Review – Prostate Cancer

Atypical Foci Suspicious but not Diagnostic of Malignancy in Prostate Needle Biopsies
(Also Referred to as “Atypical Small Acinar Proliferation Suspicious for but not Diagnostic of Malignancy”)

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Abstract

Objective: To review atypical focus suspicious but not diagnostic of malignancy in needle biopsies of the prostate, also referred to as “atypical small acinar proliferation suspicious for but not diagnostic of malignancy.”

Methods: A number of descriptive and somewhat confusing terms have been used to refer to a prostate tissue biopsy with small focus of atypical glands. Based on MEDLINE database searches, all aspects, including the synonymous terms, of atypical focus suspicious but not diagnostic of malignancy were examined.

Results: An average of 5% of needle biopsy pathology reports show a diagnosis of atypical focus suspicious for malignancy. It may be composed of acini of small size, that is, smaller than normal ducts and acini, but may also include glands with a diameter similar to that of normal ducts and acini. It encompasses a variety of lesions, including benign mimickers of cancer and small foci of carcinoma that, for a variety of reasons, cannot be accurately diagnosed. Maximal diagnostic information should be gained on section stained with haematoxylin and eosin, with immunohistochemical stains used for confirmation. Its presence in a biopsy set is a strong predictor for concurrent or subsequent adenocarcinoma. The values range from 17% to 60%, the mean being 40.7%. The precise labelling of the initial biopsies is mandatory so that rebiopsy of patients with atypical foci can be directed in a more concentrated fashion into the region of the initial biopsy.

Conclusion: The presence of atypical focus suspicious but not diagnostic of malignancy in needle biopsies is an important predictor of cancer compared with biopsies from patients who lack this finding.

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1. **Introduction**

Atypical focus suspicious but not diagnostic of malignancy, also referred to as “atypical small acinar proliferation suspicious for but not diagnostic of malignancy” [1,2], is descriptive diagnostic terminology used in the pathology report of a needle biopsy containing a small group of glands suspicious for adenocarcinoma, but with insufficient cytologic or architectural atypia to establish a definitive diagnosis [1–6]. It is a broad diagnostic “umbrella” that encompasses benign lesions mimicking malignant glandular proliferations and under-sampled, small foci of carcinoma that harbour some but not all of the features needed for a definitive diagnosis of malignancy [6]. It is not a diagnostic entity and is not synonymous with high-grade prostatic intraepithelial neoplasia (HGPIN; Fig. 1A–C).

This review describes the diagnostic implications of atypical focus suspicious for but not diagnostic of malignancy, its immunophenotype, and clinical significance in contemporary needle biopsies.

<table>
<thead>
<tr>
<th>Table 1 – Diagnostic terms</th>
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<tr>
<td>Atypical focus suspicious but not diagnostic of malignancy</td>
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<tr>
<td>Atypical small acinar proliferation suspicious for malignancy (ASAP)</td>
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<tr>
<td>Atypical glands suspicious for carcinoma (ATYP)</td>
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<tr>
<td>Atypical prostatic glandular proliferation</td>
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<tr>
<td>Atypical glands suspicious for cancer</td>
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<tr>
<td>Atypical focus suspicious for carcinoma</td>
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<tr>
<td>Focus suspicious for malignancy</td>
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<tr>
<td>Focal glandular atypia (FGA)</td>
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<tr>
<td>Small atypical glands</td>
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<tr>
<td>Atypical hyperplasia</td>
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<tr>
<td>Atypia or atypical</td>
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<tr>
<td>Borderline lesion</td>
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<tr>
<td>Atypical focus</td>
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<tr>
<td>Uncertain</td>
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</table>

2. **Terminology**

A number of descriptive and somewhat confusing terms have been used to refer to a prostate tissue biopsy with small focus of atypical glands (Table 1). There are personal preferences and recommendations [5–7].

