Single Prostatic Cancer Foci on Prostate Biopsy

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1. Pathology of small cancer foci

1.1. Definition and terminology of small cancer foci

A small focus of adenocarcinoma in a prostate needle biopsy may be defined as a lesion involving a small fraction of a prostate needle biopsy with sufficiently convincing architectural and cytonuclear abnormalities to call for a definite diagnosis of adenocarcinoma. Due to the small size of the lesion, its infiltrative nature cannot always be judged. Although the vast majority of small cancer foci in needle biopsies represent low-grade (Gleason grade 3) carcinomas, occasionally they may consist partially or even entirely of high-grade (grade 4 or 5) carcinomas [1]. Various terminology has been used to report small foci of prostatic cancer, including focal cancer [2,3], microfocal cancer [4], and minute cancer [5]. Initially, focal cancers were defined as adenocarcinomas, lacking a high-grade (Gleason grade 4 or 5) component involving <3 mm of a single prostate core biopsy [2], but some defined focal...
cancers as carcinomas involving up to 3 mm in two adjacent prostate biopsies lacking Gleason grade 4 or 5 [3]. Boccon-Gibod reported carcinomas <5 mm in a single biopsy as microfocal cancers [4]. Others used the term minimal cancer for the prostate biopsy-detected carcinomas without a high-grade component, whereas <1 mm in size or occupying less than one ×40 field in a single prostate biopsy [5]. In general, a small focus of low-grade cancer typically may range from two highly atypical glands (rarely) to a focus with a median number of 20 glands [6], whereas small foci of high-grade cancer may have a different architecture, comprising up to approximately 2 mm of the biopsy.

Most but not all single, small prostatic cancer foci in a biopsy represent a low-grade (Gleason score 6) adenocarcinoma (Fig. 1).

1.2. Pathologic work-up

The diagnosis of a small focus of prostatic adenocarcinoma on a prostate needle biopsy begins with the pathologist’s identification of an architecturally abnormal focus of epithelial structures at rather low magnification. Its recognition requires a great deal of experience with the plethora of patterns that may be adopted by benign glands. The presence of prominent nucleoli is another important feature to make a definite diagnosis of adenocarcinoma in these small lesions. Absence of prominent nucleoli does not, however, always preclude a diagnosis of malignancy, especially not in the case of a non-acinar, that is, high-grade carcinoma [1]. An additional feature for defining a prostatic cancer is the complete absence of basal cells. Unfortunately, evidence of their absence cannot be obtained by examination of slides stained with routine hematoxylin-eosin because the basal cells are often very flat, strongly resembling periglandular fibroblasts, and the basal cell layer may be interrupted. The availability of additional staining techniques capable of selectively identifying basal cells within prostatic tissue is now of great help and its use is often required to establish the diagnosis of focal cancer [7,8]. Other important features helping to distinguish adenocarcinomas are the presence of mucin substances or crystalline structures in the glandular lumen, whereas identification of corpora amylacea virtually excludes a diagnosis of adenocarcinoma. Despite all of these features the threshold for making a definite diagnosis of adenocarcinoma remains a judgment call for the individual pathologist [9]. If a diagnosis of carcinoma cannot be made with certainty, the lesion will be reported as a focus or atypical lesion suspicious for carcinoma, also referred to as atypical small acinar proliferation (ASAP) [10]. The latter term has received wide acceptance, but its use is not encouraged [11] because it suggests that this lesion represents a disease entity on its own. Indeed, this diagnosis merely indicates that the lesion raises suspicion for the presence of adenocarcinoma but lacks sufficient criteria to make the diagnosis, reflecting the uncertainty of the pathologist to make the call. The literature reports a definite adenocarcinoma diagnosis in the repeat biopsies of about 40% of men with an initially reported lesion suspicious for adenocarcinoma [10,12].

