Single Foci Prostate Cancer: Current Diagnosis and Management

Ioannis Efthimiou a Konstadinos Skrepetis a Elefteria Bournia b
Department of a Urology and b Pathology, General Hospital of Kalamata, Kalamata, Greece

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Abstract
Diagnosis of small prostate cancer foci is a real challenge for pathologists and urologists as it carries the risk of false positive or negative diagnosis with clinical consequences. Diagnosis of small prostate cancer foci requires a strict methodological approach which includes a search for major and minor features under low and high magnification. Ambiguous cases can be further clarified with the use of basal cell immunomarkers complemented by a positive indicator of malignancy. Despite the new diagnostic armamentarium, a few cases will continue to remain doubtful and might require an appropriate rebiopsy.

Introduction
Prostate cancer accounts for about 25% of newly diagnosed cancer and represents with colorectal cancer the second leading cause of male cancer deaths in USA after lung and bronchus cancer [1]. The natural history of prostate cancer is not fully elucidated and it is well known that the disease is often indolent with a long latent phase.

This may be problematic for some tumors such as prostate cancer which grow very slowly and may never become clinically important [2, 3]. Moreover, overdetection may be an important issue given that many men who develop prostate cancer do not either develop clinically relevant disease or die as a result of their disease. However, small focus of prostate cancer at biopsy might be clinical relevant especially if a significant tumor is found in the radical prostatectomy specimen [4].

Associated with this issue is the diagnosis and interpretation of small cancer foci in prostate biopsy. A standardized terminology regarding a small focus of prostate adenocarcinoma detected by needle biopsy does not exist, the true incidence is unknown and authors use various terminologies and criteria to describe it such are focal, microfocal cancer, minute cancer, and single prostatic cancer foci (table 1) [5–11].

This paper focuses on histological features and immunohistochemical markers that aid in the diagnosis of single cancer foci and presents the most common entities that lead to false negative and positive results.

Pathological Criteria for Diagnosis of Single Foci of Prostate Cancer

About 80% of prostate cancer occurs in the peripheral zone and 10–20% occurs in the transition zone. The diagnosis of prostate cancer is mainly based on the architecture of the lesion on hematoxylin and eosin...
(H&E)-stained sections (fig. 1) and ancillary studies with immunohistochemistry. The initial step in the pathological evaluation of any individual needle biopsy is to discriminate with certainty the areas of the specimen where the glands are undoubtedly benign. It is important to appreciate the normal architecture of the prostate gland before diagnosing minimal carcinoma of the prostate. The minimum number of glands required for the diagnosis of prostate adenocarcinoma is 3 malignant glands and the mean number that is usually present is 10–20 [12–15]. A summary of histological features are presented in table 2 [13]. Pathological work-up starts at lower power magnification in order to assess the morphology of the glands and epithelial structures and continues at higher magnification even if no abnormalities are observed at low magnification. In this setting glands that may initially be overlooked at low magnification can be identified by their cytological atypia or presence of abnormal luminal contents [16].

Crowded glands should raise the suspicion of prostate carcinoma. The most prominent diagnostic feature is nuclear enlargement and nuclear hyperchromatism is a cytological feature that may help to distinguish cancerous from benign glands. Studies have shown that this feature is present in more than 90% of cases [10, 12].

An infiltrative pattern is a highly reliable marker of malignancy and is indicated by the presence of small malignant glands between the bigger and more core complex benign glands. Benign glands are usually larger in size, papillary, infolding and branching. The presence of small malignant acini situated between benign glands is a manifestation of their infiltrative pattern. Another common feature of infiltration is disordered glands with random dispersion in the stroma with absence of benign glands [13]. However this criterion is difficult to interpret when only a minimum number of malignant glands is present in the specimen and perineural invasion, which is another important finding in prostate cancer diagnosis, is usually absent in minimal carcinomas [12]. Nucleolar enlargement is usually present but not a constant finding in