The term “atypical small acinar proliferation suspicious for but not diagnostic of malignancy”

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Fig. 1 – Prostate histology. (A) Normal prostate. (B) Prostatic adenocarcinoma. (C) HGPIN. (D) Atypical focus, favour benign. (E) Atypical focus, highly suspicious for malignancy (arrow). (F) HGPIN with adjacent atypical focus. (G) p63 immunostaining of the basal cells in atrophy. (H) Atypical glands lack p63 immunostaining, whereas a normal gland is positive (internal control). (The same case as in panel E). (I) AMACR immunostaining in atypical glands (negative glands serve as an internal control for normal). HGPIN = high-grade prostatic intraepithelial neoplasia; AMACR = α-methyl acyl-CoA racemase.
[1,2] has been used for many years in several laboratories throughout the world, including ours. It is the term preferred by some of the authors of this paper. The acronym ASAP (atypical small acinar proliferation) has been commonly used to refer to atypical small acinar proliferation suspicious for but not diagnostic of malignancy [1,2]. However, ASAP has been the subject of criticism and comments [8–10]. In two recent consultation meetings [5,6], participants argued against the use of ASAP. The reasons included its equation by some urologists with HGPIN and because all of the atypical foci are not always “small” acinar but may include glands with larger diameter.

Notwithstanding personal preferences or recommendations and the term used, it must be clear what the pathologist is referring to and it must convey the correct message to the urologist. Under these conditions, ASAP suspicious for but not diagnostic of malignancy/ASAP has been considered to be a valid diagnosis in those needle biopsies where only a limited sampling of the atypical epithelium has occurred [11].

3. Incidence and clinical features

An average of 5% of needle biopsy pathology reports show a diagnosis of atypical focus suspicious but not diagnostic of malignancy (range: 0.7–23.4%) [1,12–29]. No clinical features are contributory to or predictive of an atypical focus suspicious for malignancy [1–3,12,13,30–32]. The mean patient age is in the sixties, with a range of 40 to 95. The gland is typically biopsied to rule out prostate cancer, with the clinical indication being an elevated prostate-specific antigen (PSA) level or an abnormal digital rectal examination (DRE). The median PSA elevation usually is modest, ranging from 6 to 8 ng/ml, but very high PSA levels (>50 ng/ml) have been seen. Only a few transrectal ultrasound results have been reported [12].

4. Diagnostic implications

The terminology encompasses a variety of lesions including benign mimickers of cancer and small foci of adenocarcinoma which, for a variety of reasons, cannot be accurately diagnosed [33] (Tables 2–4). The specimen may be composed of acini of small size, that is, smaller than normal ducts and acini, but it may also include glands with a diameter similar to that of normal ducts and acini [6].

Benign lesions mimicking malignant glandular proliferations considered to be problematic have changed over the years. In the past, seminal vesicle tissue was considered one of the common mimickers of adenocarcinoma of the prostate [34]. Adenosis and complete atrophy were common problems in previous years (Fig. 1D) [35]. Currently, partial atrophy is one of the most common benign mimickers of cancer [36]. In part, the atypical diagnosis resulting from evaluation of partial atrophy relates to negative staining for high-molecular-weight cytokeratin, p63, and positive staining for racemase (see below).

As far as factors preventing a diagnosis of carcinoma are concerned, if carcinoma is marginally or imperfectly sampled, the microscopic focus may be very small and contain only a small number of acini (Fig. 1E). In some cases, the atypical focus is present only at the edge of the core or at its tip, where infiltration between benign acini cannot be appreciated. In these cases, if the glands do not show prominent cytologic and architectural atypia, a definite diagnosis of cancer may not be possible. Mechanical distortion from the needle biopsy can result in crush artifact of a few atypical glands and obscure cytologic detail. Problems with fixation and processing, especially with sections that are too thick or heavily stained, can also prevent definite diagnosis because of poor histologic detail. Prominent atrophy in or near a small focus of cancer confounds the diagnostic difficulty. A further confounding factor that hampers accurate interpretation is that not all
cancers display all the classical features of malignancy. The absence of convincing cytologic features of malignancy and a clustered growth pattern can prevent a definite diagnosis in these cases. Prominent inflammatory changes are common and can obscure cytologic features of a small focus of carcinoma and cause difficulty in differentiating them from reactive changes and distortion occurring in benign glands as a result of the inflammation [33].