1.3. Small foci of high-grade cancer

Mostly, high-grade cancers, defined as Gleason score 8–10 adenocarcinomas involve a large part of the prostate biopsy, but occasionally there may only be a very small focus of high-grade cancer [1]. These lesions are particularly challenging for the pathologist, in part because of the assumption that a small focus of adenocarcinoma would in general be low grade, that is, displaying glandular (acinar) formations. As a consequence they may easily be overlooked or under-reported as atypical lesion suspicious for cancer or ASAP. Because small foci of high-grade cancer in a needle biopsy may represent advanced prostate cancer, the consequences of this misjudgment may have a serious negative impact on the patient’s chance to be cured from a potentially fatal disease, due to diagnostic delay. Indeed, high-grade cancers diagnosed as a small focus in a needle biopsy may be amenable to
curative treatment because several of them are likely to be organ confined at the moment of their detection [13]. Because in some urologic practices not all men with a suspicious lesion are being rebiopsied at short term, an opportunity to provide timely curative treatment of potentially life-threatening cancer may be missed under these circumstances. For this reason pathologists are encouraged to add a comment to their report if they considered the possibility that the lesion suspicious for cancer might represent a high-grade carcinoma and to recommend early rebiopsy [1]. Alternatively, this kind of lesions could be reported as suspicious for high-grade prostate cancer.

Early repeat biopsy is required for lesions reported as suspicious for high-grade prostate cancer.

1.4. Diagnostic accuracy of small cancer foci

1.4.1. Differential diagnosis of small cancer foci

The differential diagnosis of focal cancers includes, among others, high-grade prostatic intraepithelial neoplasia (PIN), adenosis (also known as atypical adenomatous hyperplasia), (partial) atrophy, and verumontanum hyperplasia [14]. Particularly, outpouchings of benign glands, involved by dysplastic cells, constituting PIN may cause confusion because they share some features of focal cancer, such as nuclear atypia, including presence of prominent nucleoli, and architectural atypia consisting of a small aggregation of small-sized glands with rounded contours. The presence of unequivocal PIN near to a small aggregate of small-sized atypical glands generally will lead to reluctance of the pathologist to call the lesion “carcinoma.” In the latter case a diagnosis of PIN with atypical glands suspicious for carcinoma may be issued with the same clinical impact as the diagnosis “lesion suspicious for cancer” [12]. If sufficient lesional tissue is available in the biopsy, immunohistochemistry with a few markers may be helpful.

1.4.2. False-positive diagnosis

Benign prostatic glands may show a great variety in architecture and morphology, some of which may resemble adenocarcinoma glands. In the past a special variant of atrophy, postatrophic glandular hyperplasia, was most often misdiagnosed as adenocarcinoma, whereas nowadays partial atrophy probably tops the list of misdiagnosed lesions [14]. Other causes for a false-positive diagnosis may be mixing up of specimens, either at the time of the collection of the biopsies or during processing of the biopsies at the pathology laboratory or even during reporting of the biopsies. One study reported that the risk of a false-positive diagnosis is 0.4% of all biopsies [9], but growing awareness among pathologists has probably reduced its risk substantially over the course of time. Several measures can be taken to reduce the risk of a false-positive diagnosis of prostate cancer such as collegial consultation by pathologists and strict guidelines for collection and processing of biopsies.

1.4.3. False-negative diagnosis

A false-negative diagnosis of prostatic cancer may occur either as the result of a misinterpretation of a glandular formation as benign or simply the oversight of the lesion by the pathologist. Misinterpretation is uncommon, but it may occur in the presence of special variants of prostatic cancer, such as atrophic variant of prostate cancer or pseudohyperplastic prostate cancer [8,15]. More commonly, the pathologist may just overlook a small cancer focus when screening the slides. Generally, a pathologist will screen all levels of the biopsy cuttings at relatively low power, but at least one level should be screened at a higher power to avoid overlooking a lesion. One paper based on the findings in a consultation practice reported that 1.7% of potentially relevant lesions, including PIN, lesions suspicious for cancer, and focal cancers, were missed [16]. The frequency of missed diagnosis of focal cancers and suspicious lesions was about 5% of all biopsies in a population-based screening population [9]. Another study used α-methyl coenzyme A racemase (AMACR) staining as a marker for carcinoma cells (see below) on 793 biopsies previously reported as benign and an additional 9 cases (1.6%) of small cancers was revealed. All of them were small cancer foci comprising <1 mm of the core biopsy, including one Gleason score 8 carcinoma [15]. Because AMACR does not stain all carcinomas, this study may be an underestimation of false-negative diagnosis of cancer.