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<tr>
<th>Author</th>
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<tr>
<td>Weldon et al. [5]</td>
<td>focal prostate cancer</td>
<td>low grade adenocarcinoma covering &lt;3 mm in a single prostate core biopsy</td>
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<tr>
<td>Zackrisson et al. [6]</td>
<td>focal prostate cancer</td>
<td>lesions involving 2 adjacent prostate biopsies 3 mm without Gleason score 4 or 5 carcinomas 6 in Gleason score, &lt; 1 mm in size or occupying &lt;1 x40 field in a single needle specimen</td>
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<td>Allan et al. [7]</td>
<td>minute focus (&lt; 0.5 mm) of prostate adenocarcinoma</td>
<td>foci of moderately differentiated lesions, &lt; 5 mm in a single biopsy were reported as micro-focal cancers</td>
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<tr>
<td>Boccon-Gibob et al. [8]</td>
<td>micro-focal prostate cancer</td>
<td>small focus of low-grade cancer with 2–20 of highly atypical glands</td>
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<tr>
<td>Epstein [9]</td>
<td>limited adenocarcinoma of prostate</td>
<td>presence of mostly low grade adenocarcinoma in a small fraction of a prostate needle biopsy</td>
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<tr>
<td>Van der Kwast et al. [10]</td>
<td>single foci prostate cancer</td>
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Fig. 1. H&E-stained sections of prostate cancer.
prostate carcinoma. The presence of prominent nucleoli may be obscured by poor fixation, over-staining, section thickness or hyperchromatic nuclei. This last factor of lack of chromatin clearing might contribute to inability to detect nucleoli. The significance of prominent nucleoli must be taken in the context of the architectural pattern and other features present with the case.

Complete lack of basal cells is an additional feature although it may be encountered in small benign glands as well, and can potentially create confusion with atypical small acinar proliferation (ASAP).

Another common difficulty is that of distorted, crushed or poorly preserved carcinoma cells in minimal cancer foci which can mimic basal cells. Some minor criteria e.g. intraluminal eosinophilic amorphous secretions and crystalloids, hyperchromatic nuclei and amphophilic cytoplasm, when present, may be helpful although these features are not specific for carcinoma [12]. Mitoses, although not frequent in adenocarcinoma of the prostate, are much more commonly seen in cancer than in benign glands.

Minor criteria should not be used solely as a reason for rebiopsy as they may be found in benign glands as well.

**False Positive and False Negative Lesions**

Benign lesions that may be confused with minimal prostatic carcinoma in addition to a large number of benign diseases include atrophy, adenosis, prostatitis, nephrogenic remnants, Cowper and benign glands.

Adenosis can be confused with minimal well-differentiated adenocarcinoma and atrophy can be confused with moderately well-differentiated adenocarcinoma. Moreover, a minimal prostatic adenocarcinoma may include atrophic features. Atrophic prostate cancer can have significant cytoplasmic volume loss and marked nuclear enlargement. In addition high grade prostatic intraepithelial neoplasia (PIN) and ASAP suspicious for malignancy can be incorrectly reported as single foci of prostate cancer [17]. Patterns that may confuse pathologists with these entities are nuclear atypia, prominent nucleoli, loss of basal cell layer and infiltrative pattern. High grade PIN can often be difficult to distinguish from invasive adenocarcinoma in needle biopsy tissue as it can closely resemble small acinar, minimal carcinoma in its architectural presence.

Small size and lack of architectural abnormality and lesions to the border of the biopsy specimen, might lead the diagnosis of small foci of prostate cancer to be missed or misinterpreted.

In a recent study by Wolters et al. [16], the overall rate of false negative biopsy for prostate cancer including minimal prostate carcinoma was estimated to be 1.1%. All the cancers had Gleason score 6 (3 + 3).

Also experience and pathologists with a special interest in urological pathology are more confident in diagnosis of small atypal lesions as cancer. Atypical lesions can be reclassified as malignant and vice versa in 2.2–45% and 5.2–16.7% respectively [18, 19].

**Immunohistochemical Markers for the Diagnosis of Small Foci of Prostate Adenocarcinoma**

Having in mind the above pitfalls and the fact that routine stain with H&E may lead to false positive results,
immunohistochemistry may prove helpful in the diagnosis of focal prostate cancer [9, 20–22].

The markers that are used for the diagnosis of prostate adenocarcinoma are divided into those which identify the absence basal cell cytokeratins and the indicators of malignancy [23–27].

Regarding the first category we should keep in our mind that prostate carcinomas are characterized by a loss of basal cells. As monoclonal antibodies bind to basal cell cytokeratins (34betaE12, CK 5/6), the p53 homologue and p63 nuclear staining can be used separately or in combination in order to guide the pathologist to the right diagnosis and to increase their sensitivity [23, 24]. However a small minority of prostate cancer cases may express the above basal cell cytokeratins and lead to false negative results [25, 26].