The combination of HGPIN and atypical focus suspicious for malignancy is found in 16–31% of cases [1,3,37]. There are two distinct conditions where the two may occur [4]. The first condition has discrete discontinuous foci of HGPIN and atypical focus suspicious but not diagnostic of malignancy. In the second condition, a diagnosis of atypical foci results when HGPIN is definitely HGPIN but small outpouchings or tangential sections of HGPIN may involve small acini, which creates difficulty distinguishing it from cancer [39].

Table 4 – Factors resulting in the diagnosis of atypical focus suspicious for malignancy

<table>
<thead>
<tr>
<th>Small size of focus</th>
<th>Conflicting immunohistochemical findings</th>
<th>Confounding findings</th>
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<tbody>
<tr>
<td>• Small number of acini in the focus of concern (invariably &lt;24 acini)</td>
<td>• Focally positive high-molecular-weight cytokeratin</td>
<td>• Histologic artifacts such as thick sections or overstained nuclei</td>
</tr>
<tr>
<td>• Small focus size, average 0.4 mm in diameter</td>
<td>• Focally positive p63 staining</td>
<td>• Tangential cutting of adjacent high-grade prostatic intraepithelial neoplasia</td>
</tr>
<tr>
<td>• Focus at core tip or biopsy edge, indicating that the focus is incompletely sampled</td>
<td>• Negative racemase immunostain</td>
<td>• Architectural or cytologic changes (nucleomegaly and nucleolomegaly) owing to inflammation or other lesions</td>
</tr>
<tr>
<td>• Loss of focus of concern in deeper levels</td>
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</table>

5. Immunohistochemical findings

5.1. Basal cell immunostains

Absence of the basal cell layer is the single most important and consistent defining diagnostic feature of cancer. Unfortunately, basal cells are often inapparent on routine haematoxylin and eosin stains, so basal cell-specific immunostains are useful adjunctive studies to distinguish cancer from benign small acinar mimics that retain their basal cell layer.

Immunostains such as p63 [40] (nuclear stain) and high-molecular-weight cytokeratin that is detected by antibody 34bE12 [41] (cytoplasmic stain) can aid in the investigation of atypical glandular proliferations by staining basal cells. Cancer lacks a basal cell layer, so the presence of basal cells in an atypical focus effectively excludes cancer from consideration (Fig. 1G and H). Conversely, the absence of a basal cell layer in a small focus that is highly suspicious for cancer supports the diagnosis of cancer. However, negative staining for basal cell markers is by itself not diagnostic of cancer because false-negative staining can arise from technical problems, including tissue changes induced by the surgical procedure (e.g., cautery artifact with transurethral resection of the prostate), imperfect specimen fixation, and variations in processing and antigen retrieval [42]. Negative staining should be interpreted only when there is confirmatory positive staining in adjacent benign glands. Staining variability with negative staining of benign glands, including atrophy and inflammation-associated changes, has also been reported [43]. Some benign lesions may have negative or discontinuous staining with basal cell markers [43–46]. In particular, fully developed atrophy typically stains fairly uniformly and intensely with basal cell markers, whereas partial atrophy often has negative or discontinuous staining with these markers [36]. The combination of two basal cell stains (34bE12 + p63) increases the sensitivity of basal cell detection, compared with using either marker alone [47,48]. However, even with the combination of both these basal cell markers certain benign conditions and mimickers of cancer will be negative.