1.5. Ancillary techniques

It is well established that adenocarcinomas in contrast to benign glands and most benign glandular lesions, such as atrophy and PIN, entirely lack basal cells. Unfortunately, these basal cells may not be easily visualized on a standard hematoxylin and eosin-stained section because they are often very flattened and may resemble periglandular fibroblasts. In addition, the basal cell layer is interrupted in lesions such as adenosis, simple atrophy, partial atrophy, and PIN, and only an occasional basal cell may be encountered. Therefore, the availability of antibodies allowing the distinction of basal cells
from luminal cells using immunohistochemistry was a major diagnostic improvement [7,8]. These basal cell markers include high-molecular-weight cytokeratin, located in the cytoplasm of basal cells, and p63, a nuclear transcription factor, and they are now a standard tool for pathologists helping them to make a definite diagnosis of carcinoma. Another frequently used marker to distinguish tumor cells from benign glandular cells is AMACR, an enzyme involved in lipid metabolism. Its expression is strongly elevated in neoplastic cells, as in adenocarcinoma and PIN, whereas benign glands generally lack this marker [8,15]. Double immunostaining for p63 and AMACR is very helpful to establish a diagnosis of malignancy if insufficient criteria for this diagnosis are obtained on standard hematoxylin and eosin-stained sections. Nevertheless, occasionally some benign glandular lesions may lack basal cells, whereas morphologically unremarkable luminal prostate cells may express AMACR. For this reason, immunostaining findings may never be used as the sole argument of a definite diagnosis and the initial observations on hematoxylin and eosin-stained slides should always form the basis of the diagnosis of adenocarcinoma.

Because single, small prostatic cancer foci may be difficult to diagnose on routine sections stained with hematoxylin and eosin, ancillary techniques, including p63/high-molecular-weight keratin staining for basal cells and AMACR (racemase) staining for neoplastic cells are often used to establish a definite diagnosis of cancer.

2. Clinical aspects of small cancer foci

2.1. Frequency of small cancer foci

The proportion of “focal cancers” will obviously depend on the population under investigation. It is likely that in a heavily prostate-specific antigen (PSA)-tested population more “focal cancers” will be found than in a referral population. The frequency of focal carcinomas diagnosed on needle biopsies has increased by early detection using PSA testing. At the Göteborg section of the European Randomized Study of Screening for Prostate Cancer (ERSSPC), the risk of detection of a focal cancer, defined as 3-mm foci of cancer in one or a maximum of two adjacent biopsies among screened men aged 50–65 yr, was about 7.9% in the first screening round, 6.2% in the second screening round 2 yr later, and leveling off to about 6% in the fourth screening round, whereas the ratio of focal to all cancers increased from 34% to 58% in the second round [3]. In the population-based screening study among men aged 55–75 yr at the Rotterdam section of the ERSSPC the proportion of focal cancers (defined as involving <3 mm in a single biopsy, without Gleason grade 4 or 5) during the first screening round is 6% of all biopsies and about 16% of all prostatic cancers. An age-related change in frequency was also noted in this series, from 19.2% of all cancers detected in men aged 55–59 yr to 12.6% of the cancers detected in men, aged 70–74 yr (unpublished results). When the same cohort of men was screened for a second time after a screening interval of 4 yr, the proportion of focal carcinomas increased to 29% of all detected cancers [17]. At repeat screening the age relationship disappeared. Men in the highest age category have the highest percentage of focal cancers (36% vs. 33.9% in the age category 55–59 yr). These data confirm the hypothesis that focal cancers are more likely to occur in a population previously undergoing PSA testing and biopsy. Because men in the Rotterdam section of the ERSSPC undergo biopsy on the basis of an elevated PSA level (≥3 ng/ml) men in the highest age category are, in terms of percentage, more frequently biopsied as compared to men in the lowest age category, because serum PSA level is positively correlated with age.

Single, small cancer foci in a biopsy are more likely to occur in a previously PSA-tested and -biopsied population.

