Minimal Adenocarcinoma in Prostate Needle Biopsy Tissue

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Abstract

One of the major diagnostic challenges in prostate needle biopsy interpretation is definitive establishment of a malignant diagnosis based on a minimal or limited amount of carcinoma in needle biopsy tissue. Major and minor diagnostic criteria should be used for interpretation of small foci of carcinoma. The constellation of findings and a combination of the major and minor diagnostic criteria permit a definitive diagnosis of focal adenocarcinoma. The differential diagnosis of minimal prostatic adenocarcinoma in needle biopsy tissue is broad and includes many benign lesions. The benign entities most likely to be misdiagnosed as minimal prostatic adenocarcinoma are atypical adenomatous hyperplasia (adenosis) and atrophy. High-grade prostatic intraepithelial neoplasia and a descriptive diagnosis of focal glandular atypia or atypical small acinar proliferation also should be considered before diagnosing minimal adenocarcinoma. The most valuable adjunctive study for the diagnosis of minimal adenocarcinoma is immunohistochemistry using antibody 34betaE12, reactive against basal cell–specific high-molecular-weight cytokeratins. Most cases can be diagnosed based on H&E-stained sections without this immunostain. Most minimal carcinomas in prostate needle biopsy tissue are of intermediate histologic grade, and most are indicative of pathologically significant carcinoma in the whole prostate gland.

During the last 15 years, there has been a dramatic 5-fold increase in the number of American men diagnosed with prostate cancer. In 1985, there were 37,324 new cases. In the year 2000, it is estimated that 180,400 men will be diagnosed with this malignant neoplasm. Since the primary approach for establishment of a definitive diagnosis of prostate cancer is histopathologic interpretation of transrectal 18-gauge needle core biopsy specimens, there correspondingly has been a vast expansion in the number of prostate needle biopsy specimens reviewed around the United States. This striking increase is due to multiple factors, including widespread use of serum prostate-specific antigen (PSA) as a screening tool, the aging of the American population, increasing public awareness of prostate cancer, and clinical use of the 18-gauge biopsy gun, which allows for relative ease of prostate gland sampling.

Early detection efforts, including screening with PSA and digital rectal examination, also have resulted in identification of lower stage and smaller volume carcinomas of the prostate. Furthermore, many prostate cancers detected by an elevated serum PSA level are impalpable, and needle biopsy sampling of the prostate gland is thereby not directed toward a mass. These elements have resulted in the challenging task for the histopathologist of diagnosing malignant neoplasms on the basis of a limited or minimal amount of tumor in the small diameter 18-gauge needle biopsy cores of prostate tissue.

The focus of this review is histopathologic diagnosis of minimal or limited carcinoma in prostate needle biopsy specimens. Thorson et al define minimal carcinoma in needle biopsy tissue as tumor less than 1 mm in greatest dimension. Another definition of minimal adenocarcinoma is cancer involving less than 5% of needle core tissue.
section, we discuss major and minor criteria for the diagnosis of minimal prostate carcinoma based on H&E-stained sections. In the second part, we present entities in the differential diagnosis of minimal prostatic adenocarcinoma. The third segment includes information on use of ancillary diagnostic studies, particularly the use of immunohistochemical staining for basal cells. Finally, the clinical significance of these minimal carcinomas in prostate needle biopsy tissue is addressed.

Criteria for Diagnosis of Minimal Prostatic Carcinoma

A list of histologic features important for the diagnosis of minimal prostatic carcinoma is given in Table 1. This list ranks histologic attributes in order of frequency of detection and is based on experience with 50 cases of minimal carcinoma in prostate needle biopsy tissue.4

A useful conceptual approach for applying these diagnostic findings is categorization as major and minor diagnostic criteria Table 2.6 It is of interest that in 1953, Totten et al7 used these same major diagnostic criteria for diagnosing carcinoma of the prostate Table 3. It is critical at the outset to state that no single criterion, not even one of the major diagnostic criteria, is by itself diagnostic of malignancy. Rather, consideration of the constellation of findings allows for a specific diagnosis to be made in each case.4,8

To detect minimal carcinomas in needle biopsy tissues, it is best to prepare 3 levels, that is, 3 slides, each with several sections, from each paraffin block.9-11 Some laboratories save unstained slides with interval sections taken between the 3 levels. These slides can be used for H&E staining or ancillary immunohistochemical staining (see “Ancillary Studies”). It is not necessary to serially section through prostate needle core tissue. We found that this required a mean of 30 slides per block, with a mean of 4 sections per slide.12 Additional levels beyond the first 3 standard slides were critical for diagnosing minimal carcinoma only when a diagnosis of focal glandular atypia was made in the first 3 slides. In 10% of cases of focal glandular atypia, a single additional level allowed for a definitive diagnosis of carcinoma, based on a larger lesion size in the additional level.12 So, for maximal detection of minimal carcinoma in prostate needle biopsy tissue, we recommend obtaining 3 initial levels (H&E-stained slides), with procurement of an additional level (slide) if focal glandular atypia is detected in the initial 3 slides.