5.2. α-Methyl acyl-CoA racemase

Racemase is an enzyme that is involved in β-oxidation of branched-chain fatty acids [49–57]. Using immunohistochemical staining, racemase is strongly and diffusely positive in 97–100% of prostate cancers [50,51] (Fig. 1). However, with limited cancer on needle biopsy, only 80% of cases are positive [52]. Racemase staining is considered positive only if the staining is significantly stronger than that of the benign acini in the section. Less intense and more heterogeneous staining has been found in cancer variants [53]. For example, only 68%
of foamy gland carcinomas and 70% of pseudohyperplastic carcinomas are positive. Racemase staining is positive in the majority of cases of HGPIN [54]. Racemase staining is also observed in 8–12% of benign glands [49,55], partial atrophy (79%) [36], and 10–15% of atypical adenomatous hyperplasia [56]. Zhou et al. found that racemase immunoreactivity converted atypical foci to cancer in approximately 10% of cases [57]. The addition of racemase to keratin 34βE12 may allow a cancer diagnosis to be rendered in approximately 30% [33] of cases that might previously have been called atypical focus or HGPIN associated with it. Use of a p63/racemase cocktail resolved 87% of cases, more as cancer than as benign [3,58,59].

6. Clinical significance

6.1. Predictive value for subsequent cancer

The risk of detection of carcinoma on needle core biopsy due to the presence in the initial biopsy of isolated atypical foci is reported in Table 5. The values range from 17% to 60%, the mean being 40.7% (Table 6) [1–3,13,18,20,21,24,25,29–32,59,60].

Some decrease in predictive value for cancer has been claimed in recent series [3,29]. For instance, Schlesinger et al. found that isolated atypical foci have a predictive value of 37% for cancer; this is only a slight decrease from 45% observed between 1989 and 1996 [3]. Various explanations for such an observation have been put forward, including the use of extended biopsy techniques, advances in immunostaining, and previous PSA testing; biopsies in the same patient have been reported in some papers [3,29].

Attempts have been made to create three tiers, such as “favour benign,” “uncertain” (or equivocal), and “favour carcinoma” (highly suspicious) [2,30,31]. Such a stratification is not found to be significantly related to the risk of subsequent detection of carcinoma on rebiopsy. Even when a benign diagnosis is favoured, up to 44% of patients (range: 20–44%) are diagnosed with carcinoma on rebiopsy [2,30,31,61,62]. This three-tier stratification is not very reproducible, with 63% interobserver agreement in one study [30,63].

Clinical parameters have limited predictive value for cancer on repeat biopsy [64]. Initial mean PSA concentration was higher in those with atypical foci suspicious but not diagnostic of malignancy who had cancer in subsequent biopsies than in those whose subsequent biopsies were negative. Park et al. reported that DRE and patient age were independent predictors of cancer in 45 patients with “atypia” [32]; conversely, other studies found that serum PSA and DRE findings were not predictive of cancer on subsequent biopsy [3,59,65].

The mean cancer detection rate in patients who have an atypical focus and HGPIN is 53%, that is, significantly higher than that in patients who have an isolated atypical focus [11]. A high frequency of cancer was observed by Leite et al. They found prostate cancer in 72.5% of men with HGPIN associated with an atypical focus in the initial biopsy [65]. Scattoni et al. observed adenocarcinoma in 58% of repeat biopsies in patients with both