2.2. Findings in matched prostatectomy findings

2.2.1. Focal cancer and minimal cancer

Minimal cancer is defined as a cancer that would not be life-threatening if left untreated. Somewhat arbitrarily, cancers with a volume <0.5 ml lacking a Gleason pattern 4 or 5 are often considered minimal cancer [18,19]. Indeed, the prognosis of minimal cancer after prostatectomy is excellent [17], with a PSA failure rate of <5% after a median follow-up of 45 mo and PSA progression strongly related to positive margin status [17]. It is well-known that the correlation between amount of cancer in the biopsy and the volume and stage of cancer detected in a prostatectomy is weak [20], due to sampling problems, with cancers located in the anterior areas or in the most superior parts of a prostate less likely to be targeted by the biopsy. After a biopsy diagnosis of focal cancer, some studies reported the finding of a minimal cancer in corresponding prostatectomy specimens in about 30% [3,4], and other studies in about 70% [17,21] of the specimens. This variation in proportion of minimal cancer may be attributed to variations in carcinoma volume measurements, different definitions of focal cancer, and different
patient populations. A substantial proportion of men with a small cancer focus in their biopsies harbor clinically insignificant cancer. Unfortunately, the risk of finding a more advanced cancer is not entirely negligible in this group of men and pT3 cancers were reported in 5–6% of corresponding prostatectomies [4,5,17].

2.2.2. Small cancer foci and “vanishing cancer”
Vanishing cancer or pT0 prostate cancer refers to the absence of prostate cancer in prostatectomy specimens of men who had a previous biopsy with a positive diagnosis of prostate cancer, after ruling out the mix up of specimens or a false-positive diagnosis [22] or incomplete prostatectomy [23]. Although this is fortunately a rare event in older prostatectomy series, now percentages between 0.3% and 0.7% are reported [23–26]. It is striking that in the study of Herkommer [24] most patients with a pT0 carcinoma had only one positive biopsy. In a selected series of 105 prostatectomies after diagnosis of a focal cancer (one core positive, not more than 3 mm involvement) detected in a population-based screening setting, three “vanishing cancers” were noted [17]. The data strongly suggest that the diagnosis of small cancer foci in a biopsy increases the risk of “vanishing cancer” in the subsequent prostatectomy.

“Vanishing cancers” or pT0 cancers tend to occur more frequently when prostatectomy for a single small focus of cancer in a biopsy is performed.

2.2.3. Prediction of minimal cancer
One study analyzed to which extent the size of small cancer foci in a biopsy would be related to the volume of cancer found in the corresponding radical prostatectomy specimens [3]. They did not note a correlation with prostate tumor volume for lesions varying up to 10 mm in size in the biopsy. Noguchi et al [20] found that the combination of one positive core with a cancer <3 mm and no Gleason grade 4 or 5 is the best predictor for insignificant or minimal cancer (with 10% of their population having minimal cancer). Egevad et al [27] reported that the best predictor for a minimal cancer was a focus <2 mm if 10 needle biopsies were taken.

An additional, somewhat unexpected, finding is that prostate gland volume is inversely related to prostate cancer volume [17,28]. In line with this observation, additionally reported predictors for minimal cancer are parameters, including the prostate gland volume, such as PSA density [17,21,28]. In the study by Postma et al on a population-based screening program 95% of men with a focal cancer and PSA density <0.1 ng/g had minimal cancers in the corresponding prostatectomy. Similarly, Ochiai et al reported that the combination of a single positive core involved by <2 mm prostate cancer, a Gleason score 3 + 4 or less and a prostate gland volume >50 cc was a strong predictor for minimal cancer [28]. Finally, Warlick et al [29] showed that expectant management would not compromise curability of men >63 yr old with small lower-grade cancers, PSA level <6 ng/ml as well as PSA density <0.1 ng/ml/cm³.

Active surveillance should be considered as an alternative treatment option for men with a single, small, low-grade cancer focus in their prostate biopsy.

2.3. Small cancer foci and multifocality of prostatic cancers
Prostate mapping studies showed that about 70% of specimens containing small prostatic cancer foci (<0.5 ml) are multifocal [30]. Another study observed that multifocality of prostate cancer after a prostate biopsy diagnosis of focal cancer was observed in 72% of corresponding prostatectomy specimens [4]. This matches their finding that on extended repeat biopsy for a focal cancer the localization of the carcinoma is identified at a different site in about 50% of the repeat biopsies [31].