The initial step in the evaluation for the features listed in Table 1 and the criteria in Table 2 is to study, in the needle biopsy case being examined, glands that one is certain are benign. This is crucial, since fixation, staining, and section thickness can affect appearance of the prostatic epithelium. By first inspecting benign glands, one can “calibrate” one’s eye for each individual case, for the purpose of later comparison with focal atypical glands.

It is important to scan every core section and examine all levels of tissue, since different levels may provide additional information.8-11 It is also important to appreciate the

| Table 1 |
|--------------|------------------|------------------|
| Histologic Feature | No. (%) of Cases |
| Nuclear enlargement | 48 (96) |
| Infiltrative growth pattern (Gleason score >4)† | 41 (82) |
| No. of glands (>10 malignant glands per focus)† | 50 (82) |
| Intraluminal secretion | 39 (78) |
| Prominent nucleoli | 32 (64) |
| Associated high-grade PIN | 20 (40) |
| Crystalloids | 11 (22) |
| Perineural invasion | 1 (2) |
| Collagenous micronodules | 1 (2) |
| Mitotic figures | 1 (2) |
| PIN, prostatic intraepithelial neoplasia. |
| * Adapted from Thorson et al.4 |
| † The percentage is calculated based on 61 positive cores. |

| Table 2 |
|--------------|------------------|------------------|
| Major criteria | Architectural: infiltrative small glands or cribriform glands too large or irregular to represent high-grade PIN | Single cell layer (absence of basal cells) |
| Nuclear atypia: nuclear and nucleolar enlargement | Nuclear atypia: nuclear and nucleolar enlargement |
| Minor criteria | Intraluminal wispy blue mucin (blue-tinged mucinous secretions) | Pink amorphous secretions |
| Mitotic figures | Intraluminal crystalloids | Adjacent high-grade PIN |
| Amorphophilic cytoplasm | Nuclear hyperchromasia |
| PIN, prostatic intraepithelial neoplasia. |
| * Adapted from Algaba et al.6 |

| Table 3 |
|--------------|------------------|------------------|
| Glandular pattern: small irregular glands with no particular relation to the adjacent stroma or normal glands | Arrangement of glandular epithelium: lack of basal cells in cancer | Cellular details: large deeply staining nucleoli |
| * Adapted from Totten et al.7 |
normal architecture of the prostate gland before diagnosing minimal adenocarcinoma of the prostate. Normal prostate glands are complex and branching, with 2 cell layers, basal cells and luminal cells. The basal cells often are flattened, spindled, elongated, cuboidal, rounded, or triangular, lying parallel to the basement membrane and most often perpendicular to the luminal cells. Basal cells contain only a scant amount of dense cytoplasm. The nuclei of basal cells are small, homogeneous, smooth, and dark and usually lack conspicuous nucleoli. The luminal cells or secretory cells are cuboidal to columnar, with nuclei positioned in the basal to mid portion of the cells. Luminal cells have clear cytoplasm with round to oval bland nuclei.

The major and minor criteria and diagnostic attributes of minimal carcinoma (Tables 1-3) should be assessed specifically at low- and high-power magnifications. While epithelial-stromal relationships and pattern of minimal carcinoma growth are best surveyed at lower magnification, scrutiny at high magnification is necessary to evaluate for major criteria of basal cell absence and nuclear atypia. Detection of many of the minor diagnostic criteria also necessitates use of high-magnification objectives.

The first assessment one should perform is a search for the first of the major criteria, an infiltrative growth pattern, which frequently presents as the presence of small malignant glands between larger, more complex (and often paler), benign glands Image 1 and Image 2. In one series of minimal (limited) carcinoma, this pattern accounted for fully 80% of cases Table 4. The presence of the few malignant acini between the benign glands is indicative of invasion, even though the glands appear embedded only within the stroma. This deceptive appearance is because the invading glands usually do not elicit a desmoplastic or inflammatory response, which characterizes many other types of invasive carcinoma, and the glands still can appear rounded. The second most common pattern of infiltration was a haphazard or disorderly arrangement of glands, with random dispersion of glands in stroma, without availability of benign glands as a reference point Image 3. On occasion, the invasive glands formed a column spanning the width of the needle Image 4. Uncommon patterns of growth seen accompanying the most common pattern were cords of cells, single cells, and cribriform glands. These infiltrative growth patterns are a hallmark of moderately to poorly differentiated, Gleason score 5 to 10 adenocarcinoma of the prostate and were found in 82% of the minimal carcinoma cases.4

