolute certainty exclude the possibility. Conversely, we used ASAPH for cases in which the focus was almost certainly carcinoma, but we were unable or unwilling to render a definite diagnosis of cancer in these small foci owing to the lack of the full complement of architectural and cytologic criteria for malignancy. We used ASAP for cases with intermediate suspicion. Occasional cases with discrepancies between the observers were resolved by consensus.

The maximum linear extent of small acini in each focus was quantitated using a micrometer. When more than one small acinar focus was present, we recorded the sum of the number of acini of concern and linear extents. Nuclear hyperchromasia was considered present if nuclear details were obscured at maximum illumination. The degree of nuclear enlargement was subjectively considered based on the ratio of nuclear diameter of the cells of concern to nonneoplastic cells: mild (1+) if less than 1.5X, moderate (2+) if 1.5 to 2.0X, and severe (3+) if greater than 2.0X. We noted whether prominent nucleoli were present in at least 10% of nuclei, a figure often used to distinguish well-differentiated adenocarcinoma from benign acini and some forms of prostate intraepithelial neoplasia (PIN). The degree of atrophy (including the specialized form, postatrophic hyperplasia) was considered mild.

| Table 1. Comparative Histologic Findings in Prostate Needle Biopsies with ASAP or Minimal Cancer† |
|------------------|------------------|------------------|------------------|
| Finding          | ASAP§             | Minimal          | Cancer§          |
|                  | Mean (mean ± SD)  | Cancer References | Mean (mean ± SD)  | Cancer References |
| Architectural    |                  |                  |                  |
| Number of foci (mean ± SD) | 1.2 ± 0.4         | 1.3 ± 0.5         |                  |
| Linear extent (mm, mean ± SD)** | 0.4 ± 0.3         | 0.8 ± 0.5         |                  |
| Number of acini (mean ± SD)** | 11 ± 10           | 17 ± 14           |                  |
| Infiltrative growth (%)* | 75                | 100              | 68              |
| Perineural invasion (%) | 6                 | 0                | 82–100          |
| Cytologic        |                  |                  |                  |
| Microvacuolated cytoplasm (%) | 33                | 44              |                  |
| Nuclear hyperchromasia (%)* | 44                | 9                |                  |
| Nuclear enlargement (scale of 0–3, mean ± SD)* | 1.2 ± 0.8         | 1.8 ± 0.7        |                  |
| Prominent nucleoli in at least 10% of cells (%)* | 55                | 100             | 64–76           |
| Mitotic figure(s) (%)* | 0                 | 10              |                  |
| Luminal          |                  |                  |                  |
| Eosinophilic granular secretions (%) | 66                | 73              | 53–72           |
| Blue mucin (%)* | 6                  | 33              | 42              |
| Crystalloids (%) | 16                 | 19              | 6–22            |
| Stroma and adjacent acini |                  |                  |                  |
| High-grade PIN in same slide (%)* | 23                | 57              | 14–31           |
| Moderate–severe atrophy (%)* | 59                | 35              | 40–53           |
| Associated inflammation (%) | 30                | 20              |                  |
| Collagenous micronodules (%) | 2                 | 5                |                  |

† ASAP indicates atypical small acinar proliferation (suspicious for malignancy); Minimal cancer, adenocarcinoma involving less than 5% of total tissue; and PIN, prostatic intraepithelial neoplasia.

§ Sixty-four biopsies, including 7 cases in which the same patient had 2 biopsies.

§ One hundred five biopsies, including 5 cases in which the same patient had 2 biopsies.

* P < 0.05, Fisher’s exact test.

** P < 0.05, Mann-Whitney test.
For continuous variables and by (ASAP-B, ASAPS, ASAPH) were evaluated by Kruskal-Wallis test between means in ASAP cases according to the 3 levels of suspicion (sinophilic granular secretions, or crystalloids). Differences between group means (biopsy specimens with the diagnosis of ASAP) were evaluated by the Mann-Whitney U test for continuous variables (patient age, number of foci, number of acini, linear extent, and degree of nuclear enlargement) and chi-square test for nominal variables (infiltrative growth, perineural invasion, microvacuolated cytoplasm, nuclear hyperchromasia, prominent nucleoli, mitotic figures, atrophy, high-grade PIN, associated inflammation, and luminal findings of blue mucin, eosinophilic granular secretions, or crystalloids). Differences between means in ASAP cases according to the 3 levels of suspicion (ASAP-B, ASAPS, ASAPH) were evaluated by Kruskal-Wallis test for continuous variables and by chi-square test for nominal variables. Significance level for all tests was .05.