The above pitfalls may be overcome if these basal cell markers are complemented by indicators of malignancy. Cancer is a complex and multifactorial disease and it is unlikely to be defined by a single marker alone [20–22]. A commonly used marker for this purpose is that which stains alpha-methylacyl coenzyme A racemase (AMACR), an enzyme involved in lipid metabolism. Positive stain for AMACR combined with absence of p63 and high molecular weight cytokeratin (34betaE12) can overcome the limitations of stain with H & E. Studies have shown that immunohistochemical cocktails are particularly useful not only in evaluating small foci of atypical glands but also in substantiating a diagnosis of minimal adenocarcinoma [27]. This combination can significantly reduce false negative results by cytoplasmatic, nuclear or both types of reactivity in neoplastic acini [9].

AMACR in combination with basal cell markers can significantly increase diagnostic accuracy and help to avoid unnecessary rebiopsies [23]. However, AMACR expression can be heterogeneous, and interpretation of an AMACR staining requires experience. A minority of prostate cancer cases is AMACR-negative and common benign mimicker lesions of prostate cancer can display significant AMACR immunoreactivity [28, 29].

Another positive marker of malignancy is fatty acid synthase protein which is over expressed in prostate cancer cells. Studies have shown that it is a very good marker, particularly in AMACR-negative cases, which are almost always positive for fatty acid synthase protein [30, 31].

Also GOLM1, a Golgi phosphoprotein has proven helpful in the majority of AMACR-negative cases (84%), justifying its use as an additional ancillary marker for prostate cancer [32].

Clinical Management of Single Foci Prostate Cancer

Prostate cancer is usually multifocal with 2 or 3 tumors of different volumes [33]. Most of both peripheral and transitional zone tumors are less than 2 cm³ in volume and are confined to their zone of origin whereas a small fraction of tumors are 2–4 cm³ in volume, found in both zones and are confined to the prostate [34, 35].

The principal question that faces an urologist in the setting of a single focal cancer is if it could be managed as a clinical insignificant cancer or the lesion represents a bigger lesion that was not adequately sampled.

Clinical insignificant cancer is defined as a lesion that would not be life threatening if left untreated. Small, low grade lesions are deemed indolent or clinically insignificant and values up to 0.2, 0.5 and 1.3 cm³ have been proposed [36]. However the exact value of this volume threshold is unknown and it may depend on other factors such as age, comorbidities and life expectancy. It seems that the best predictor for lesions < 1 cm³ is a single focus < 3 mm with Gleason score < 7, provided an extended biopsy protocol has been used [37]. Also studies have shown that prostate volume is inversely related to prostate cancer volume and is a prognostic factor for minimal cancer [38].

A repeat prostate biopsy with an appropriate prostate biopsy scheme seems to be the best strategy to decrease the chance of missing a clinically significant cancer. If the exact site of a suspicious core is known, a repeat biopsy may focus on this area and around this area as well [39].

In a recent study from Scattoni et al. [40], 3 different rebiopsy protocols were proposed for patient suspicious for prostate cancer considering ASAP and the ratio of free prostate-specific antigen (fPSA) to total PSA (%fPSA). Specifically for patients with previous ASAP or patients with no previous ASAP and %fPSA 10%, two schemes with different combinations of 14 cores were most favorable. The optimal sampling for patients with no previous ASAP and %fPSA >10% was a scheme with a combination of 20 cores.

It is unknown if separate cores from the transitional zone are important or if it is adequate to simply include this in the parasagittal cores. Another practical issue is that prostate biopsies with end-fire transrectal ultrasoundography probes facilitate anterior apex sampling in the parasagittal cores, something that does not happen with side-fire ultrasonography probes [41, 42]. In other words, the type of probe significantly affects the overall prostate cancer detection rate, particularly in patients with a PSA...
greater than 4 ng/ml and/or non-saturation prostate biopsy [42]. This is an important issue because the apex may become the site of many missed cancers [40].

Conclusion

Prostate needle biopsy specimens with minimal foci of cancer are real diagnostic challenges for both histopathologists and urologists. Ongoing immunohistochemical developments are trying to elucidate further this difficult problem. Despite the new diagnostic armamentarium, a few cases will continue to remain doubtful and it might be better to require an appropriate rebiopsy.

References

7 Allan RW, Sanderson H, Epstein JJ: Correlation of minute (≤0.5 mm or less) focus of prostate adenocarcinoma on needle biopsy with radical prostatectomy specimen: role of prostate specific antigen density. J Urol 2003;170:370–372.
9 Epstein JJ: Diagnosis and reporting of limited adenocarcinoma of the prostate on needle biopsy. Mod Pathol 2004;17:307–315.