In a very small minority of cases, an infiltrative pattern is not evident. These are well-differentiated, Gleason score 2 to 4 carcinomas that are, by definition, well-circumscribed. The key low-power recognition clue here is that there is a high density of closely packed, pale, small acini Image 5. In these cases, establishment of a diagnosis of malignant

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**Table 4**

Patterns of Invasion by Minimal Prostatic Carcinoma

| Presence of small glands between benign glands (most common) | Haphazard growth without adjacent benign glands | Uncommon: cords of cells, single cells, cribriform structures |

* Adapted from Epstein.8
neoplasm requires the absence of basal cells and nuclear atypia. Thirteen percent to 18% of minimal carcinomas in needle biopsy tissue fall into this well-differentiated category.\(^4,8\) Recently, it was proposed that well-differentiated, Gleason score 2 to 4 adenocarcinoma should not be diagnosed in prostate needle biopsy tissue,\(^13\) since in the vast majority of cases, this represents an undergrading of the carcinoma in the whole gland. This was the experience of Thorson et al,\(^4\) as 8 (89%) of 9 minimal adenocarcinomas deemed well-differentiated and Gleason score 3 or 4 in needle biopsy tissue had a moderately differentiated component in the whole gland. A diagnosis of well-differentiated, Gleason score 2 to 4 adenocarcinoma may be unavoidable in a few cases (Image 5), but overall this should be an uncommon to nonexistent diagnosis in needle biopsy tissue.

The second of the major criteria is absence of basal cells in the atypical glands. Basal cells may assume a range of appearances,\(^14,15\) making careful study of basal cells in glands that are clearly benign a vital exercise to rule out their presence in malignant glands. Thin well-fixed sections with quality H&E staining are crucial for the appreciation of a single cell lining layer in malignant glands. A historic challenge for the surgical pathologist has been the distinction of periglandular stromal fibroblasts from basal cells. Another common difficulty is that distorted, crushed, or poorly preserved carcinoma cells in minimal cancer foci can mimic basal cells (Image 6). In cases such as these, application of a basal cell–specific immunohistochemical stain for high-molecular-weight cytokeratin can be diagnostically advantageous. (See the section on ancillary studies.) However, this immunostain is not a “malignant stain,” and Totten and colleagues\(^7\) put basal cells in their proper context when they noted the following, based on scrutiny of H&E-stained sections:

“This basal cell layer is not always present in benign small glands, so that its absence is not an absolute criterion of carcinoma. Conversely, however, we have not seen it in any case in which the diagnosis was cancer.”\(^7\)

Thus, absence of basal cells is a central finding in an atypical small acinar proliferation, but by itself, it is not fully diagnostic.

Nuclear atypia in the form of nuclear enlargement and nucleolar enlargement is the third of the major criteria. Nuclear atypia in malignant glands most often manifests itself as nuclear enlargement and prominent nucleoli. Nearly every one of our cases of minimal carcinoma exhibited nucleomegaly, and a majority (64%) had prominent nucleoli (Image 7). In a second series\(^8\) of minimal (limited) carcinomas, 24% of the cancers lacked prominent nucleoli, and another 25% had only rare prominent nucleoli. Although a third study found prominent nucleoli in at least 10% of cells in all minimal carcinoma cases,\(^5\) evidence exists that not all prostatic carcinomas harbor prominent (>1.5 µm) nucleoli.\(^16\) How to define “prominence” is a matter of some debate, and nucleoli with a diameter anywhere from 1- to 3-µm or more have been deemed prominent in the past. Failure to detect prominent nucleoli in prostatic carcinoma nuclei is likely multifactorial; large nucleoli might be present but undetectable owing to poor preservation, poor fixation, overstaining, or section thickness. This last factor of overly thick
sections is an extremely common problem. In addition, lack of chromatin clearing might contribute to inability to detect nucleoli. Last, it is possible that some prostate cancers do not harbor macronucleoli. An essential point is that when macronucleoli are absent, there should be significant nucleomegaly with or without nuclear hyperchromasia to definitively diagnose carcinoma.