Differences between group means (biopsy specimens with ASAP and minimal cancer) were evaluated by the Mann-Whitney U test for continuous variables (patient age, number of foci, number of acini, linear extent, and degree of nuclear enlargement) and chi-square test for nominal variables (infiltrative growth, perineural invasion, microvacuolated cytoplasm, nuclear hyperchromasia, prominent nucleoli, mitotic figures, atrophy, high-grade PIN, associated inflammation, and luminal findings of blue mucin, eosinophilic granular secretions, or crystalloids). Differences between means in ASAP cases according to the 3 levels of suspicion (ASAP-B, ASAPS, ASAPH) were evaluated by Kruskal-Wallis test for continuous variables and by chi-square test for nominal variables. Significance level for all tests was .05.

**RESULTS**

**Patient Age and Frequency of ASAP and Minimal Cancer**

During the study period, 319 prostate needle biopsy specimens were reviewed, and 56 patients (18%) were diagnosed as having ASAP, including 7 with ASAP in 2 biopsy specimens from different sites. One hundred patients (31%) were diagnosed as having minimal foci of adenocarcinoma by 105 needle biopsies; in 5 patients, 2 biopsy specimens from different sites were diagnostic. Patients with the diagnosis of ASAP ranged in age from 46 to 86 years (mean, 64.2 years; median, 63.5 years), similar to those with minimal cancer (range, 47–80 years; mean, 63.3 years; median, 63.0 years; P = .65). Patients diagnosed as having ASAP did not differ in age according to level of suspicion for cancer (P > .05). The presence of atrophy, associated inflammation (acute or chronic), and high-grade PIN was unrelated to age (P > .05).

**Histologic Findings**

The diagnosis of ASAP was made in 64 biopsy specimens, including ASAP-B in 17 (27%), ASAP-S in 16 (25%), and ASAP-H in 31 (48%). Among 7 patients who had a pair of suspicious biopsy specimens, we assigned disparate levels of suspicion to 5 pairs. Among 100 patients with adenocarcinoma, Gleason scores were 3 in 1 patient, 5 in 3 patients, 6 in 89 patients, 7 in 4 patients, and 8 in 3 patients. Infiltration into skeletal muscle was noted in one case.

In 10 of the 17 criteria examined, ASAP differed significantly from minimal cancer; our findings are compared with those of prior investigators (Table 1). Foci of minimal cancer were twice as large as ASAP (mean, 0.8 vs 0.4 mm) and contained almost twice as many acini (mean, 17 vs 9) (both P < .0001), although there was overlap in both. Minimal cancer contained luminal blue mucin secretions in 91% of cases (Figure 6), more than double that of ASAP (45%) (both P < .0001) (Figure 4). Both findings were present in all minimal cancers but also in more than half of ASAP cases. Nuclei were more enlarged (mildly; mean, 1.2+) in cancer than ASAP (moderate; mean, 1.8+) (P = .0002) but were less often hyperchromatic (P < .0001). Mitotic figures were present in 10% of minimal cancers but in no ASAP cases (P = .01). The acini of minimal cancer contained luminal blue mucin secretions in one third of cases, more than 5 times more frequent in cancer than in ASAP (P < .0001). Eosinophilic proteinaceous secretions were similar in frequency in ASAP (Figures 3, 5, and 7) and cancer. High-grade PIN was present in 57% of minimal cancers (Figure 6), more than double its frequency in ASAP (P < .0001) (Figure 8). Finally, moderate-to-severe atrophy in benign acini confined 59% of ASAP diagnoses (Figure 7); minimal cancer was less commonly accompanied by atrophic acini (P = .003). Notably, 20% of minimal cancers were associated with luminal or stromal inflammation (Figure 6). Infiltration was similar in frequency in ASAP and minimal cancer (P = .2), despite the morphologic overlap between reactive and neoplastic atypia that often prompts an ASAP diagnosis (Figure 7).