<table>
<thead>
<tr>
<th>Reference and publication year</th>
<th>Study dates</th>
<th>No. of subjects with repeat biopsies</th>
<th>No. of cores</th>
<th>No. cases with cancer at follow-up, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renshaw et al. [16]</td>
<td>1989–1996</td>
<td>59</td>
<td>Not specified</td>
<td>34</td>
</tr>
<tr>
<td>Chan et al. [31]</td>
<td>1992–1993</td>
<td>144</td>
<td>&lt;6</td>
<td>49</td>
</tr>
<tr>
<td>Iczkowski et al. [23]</td>
<td>1990–2002</td>
<td>129</td>
<td>2–6</td>
<td>45</td>
</tr>
<tr>
<td>Postma et al. [29]</td>
<td>1993–1999</td>
<td>96</td>
<td>10</td>
<td>36.7</td>
</tr>
<tr>
<td>Pottele et al. [47]</td>
<td>1987–2004</td>
<td>47</td>
<td>10</td>
<td>17.0</td>
</tr>
<tr>
<td>Moore et al. [60]</td>
<td>1998–2003</td>
<td>53</td>
<td>&gt;8</td>
<td>36</td>
</tr>
<tr>
<td>Scattoni et al. [59]</td>
<td>1998–2004</td>
<td>84</td>
<td>10–12</td>
<td>35</td>
</tr>
</tbody>
</table>

* First round of investigation.
† Second round of investigation.
lesions, whereas cancer was present in 35% with an isolated atypical focus in the initial biopsy [59]. These figures are similar to those reported by Kronz et al., who found that HGPIN with adjacent small atypical glands on prostate biopsy had a 46% follow-up cancer detection rate [38]. Conversely, Schlesinger et al. reported that ASAP associated with HGPIN predicted cancer in 33% of the cases, slightly lower than for ASAPs suspicious for malignancy alone (37%) [3] (Table 6).

The adenocarcinomas found on rebiopsy are mainly of intermediate grade, with Gleason scores of 5 and 6, but 30% are of high grade, with Gleason scores 7–10 [30,31] (Table 7).

Of particular interest is the unique observation by Brausi et al. who found that 100% of 25 patients with isolated ASAPs suspicious for malignancy who underwent prostatectomy had cancer [24]. This led these authors to suggest that immediate surgery was the treatment of choice for young patients with ASAPs suspicious for malignancy.

6.2. Rebiopsy strategy

Given the documented high risk of cancer in patients with atypical foci suspicious but not diagnostic of malignancy, it is reasonable to consider rebiopsy within 3–4 mo after an initial biopsy observation of atypical glands. Most carcinomas on rebiopsy are found within 6 mo [30,31].

It is intuitive that a greater diagnostic yield for malignancy will be provided by focusing on sites with documented atypical foci. However, the most useful repeat-biopsy strategy is controversial. Some authors recommend a sextant biopsy technique and additional biopsies directed to the site of atypical biopsy findings or to the ipsilateral site [31]; conversely, based on finding 85% of all cancers detected with repeat biopsies in the same sextant site, adjacent ipsilateral and adjacent contralateral sextant biopsies, Allen et al. suggested rebiopsy should include several cores from the atypical location, two cores each from adjacent locations, and one each from other sextant locations [66]. Park et al. calculated significant increased odds of finding cancer at the same site of atypical prostate biopsy: 65% probability, which increases to 88% when including adjacent sites [32]. On a multisite scheme study, Scattoni et al. found precise spatial concordance between ASAP and cancer in only 33% of the cases, similar to the likelihood of finding cancer in an adjacent site or in a nonadjacent site [59]. Repeat biopsy results in a second diagnosis of atypical focus in about 6% of cases. These patients probably should undergo a second rebiopsy. Consideration for additional rebiopsy sessions probably should be also based on clinical findings (serum PSA and DRE results) and judgement [2,13,31,67].

7. Conclusion

When dealing with atypical focus suspicious for malignancy, maximal diagnostic information should be gained on haematoxylin and eosin-stained sections, with immunohistochemical stains used for confirmation.

Its presence in a biopsy set is a strong predictor for concurrent or subsequent cancer. The precise labelling of the initial biopsies is mandatory so that rebiopsy of cases with atypical glands suspicious for malignancy should be directed in a more concentrated fashion into the region of the initial biopsy. Other sites should be biopsied as well because cancer may also be found away from the initial atypical site.

References

[2] Iczkowski KA, MacLennan GT, Bostwick DG. Atypical small acinar proliferation suspicious for malignancy in


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