The major criteria do not include a quantitative threshold for the number of glands required to establish a diagnosis of malignant neoplasm. In the series of Thorson et al., 80% of minimal carcinoma foci contained more than 10 glands. In another series, the median number of malignant glands was 20. The mean ± SD number of acini in a third study was 17 ± 14. It is possible to diagnose invasive carcinoma based on just a few glands. In our experience, the smallest number of atypical glands that formed the basis for a definitive diagnosis of malignant neoplasm was 4. In this case, there was excellent preservation of cellular detail, without tangential sectioning, such that it was clear on the H&E-stained sections that basal cells were absent and

![Image 5](Image 5.png) Well-differentiated minimal adenocarcinoma. An aggregate of closely packed, small, pale acini is evident (H&E, ×300).

![Image 6](Image 6.png) A few glands of carcinoma with scattered darker nuclei. These are not basal cell nuclei, but rather, are distorted carcinoma cell nuclei. The 34betaE12 antibody did not bind to these cells (H&E, ×400).

![Image 7](Image 7.png) Macronucleoli in prostatic adenocarcinoma nuclei (H&E, ×500).

![Image 8](Image 8.png) Prostatic adenocarcinoma with hyperchromatic nuclei (H&E, ×400). Reprinted by permission from Thorson et al. 4
that significant nuclear atypia was present. Both of these major criteria are of immense importance for these most minimal of the minimal carcinomas, in which architectural abnormalities are difficult to impossible to discern. In another series on minimal (limited) carcinoma, the lowest number of diagnostic glands was 2.8 At a consensus conference,6 most urologic pathologists believed that 3 glands constituted the typical lowest numeric cutoff, but in rare cases, some hold the opinion that carcinoma may be diagnosed by the presence of a single neoplastic gland.6,17 So, opinions vary about the number of glands required for a definitive diagnosis of malignant neoplasm, but 3 glands seems to be the lower limit for many diagnosticians.

Minor diagnostic criteria are found, on an individual basis, in a lower proportion of cases compared with major diagnostic criteria, with the exception of intraluminal amorphous pink material (Table 1). These minor or “soft” diagnostic attributes are not specific for carcinoma but are useful for prompting in-depth study of the glands harboring these changes, with a view toward assessment of the aforementioned major diagnostic criteria.6 With the exception of high-grade prostatic intraepithelial neoplasia (PIN), none of the listed minor criteria should, by themselves, be considered a sufficiently atypical finding to warrant rebiopsy. For example, wispy blue mucin can be seen in mucinous metaplasia,18 and crystalloids can be found in benign glands.19,20

Diagnostic findings that have been forwarded as specific for malignant neoplasm6,21—perineural invasion, collagenous micronodules (also known as mucinous fibroplasia),22 and glomeruloid intraglandular projections23—are rare in minimal prostatic adenocarcinoma,21 and this obviously diminishes their diagnostic usefulness in this setting. Perineural invasion was identified in only 0% to 3% of minimal or limited prostate cancer cases4 and collagenous micronodules were seen in 0.1% to 5% of cases.4,5,21 Thorson et al4 saw only 1 case with a suggestion of glomeruloid intraluminal tufting. In another series,21 not a single case had glomerulations as a key feature in diagnosing very limited cancer. True perineural invasion, which is characteristic of adenocarcinoma of the prostate, needs to be distinguished from benign glands abutting prostatic peripheral nerve.24,25 Collagenous micronodules are a distinctive,
but uncommon, type of stromal response to invasive prostatic carcinoma, which often exhibits mucinous differentiation.22,26 Adenocarcinomas of the prostate with glomeruloid features are remarkable for intraglandular tufts of malignant cells that resemble renal glomeruli in their low-power appearance.

To reiterate, it is a combination of features that will allow for establishment of a diagnosis of prostatic adenocarcinoma based on a minimal amount of tumor. No definite number of criteria must be fulfilled, but rather, each case must be individualized and interpreted based on its own unique set of findings.