2.4. Diagnostic work-up of men with a small focus of cancer
Active surveillance is currently considered a feasible treatment option, particularly for older men with one small cancer focus detected in their biopsies, deferring curative treatment to the moment that the prostate cancer shows unfavorable features such as increase in grade, extent of involvement of the biopsy, or rapid PSA rise [32]. Decisions will depend on the patient’s age, presence of a comorbidity, and the ability of the man to cope with the psychological stress related to follow-up and awareness of the disease. The impossibility to exclude the presence of a significant prostate cancer on the basis of the original biopsy findings, the PSA level, or imaging findings led to the strategy of prostate saturation biopsy [21] or extended biopsy procedures. This strategy is increasingly used to increase the chance that the detected cancer indeed represents a clinically insignificant cancer. Interestingly, the same approach may also be followed in case of the finding of an atypical lesion suspicious for prostate cancer. A drawback of this approach is the exposure of the man to another large set of up to 44 biopsies, with the associated risk of complications such as infections, voiding problems, and
bleeding. In men who are on anticoagulant therapy for cardiovascular diseases, the temporary discontinuation of this therapy is also not without risk [30]. In about 30% of the men undergoing saturation biopsy after diagnosis of a focal prostatic cancer no cancer is found, which is in line with previous ex vivo studies on prostatectomy specimens. Upgrading to Gleason score 7 occurred in one series in about 20% of the cases and in 50% multiple sites were positive [31].

3. Future developments

3.1. Imaging techniques

Improvement in imaging techniques, most notably in magnetic resonance imaging (MRI) techniques, but also in ultrasound technology, may be able to visualize tumor of <0.5 ml in the peripheral zone using dynamic contrast-enhanced MRI sequences. The positive and negative predictive values for cancer detection by MRI for foci >0.5 cc were reported to be 77% and 95% [33]. Further improvements of the technique are possible and this instrument might therefore be used to determine with more certainty if patients can enroll in an active surveillance program. Coupled with site-directed biopsies additional prognostic features of the tumor, such as grade, can be established. Of course, it would be necessary to look into the cost effectiveness of such approaches as compared to immediate curative treatments such as one of the radiotherapy modalities or prostatectomy.

3.2. Novel biomarkers

A few novel markers for detection of prostate cancer are currently being developed, which may prove to be more sensitive and more specific than the current PSA testing [34]. Depending on the characteristics of these novel markers their application may lead to increased detection rates of small cancer foci. An intelligent approach is required to avoid soaring numbers of men being diagnosed with focal cancer as a consequence of these improved tests.

References


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CME questions

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1. Which of the following statements on small atypical foci in a prostate biopsy is the most correct?
   A. Small atypical foci have by definition a glandular (acinar) architecture.
   B. Small atypical foci represent by definition Gleason score 6 (3 + 3) adenocarcinomas.
   C. Small atypical foci can always be diagnosed as cancer on the basis of objective, well-established, and stringent criteria.
   D. Some small atypical foci in a biopsy can be diagnosed as cancer even if they consist of no more than two acini (glands).

2. A glandular structure with benign architecture, but cytonuclear atypia, staining positive for both p63 (basal cell marker) and α-methyl coenzyme A racemase (AMACR) most likely represents
   A. High-grade prostatic intraepithelial neoplasia.
   B. Atrophy.
   C. Carcinoma.
   D. Seminal vesicle glands.

3. Single prostatic cancer foci in a biopsy occur more frequently in
   A. Men with smaller prostate volumes as compared to men with larger prostate volumes.
   B. Men with a high prostate-specific antigen (PSA) density.
   C. Men with a previously benign prostate biopsy diagnosis.
   D. In PSA-tested men.

4. The term “vanishing cancer” relates to
   A. The absence of a cancer in a repeat biopsy although a previous biopsy in the same patient was diagnostic for cancer.
   B. The impossibility to detect cancer in a prostatectomy following a previous cancer diagnosis in a biopsy of the same patient.
C. A false-negative biopsy diagnosis of prostate cancer.
D. Disappearance of cancer in prostate biopsies following radiotherapy of men previously diagnosed with cancer.

5. The proportion of false-negative diagnosis of prostate cancer in biopsies is approximately
A. ≪0.1%.
B. <1%.
C. 1–5%.
D. 5–10%.

6. Which of the following statements on the prostatectomy findings after a diagnosis of a small prostatic cancer focus in a single biopsy holds most true?
A. In >50% of the corresponding prostatectomy specimens a multifocal cancer is detected.
B. In >20% of the corresponding prostatectomy specimens a pT3 adenocarcinoma is found.
C. In 20% of the corresponding prostatectomy specimens a minimal cancer (ie, <0.5 ml, stage pT2, no Gleason grade 4 or 5 present) is present.
D. In >10% of the corresponding prostatectomy specimens a Gleason score 8 (4 + 4) adenocarcinoma is found.