In stratifying ASAP into 3 levels of suspicion (ASAP-B, ASAP-S, ASAP-H), 3 criteria emerged as significant (Table 2). Infiltrative growth was present in just more than half of ASAP-B cases but almost all ASAP-H cases (P = .03). There was a greater degree of nuclear enlargement in ASAP-S and ASAP-H than in ASAP-B (P = .049), but this worrisome finding was confounded more frequently in ASAP-B cases. Nuclei were more enlarged (mildly; mean, 1.2+) in cancer than ASAP (moderate; mean, 1.8+) (P = .0002) but were less often hyperchromatic (P < .0001). Mitotic figures were present in 10% of minimal cancers but in no ASAP cases (P = .01). The acini of minimal cancer contained luminal blue mucin secretions in one third of cases, more than 5 times more frequent in cancer than in ASAP (P < .0001). Eosinophilic proteinaceous secretions were similar in frequency in ASAP (Figures 3, 5, and 7) and cancer. High-grade PIN was present in 57% of minimal cancers (Figure 6), more than double its frequency in ASAP (P < .0001) (Figure 8). Finally, moderate-to-severe atrophy in benign acini confined 59% of ASAP diagnoses (Figure 7); minimal cancer was less commonly accompanied by atrophic acini (P = .003). Notably, 20% of minimal cancers were associated with luminal or stromal inflammation (Figure 6). Infiltration was similar in frequency in ASAP and minimal cancer (P = .2), despite the morphologic overlap between reactive and neoplastic atypia that often prompts an ASAP diagnosis (Figure 7).

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### Table 2. Selected Histologic Findings in Prostate Needle Biopsies Diagnosed with ASAP, by Level of Suspicion†

<table>
<thead>
<tr>
<th>Finding</th>
<th>ASAP-B (n = 17)</th>
<th>ASAP-S (n = 16)</th>
<th>ASAP-H (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architectural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of foci (mean ± SD)</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Linear extent (mm, mean ± SD)</td>
<td>0.34 ± 0.3</td>
<td>0.55 ± 0.4</td>
<td>0.42 ± 0.3</td>
</tr>
<tr>
<td>Number of acini (mean ± SD)</td>
<td>11 ± 15</td>
<td>13 ± 9</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>Infiltrative growth (%)</td>
<td>53</td>
<td>75</td>
<td>87</td>
</tr>
<tr>
<td>Cytologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear hyperchromasia (%)*</td>
<td>12</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Nuclear enlargement (scale of 0–3, mean ± SD)**</td>
<td>0.8 ± 0.7</td>
<td>1.3 ± 0.8</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Prominent nucleoli in at least 10% of cells (%)</td>
<td>35</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>Adjacent acini</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade PIN in same slide (%)</td>
<td>12</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Moderate–severe atrophy (%)</td>
<td>71</td>
<td>75</td>
<td>45</td>
</tr>
</tbody>
</table>

† ASAP indicates atypical small acinar proliferation; ASAP-B, atypical small acinar proliferation suspicious for but not diagnostic of malignancy, favor benign; ASAP-S, atypical small acinar proliferation suspicious for but not diagnostic of malignancy; ASAP-H, atypical small acinar proliferation highly suspicious for but not diagnostic of malignancy; and PIN, prostatic intraepithelial neoplasia.

* P < .05, χ² test.

** P < .05, Kruskal-Wallis test.
nuclear hyperchromasia ($P = .01$). Hyperchromasia, involving nuclei in more than half of cases in the 2 most suspicious categories, often obscured nuclear detail and nucleoli (Figure 9); nevertheless, we noted a nonsignificant trend toward prominent nucleoli in a higher percentage of the cases as suspicion increased ($P = .09$). Two other nonsignificant trends were noted with increasing suspicion for malignancy: more frequent accompanying high-grade PIN ($P = .09$) (Figure 8) and less frequent moderate-to-severe atrophy ($P = .08$).

**COMMENT**

We found 10 diagnostic criteria that differed significantly between ASAP and minimal cancer. First, ASAP, averaging 11 acini, was half the mean length and had about half as many acini as minimal cancer (17 acini). We previously had cited the small size of a focus of concern as the most common source of difficulty in ASAP, involving 70% of cases.$^3$ The number of foci did not differ significantly between ASAP and cancer; both tended to be unifocal in this series and in other biopsy series.$^3,5$
Infiltrative growth was present in all cases of cancer but only 75% of ASAP cases. All minimal cancers had at least mild (1+) nuclear enlargement, nearly an absolute requirement for a cancer diagnosis. Average enlargement was moderate (1.8+) in contrast to mild enlargement (1.2+) in ASAP. Further, all our minimal cancers contained prominent nucleoli. These 2 cytologic findings agree with some studies but differ from previous reports examining only adenocarcinoma, in which some cancers lacked prominent nucleoli or nuclear enlargement. These 2 studies examined cancer with a larger mean number of acini than in our series, rendering our diagnoses more difficult without mild nuclear enlargement or prominent nucleoli in 10% of cells. In studies in which the focus of concern was larger, however, and architectural and cytologic features were compelling, cancer may have been diagnosed confidently despite obliteration of prominent nucleoli by nuclear hyperchromasia. Hyperchromasia was more common in ASAP than in minimal cancer. Nuclear hyperchromasia is a staining artifact encountered by many laboratories. Paradoxically, a cancer diagnosis can be both supported and hindered by the cells' tendency to have...
hyperchromatic nuclei. In ASAP, small size of the focus compounds the diagnostic dilemma. Avoidance of long exposure when staining with hematoxylin helps lessen this artifact.