**Differential Diagnosis of Minimal Prostatic Carcinoma**

Numerous entities should be considered in the differential diagnosis of minimal prostatic adenocarcinoma. Recent reviews have highlighted these benign lesions, or pseudoneoplasms **Table 5**, that may mimic prostatic adenocarcinoma.27-30 In-depth discussion of these benign entities is beyond the scope of this review. It is important to note that atypical adenomatous hyperplasia (adenosis) and atrophy are the benign conditions that are most likely to be misdiagnosed as prostatic carcinoma.6,29-31 Atypical adenomatous hyperplasia (or adenosis) is an atypical small acinar proliferation that can masquerade as minimal well-differentiated adenocarcinoma in needle biopsy tissue.32 While both proliferations are characterized by a circumscribed, high-density collections of small acini, atypical adenomatous hyperplasia is often in continuity with larger, more complex glands; atypical adenomatous hyperplasia exhibits a fragmented basal cell layer, and the luminal cells typically have bland nuclei.32,33 Atrophy, on the other hand, is more likely to be confused with a moderately differentiated adenocarcinoma. Atrophy is separated from minimal prostatic carcinoma by the presence of basal cells, cytoplasmic volume loss, and, typically, a lesser degree of nuclear atypia.34-36 However, nuclear enlargement and prominent nucleoli can be observed in atrophy, especially when there is accompanying inflammation.36 A lobular architecture sometimes can be seen in atrophy, but background fibrosis can simulate a fibrogenic response in sclerotic atrophy, with a resultant infiltrative-like picture. Foci of postatrophic hyperplasia,37 with its crowded acini, and partial atrophy38 also can be mistaken for minimal prostatic adenocarcinoma. One should also be aware that adenocarcinoma of the prostate can have atrophic features, with significant cytoplasmic volume loss.39-41 We have seen rare examples of minimal prostatic adenocarcinoma with atrophic features in needle biopsy specimens. In these cases, continuity with usual adenocarcinoma, in which the cells had a moderate amount of cytoplasm, and substantiation of basal cell absence by a 34betaE12 immunostain were instrumental in diagnosing malignant neoplasm.

Two additional proliferations that figure prominently in the differential diagnosis of minimal prostatic adenocarcinoma are high-grade PIN and a descriptive diagnosis of atypia. It can be exceedingly difficult to differentiate small foci of cribriform high-grade PIN from cribriform invasive carcinoma in needle biopsy tissue. Cribriform high-grade PIN is, however, in pure form, quite rare in prostate needle biopsy tissue,32 and the uncommon cases (7/300) of minimal

**Table 5**

**Differential Diagnosis of Minimal Prostatic Adenocarcinoma: Pseudoneoplasms of the Prostate**

1. Atypical adenomatous hyperplasia (adenosis)
2. Atrophy
3. Basal cell hyperplasia
4. Sclerosing adenosis
5. Cribriform hyperplasia
6. Mesonephric hyperplasia
7. Nephrogenic metaplasia (adenoma)
8. Verumontanum mucosal gland hyperplasia
9. Squamous metaplasia
10. Transitional cell metaplasia
11. Radiation atypia
12. Prostatitis
13. Malacoplakia
14. Endometriosis
15. Postoperative spindle cell nodule
16. Atypical stromal cells
17. Extramedullary hematopoiesis
18. Cowper glands
19. Paranganglia in prostate
20. Benign glands adjacent to nerves and skeletal muscle

* Adapted from Young.37
carcinoma with cribiform architecture also had a small acinar component. If any basal cells are identified in a pure cribiform proliferation of neoplastic cells on H&E-stained sections or by 34betaE12 immunostain (see “Ancillary Studies”), caution is advised, and a diagnosis of high-grade PIN should be given. Focal, flat, high-grade PIN also can be problematic as it can closely resemble small acinar, minimal carcinoma, but it also is uncommon in pure form in needle biopsy tissue, and, again, basal cell presence will exclude invasive carcinoma. Finally, a striking conundrum can be the diagnostic distinction of high-grade PIN with out-pouching vs high-grade PIN with adjacent invasive glands. One should exercise caution if confronted with a few atypical small acini immediately adjacent to high-grade PIN since these could represent protrusions from the high-grade PIN. Basal cells should be sought specifically in these glands. If there are more than a few atypical small acini, and these exhibit a degree of stromal separation from the high-grade PIN, and if these small glands lack basal cells, a diagnosis of carcinoma should be considered. Image 12A. No quantitative criteria exist for number of glands or amount of stromal distance separation required to definitely diagnose invasion.

In borderline cases, we have used the descriptive diagnosis of “high-grade prostatic intraepithelial neoplasia with associated atypical small acinar proliferation” with a description of the differential diagnoses in a comment.

Diagnoses of atypia have been forwarded as a viable diagnostic category. These terms include focal glandular atypia, atypical, atypical suspicious for carcinoma, and atypical small acinar proliferation suspicious for malignancy. This category of atypia is undoubtedly a broad diagnostic umbrella and likely encompasses benign and reactive but atypical epithelium to small foci of carcinoma that harbor some but not all features needed for a definitive diagnosis of malignant neoplasm. Some have suggested 3-tiered stratification of the atypia into favor benign, uncertain (or suspicious), and highly suspicious or favor benign, favor cancer, and undetermined. We have used a 2-tiered scheme of focal glandular atypia and focal glandular atypia, suspicious for malignancy. Thus far, these stratifications have not been proven to be reproducible or clinically significant.

In our definition of atypia, focal glandular atypia was classified as a gland or groups of glands with architectural atypia, cytologic atypia, or both that are atypical but not diagnostic of atypical adenomatous hyperplasia, high-grade PIN, or carcinoma. Most studies have found that clinical features such as serum PSA level or digital rectal examination findings are not useful in the differential diagnosis of atypia vs minimal carcinoma. No set combination of histologic criteria exist to distinguish atypia and, in particular, atypical glands that are suspicious for malignancy from minimal carcinoma. In 1 study, minimal carcinoma foci, in comparison with atypical small acinar proliferation, tended to be larger, more infiltrative, and with greater nuclear atypia, including nucleomegaly and prominent nucleoli. Mitotic figures more often were seen in minimal carcinoma (10% of cases) compared with atypical small acinar proliferation (0%), but in the series of Thorson et al, they were seen in only 2% of minimal carcinomas, which suggests little diagnostic usefulness. Luminal blue mucin, concomitant high-grade PIN, and absence of moderate to severe atrophy also were more common in focal carcinoma vs atypical small acinar proliferation.

However, there is overlap of all of these features in minimal carcinoma vs atypical small acinar proliferation, such that different thresholds exist among histopathologists in the diagnosis of minimal carcinoma vs atypia. Some cases of atypical glands suggestive of malignancy most likely represent prostate cancer that is distorted, poorly preserved, thickly sectioned, poorly stained, and/or clinically or histologically undersampled. In 10% of cases of focal glandular atypia, additional sections from the block reveal definitive carcinoma. So, we recommend obtaining additional sections after an initial diagnosis of atypia in the first 3 slides. This further sampling of tissue in the block can be additional H&E-stained sections, a 34betaE12 immunostain, (see “Ancillary Studies”), or both. Even after additional levels and/or a 34betaE12 immunostain, some cases are borderline, so a descriptive diagnosis of atypia is warranted. The incidence of such an atypical diagnosis varies from 2% to 9%, depending on the series. The mean incidence in the literature, based on compilation of these data, is
about 3% of all prostate needle biopsy specimens. Patients with a focus of atypical glands suspicious for malignancy are at high risk for subsequent detection of cancer, with 34% to 60% of patients given a diagnosis of carcinoma based on repeated biopsy.\(^{45,50}\) So, just as for patients with high-grade PIN, a diagnosis of “atypical, suspicious for malignancy” in a prostate needle biopsy specimen should prompt sextant rebiopsy (usually in 3-6 months).\(^{55}\)

### Ancillary Studies

The most valuable adjunctive study for the diagnosis of minimal adenocarcinoma of the prostate is immunohistochemistry with monoclonal antibody 34betaE12, which binds to high-molecular-weight cytokeratins expressed in basal cells rather than luminal cells.\(^{56-60}\) This antibody, which also has been identified by its commercial catalog number, CK903, is useful for documenting the absence of basal cells in focal atypical small acinar proliferations, yet there are caveats in the use and interpretation of this immunohistochemical staining reaction. First, basal cell absence is an important criterion for the histologic diagnosis of prostatic carcinoma but is only one of several of the major criteria. That is, this immunostain, like other adjunctive studies, should be interpreted in the context of all histologic findings in the case.\(^{6}\) Also, as Totten et al\(^{7}\) noted almost half a century ago, based on examination of H&E-stained sections, not all benign glands have basal cells. This has been substantiated by the 34betaE12 immunostain, as a minority of benign glands can have a discontinuous or absent basal cell layer. Indeed, one of the benign entities most often misdiagnosed as carcinoma—atrophy—can reveal scattered negative glands in up to 11% of cases.\(^{57,61}\) Up to 12% of basal cell hyperplasia glands fail to stain,\(^{57}\) and 10% to 90% (average, 50%) of glands in atypical adenomatous hyperplasia do not stain.\(^{32,33}\) Finally, this immunohistochemical stain is based on a negative result to give a positive diagnosis of malignant neoplasm. Many factors can cause failure of immunohistochemical staining, and absence of proof is not proof of absence. So, it is absolutely critical to study the immunostained cores for a positive internal control—benign glands with a strong, positive basal cell signal. Preferably, these benign glands are located near the adjacent carcinoma or are at least in the same core.