The 10% frequency of mitotic figures in cancer contrasts with that of ASAP acini and concurs with a previous report. However, mitotic figures are too rare to be a reliable diagnostic finding in small foci.

Among several luminal findings, only blue-tinged mucin was a significant discriminator between ASAP and minimal cancer (6% vs 33% of cases, respectively). Blue acidic mucin had been reported previously in up to 60% of cases of cancer and ASAP and 63% of cases of atypical adenomatous hyperplasia. However, blue mucin was not present in benign acini or the acini of postatrophic hyperplasia in 51 biopsy specimens or in prostatectomy cases. Fortunately, atypical adenomatous hyperplasia is mostly found in the transition zone, which is rarely sampled by biopsy, unlike postatrophic hyperplasia, which predominates in the peripheral zone.

Two other luminal findings had low discriminant value. Seen more frequently than blue mucin, eosinophilic pro-
teinaceous secretions were present in 73% of minimal cancers. They were nonspecific, however, occurring in 66% of ASAP cases. Crystalloids were a less common finding, occurring in 19% of cancers and 16% of cases of ASAP. Prior studies from our laboratory described similar crystalloid frequencies in atypical adenomatous hyperplasia and cancer in biopsy specimens. Crystalloids were reported in 5% of benign biopsy specimens. These data confirm that crystalloids do not pose an increased risk for cancer in subsequent biopsy specimens.

A novel finding was that high-grade PIN accompanied 57% of minimal cancers but only 23% of ASAP cases. Studies examining cancer or ASAP in isolation obtained similar data. It is understandable that PIN would often accompany cancer, since it is strongly associated spatially with cancer. The less frequent coexistence of high-grade PIN with ASAP is in line with the observation that about half of ASAP cases are benign on subsequent biopsy specimens. Also, for the half of ASAP cases that probably are marginally sampled cancer, the smaller mean size of ASAP foci decreases the likelihood of sampling accompanying high-grade PIN. Finally, the presence of PIN may increase definite diagnosis of minimal cancer in adjacent acini by sharing cytologic features with these acini that stand in contrast to those of acini elsewhere in the specimen.

Moderate-to-severe atrophy more often accompanied ASAP than cancer. Small foci of postatrophic hyperplasia (which is invariably associated with typical atrophy and has “moderately enlarged” nuclei in 39% of cases) and typical atrophy probably accounted for some ASAP diagnoses. Associated or obscuring inflammation played a role in ASAP diagnoses in 30% of cases. However, 20% of minimal cancers had associated acute or chronic inflammation. This similarity of frequency indicates that cancer can often be confidently diagnosed amid inflammation. Basal cell cytokeratin immunohistochemistry has a limited role in diagnosing small foci, since (1) the focus of concern may be lost on deeper levels and (2) lack of staining is nonspecific. Finally, collagenous micronodules, first described in cancer with associated mucin extravasation in the stroma, were too rare a finding in ASAP or cancer to be helpful.

Assigning a level of suspicion in ASAP, although useful as a teaching tool, amounts to splitting hairs from a practical standpoint. Our current observations lend some histologic support for stratification, since the frequencies of infiltrative growth, nuclear hyperchromasia, and nuclear enlargement differ among the 3 strata of suspicion level. However, the stratification scheme is too subjective to be reproducible among expert diagnosticians in contrast to the separation between ASAP and cancer, which is reproducible. Moreover, 3-category stratification of suspicion...
Figure 8. Atypical small acinar proliferation, highly suspicious for cancer. At right, the larger, preexisting acini of high-grade prostatic intraepithelial neoplasia (PIN) are lined by cells with stratified, overlapping, and hyperchromatic nuclei. A few small acini arise in conjunction with this focus (left) but may represent tangentially sectioned outpouchings of the PIN (hematoxylin-eosin, original magnification ×400).