With these pitfalls in mind, the 34betaE12 immunostain can be useful as a confirmatory measure in specific circumstances. It should not be used as a screening test in all prostate needle biopsy specimens, but rather should be applied specifically in selected cases with selection and the differential diagnosis driven by the histologic appearance of the H&E-stained slides. It is unnecessary to use the 34betaE12 immunostain on all minimal carcinomas to confirm basal cell absence; indeed, in 1 series of 50 minimal carcinomas in needle biopsy tissue, all diagnoses were made on H&E-stained sections alone.\(^{4}\) In a large series,\(^{59}\) only 2.8% of all prostate needle biopsy specimens were immunostained with antibody 34betaE12. It most often was ordered to evaluate a focus of atypical glands and also was ordered in selected cases in which the differential diagnosis encompassed atypical adenomatous hyperplasia (adenosis), PIN,
basal cell hyperplasia, and atrophy. The immunostain also can be used to distinguish cribriform high-grade PIN from cribriform invasive carcinoma. When it was requested to assess a focus of atypical glands, the number of glands per case was usually 4 to 30. Overall, in needle biopsy tissue, this immunostain was believed to be confirmatory in 58% of cases, was equivocal in 18% of cases, established the diagnosis in 14% of cases, was of no use in 8% of cases, and changed the favored diagnosis in 2% of cases. In needle biopsy cases stained with 34betaE12, there was a tendency for cases with fewer glands to be diagnosed as equivocal rather than minimal cancer, but there was extensive overlap in number of glands on which a diagnosis was based, which again speaks to use of this immunostain as a supplementary tool. In another series of needle biopsy specimens, it was concluded that the 34betaE12 immunostain substantially reduced the percentage of prostate needle biopsy cases diagnosed as atypical. In addition to basal cell identification, we have found that the 34betaE12-immunostained sections, in which a hematoxylin counterstain is used and eosin staining is absent, allow for better visualization of nuclear atypia.

The 34betaE12 immunostain can be particularly valuable when the differential diagnostic consideration is radiation-induced atypia vs focal minimal residual carcinoma in patients with prostate cancer treated by radiation therapy. In this setting, reactive basal cells can mimic cancer cells cytologically in nuclear alterations, and, here, the 34betaE12 immunostain can provide important diagnostic information. Minimal residual carcinoma after hormonal therapy also can pose diagnostic challenges, and positive immunostains for PSA and pan-cytokeratin, with a negative 34betaE12 immunostain, sometimes can be helpful.

The cost and practical methodologic approaches for the 34betaE12 immunohistochemical stain should be noted. The estimated cost of actual performance of the immunostain has been estimated at $5.00 per case, but the charge to the patient at one hospital was $568.00, including professional fees and all hospital and laboratory charges. This charge is much less than that of rebiopsy.

There are important technical considerations in performance of 34betaE12 immunohistochemistry. First, the immunostain works well on sections of formalin-fixed paraffin-embedded prostate needle biopsies and on Bouin fixed-needle biopsy specimens. Second, to optimize the binding reaction, one should use an epitope-retrieval technique with protease digestion, heat-induced antigen retrieval, or both. Last, the immunostain procedure can be performed on unstained interval sections (on sialiated slides), on deeper sections from the block, or even on destained H&E-stained slides. For cases with just a few glands on an H&E-stained slide, the latter procedure is feasible in a majority of cases. In a minority of cases, there is staining failure, or the tissue section is lost from the slide during the staining procedure.

Finally, in rare cases, additional immunohistochemical studies are indicated. For example, in the differential diagnosis of focal granulomatous prostatitis vs focal poorly differentiated prostatic adenocarcinoma, a panel of antibodies to cytokeratins (AE1/AE3), PSA, prostatic acid phosphatase (PSAP), lysozyme, antimacrophage M, and leukocyte common antigen (CD45) reliably distinguished the disorders. The differential diagnostic workup of focal prostatic carcinoma vs transitional cell carcinoma in prostate needle biopsy tissue likewise can be aided by use of a targeted panel of antibodies, including PSA, PSAP, 34betaE12, monoclonal carcinomaembryonic antigen, p53, cytokeratin 7, and cytokeratin 20. PSA and PSAP are the best prostatic markers in general, but they are not absolutely specific and can stain benign and malignant nonprostatic cells and tissues. Although usually resolved by examination of H&E-stained slides, the distinction of small seminal vesicle glands and minimal prostatic adenocarcinoma also can be accomplished by PSA, PSAP, and 34betaE12 immunohistochemical studies, in which seminal vesicle glands and minimal prostatic adenocarcinoma also

Clinical Significance of Minimal Carcinoma in Needle Biopsy Tissue

The clinically most useful and well-established features of acinar prostatic adenocarcinoma in needle biopsy tissue are histologic grade and extent of tumor. Histologic grade commonly is used to stratify patients into prognostic and therapeutic groups. Clinically, the Gleason histologic grade in the needle biopsy specimen is used in conjunction with the pretreatment serum PSA level and clinical stage to predict pathologic stage of disease. Data on these 3 parameters have been used to generate the so-called Partin tables, which yield specific risk categories for patients. In the experience of Thorson et al., most minimal carcinomas in needle biopsy tissues (39/50 [78%]) were of intermediate grade (Gleason score, 5 or 6), 18% were well-differentiated (Gleason score, 2-4), and 4% had a high-grade component (Gleason score, 7-10). Gleason grading can be performed accurately on most minimal prostatic adenocarcinomas. In our experience, the Gleason score in the needle biopsy specimen was within 1 score unit in 94% of cases.
Others\textsuperscript{78,79} also have concluded that the amount of tumor in the needle biopsy specimen does not influence grading error. Such error is more likely to occur as a result of sampling error and prostate cancer grade heterogeneity.\textsuperscript{78-81} The typical problem for Gleason grading in needle biopsy specimens for minimal and nonminimal carcinomas is undergrading in the needle core tissue. As previously noted, when Thorson et al\textsuperscript{4} assigned a well-differentiated Gleason score of 3 or 4 in 9 cases, only 1 of these was well-differentiated in the radical prostatectomy specimen (Gleason score, 4), while the other 8 were an intermediate Gleason score of 5. A small amount of tumor in prostate needle biopsy specimens is not equivalent to low-grade tumor. On the other hand, minimal high-grade carcinoma in needle biopsy tissue was predictive in most cases of high-grade carcinoma in the whole gland: Men with minimal high-grade (Gleason score, 7 or more) carcinoma in needle biopsy specimens had high-grade carcinoma in the whole gland in 79% of cases, while 21% had a Gleason score of 6.\textsuperscript{82} Most of these men had organ-confined and margin-negative disease.\textsuperscript{82}

A minimal amount of carcinoma in prostate needle biopsy tissue does not predict, for the individual patient, a small amount of cancer in the whole gland,\textsuperscript{3,83-86} even when 6 core biopsy specimens (sextant biopsy specimens) are obtained. This should not be so surprising, given that the tissue in an 18-gauge prostate needle biopsy specimen represents 0.03% of all prostate gland tissue. Thorson et al\textsuperscript{4} found that the mean whole gland tumor volume of carcinomas corresponding to minimal carcinoma in needle biopsy specimens was significantly ($P = .029$) smaller at 1.1 cm$^3$ than it was for tumors greater than 1 mm in needle biopsy specimens at 1.6 cm$^3$. Depending on the definition of pathologic significance, the percentage of significant tumors ranged from 68% to 98%.\textsuperscript{4} Thus, most minimal carcinomas in needle biopsy specimens are moderately differentiated, and most indicate pathologically significant carcinoma in the whole gland, as assessed using a combination of grade, tumor volume, and stage.\textsuperscript{4}

The amount of tumor in needle biopsy tissue, when used in conjunction with other pretreatment parameters including serum PSA (and its permutations such as percentage of free serum PSA\textsuperscript{87,88} and PSA density\textsuperscript{3}), Gleason grade, and clinical stage may provide useful pretreatment clinical information about tumor volume and pathologic stage.\textsuperscript{2,88} While “minimal adenocarcinoma of the prostate” should not be given as a specific histopathologic diagnosis, it is recommended that the amount of tumor in the needle biopsy specimen be provided in the surgical pathology report.\textsuperscript{89-91} We report the number of positive cores out of the total number of cores submitted and provide a visual inspection estimate of the percentage of prostate needle core tissue involved by carcinoma. One could also provide a measurement of linear millimeters of tumor extent using an ocular micrometer or ruler, although this is more time consuming. Here is an example of our approach to reporting a Gleason score 6 minimal carcinoma in sextant biopsy specimens (where 3 needle cores were submitted from the right and 3 from the left side in separate containers):

Prostate, Right Side, Needle Biopsy

- Adenocarcinoma, Gleason grade 3 + 3 = score of 6, in 1 of 3 cores, involving less than 5% of needle core tissue

Prostate, Left Side, Needle Biopsy

- Benign prostatic tissue

Summary

Needle biopsy specimens from the prostate with a small amount of carcinoma confront the histopathologist with a challenging diagnostic task. In most cases, a definitive diagnosis can be given using H&E-stained sections and a constellation of major and minor diagnostic criteria. In a minority of cases, immunohistochemical staining with antibody 34betaE12 can be diagnostically useful. Most minimal carcinomas in prostate needle biopsy specimens are of intermediate grade (Gleason score 5 and 6) and most of the corresponding prostatic carcinomas in the whole prostate gland are pathologically significant.

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