Figure 9. Atypical small acinar proliferation, highly suspicious for cancer. Acini are infiltrative and have eosinophilic granular luminal secretions. Nuclei seem mildly enlarged, but their detail and nucleoli are obscured by hyperchromatic staining. Recuts were not helpful (hematoxylin-eosin, original magnification ×200).
cannot predict cancer on subsequent biopsy specimens: 2 studies of 335 and 489 patients with ASAP revealed only a nonsignificant trend for increasing risk of subsequent cancer with increasing suspicion. Stratification also did not predict the percentage of involvement by cancer on subsequent biopsy specimens positive for cancer. Thus, suspicion level should not alter follow-up recommendations.

Advanced age is a clinical risk factor for prostate cancer. Interestingly, older men were more likely to undergo multiple subsequent biopsies than were younger men. Patients who were previously diagnosed as having ASAP, their cancer risk was no longer age related.1,2 Our present results indicate that patients with ASAP and cancer do not represent separate populations with respect to age.

In addition, ASAP signifies a set of acinar findings in a prostatic needle biopsy specimen that fall below the threshold for cancer. Unlike PIN, ASAP is not a unique entity, but it is a useful diagnostic category, which acknowledges that all features of cancer morphologically overlap with benign entities: crystalloids are found in atypical adenomatous hyperplasia,2-24 nuclei and nucleoli are enlarged in reactive acini, and basal cells are difficult to find in atrophy. The diagnosis of ASAP by biopsy carries a positive predictive value for prostate cancer at least as high as the 22% to 53% reported for high-grade PIN.2,5,6,30-33 The predictive value of ASAP for cancer on a second biopsy in our laboratory was 45% of 33 cases,2 60% of 25 cases,3 and 42% of 295 cases4 and was 34% to 60% in other studies.5,6,10,11,23,25 Slides with ASAP foci also may warrant more than the recommended 3 levels per core5,25 deeper sections revealed carcinoma in 10% of cases of ASAP but in no cases with benign prostatic tissue or high-grade PIN. If step sections still have ASAP, a second biopsy is encouraged. False-negative findings occur in 19% to 22% of initial biopsies in patients with abnormal rectal examination results and PSA,35 and may occur in the second biopsy. Based on second biopsies of patients with a prior cancer diagnosis, 23% of the results of second sextant prostate biopsies were false-negative;9 9% of cancers diagnosed after an initial diagnosis of ASAP were detected by biopsies subsequent to a false-negative result in a second biopsy.12

Just as no single histologic finding of ASAP, such as crystalloids, luminal mucin, or abnormal cytologic features, predicts cancer on subsequent biopsy specimens,3,12 no findings are always absent in ASAP or present in cancer. The best distinction one can make, as accomplished by this study, is to establish each finding that differs significantly in frequency between these 2 groups. Prior studies analyzed the histologic findings of adenocarcinoma in isolation.15,16 They attempted to define the minimal criteria for cancer without including an ASAP control group, hindering the usefulness of the data. One study also included all cancers with no maximum size criterion; the mean number of acini in cancer was 31,15 almost twice as many as in the cancer group in our study. Thus, it probably included more cases far above the minimal threshold for cancer. For these reasons, our qualitative criteria for cancer are not comparable with those of that report. Likewise, prior analyses of ASAP by us4,5,12 and others6,8,25 have not compared it directly to minimal cancer, leaving residual subjectivity in the diagnosis of ASAP. The current study reduces but does not eliminate subjectivity and makes ASAP more tangible by isolating the criteria that experts use in its diagnosis.

Another strength of our study is its reliance on consecutive cases of ASAP and cancer diagnosed by the same observers. Our study has some inherent limitations. The rates of diagnosis of ASAP (18%) and minimal cancer (31%) were high, owing to derivation of biopsy material from a consultation practice. Specimens originated from different laboratories, so we could not control for variations in processing, number of tissue sections per slide, or number of slides. The PSA was not available for analysis with the histologic findings. Also, it was not our intent to correlate histopathologic features of patients with ASAP with subsequent biopsy results or outcome; this has been reported previously.5,8

In summary, our study reveals 10 histologic findings that, in combination, helped to diagnose minimal cancer rather than ASAP. Findings included larger size of the focus of concern, greater number of acini, infiltrative growth, mitotic figures, prominent nucleoli in at least 10% of cells, nuclear enlargement and hyperchromasia, blue mucin secretions, concomitant high-grade PIN, and absence of moderate-to-severe atrophy.

References


Criteria for Prostate Cancer Diagnosis—Iczkowski & Bostwick


