The place of prostate rebiopsy in the diagnosis of prostate cancer

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Abstract

Aim: To highlight the role of prostate rebiopsy in the diagnosis of prostate cancer (PCa) in cases with an atypical small acinar proliferation (ASAP) diagnosis on the initial biopsy. Materials and Methods: A retrospective study on 1525 patients who underwent prostate needle biopsy (PB) over a period of four years (2009–2012) was performed. For each patient the following were analyzed: age, prostate volume, digital rectal examination (DRE), serum total prostate specific antigen (tPSA), number of the cores taken. All PB were examined in HE staining and in difficult cases, immunohistochemistry (IHC) for basal cell markers was performed in order to establish a correct diagnosis. According to morphological criteria and IHC results, all PB were classified into four category: PCa, ASAP, high-grade prostate intraepithelial neoplasia (HGPIN) and benign (including normal tissue, inflammatory lesions, and prostatic atrophy). In ASAP cases, a rebiopsy was performed. Results: PCa detection on the first biopsy was 69.77%, with a 3% incidence of ASAP and 1% of HGPIN, values similar with those in the literature. After rebiopsy the overall detection rate of PCa was improved to 71.01%, with a detection rate of 41.17% on the second biopsy. Conclusions: PCa diagnosis is the result of a complex algorithm including DRE, tPSA, transrectal ultrasound (TRUS) examination and TRUS-guided prostate biopsy. TRUS-guided prostate biopsy is the key step of this algorithm; it confirms the diagnosis of PCa and must be repeated in cases with a solid clinical suspicion of PCa, whenever histopathological features are inconclusive even after IHC staining.

Keywords: prostate cancer, prostate needle biopsies, atypical small acinar proliferation, high-grade prostate intraepithelial neoplasia.

Introduction

PCa is the fifth most common type of cancer worldwide and the second most frequent one among men [1–5]. The relative survival for PCa increased from 73.4% in 1999–2001 to 83.4% in 2005–2007, due to the introduction of extended biopsy, efficient surgical and/or multimodal treatment options [6–9].

The diagnosis of PCa is a complex one; it may be suggested by the digital rectal examination (DRE), serum total prostate specific antigen (tPSA) level, transrectal ultrasound examination (TRUS), and/or clinical suffering, but prostate needle biopsy (PB) is the only examination which can confirm the clinical suspicion of prostate carcinoma and also provide data with prognostic value (Gleason grade, number of positive cores) [1, 2, 6, 8].

The systematic TRUS-guided prostate biopsy is the most recommended method to perform if there is a clinical suspicion of PCa, and it represents the current gold standard for PCa detection [6]. Most of the authors recommend 10–12 systematic, laterally directed cores on the initial biopsy [5, 6]. In patients with several negative extended PB and high risk of cancer, performing a saturation prostate biopsy protocol with up to 24 cores is suggested [10].

In daily urological practice, the negative histopathological findings or precancerous lesions are relatively frequently encountered, in spite of certain clinical suspicion (positive DRE, increased tPSA level).

In these uncertain cases, immunohistochemistry (IHC) is used for clarifying the diagnosis. Because the diagnosis of PCa is supported by lack of basal cell staining, it is critical to use the basal cell marker with the highest possible sensitivity and lowest variability to ensure that negative staining is truly due to lack of basal cells and not to technical problems [11]. The most frequently used IHC basal cell markers are high molecular weight cytokeratin and p63 [12].

If even after IHC staining a definite diagnosis of malignancy cannot be established, these PB with histological aspects suggestive of but insufficient for a cancer diagnosis are considered either atypical small acinar proliferation (ASAP) or high-grade prostate intraepithelial neoplasia (HGPIN), a precursor lesion for PCa, requiring a careful follow-up and possibly a rebiopsy [6, 10, 11, 13].

Thus, Aganovic et al. found 4.95% ASAP and 7.2% HGPIN of 515 biopsy specimens analyzed [5] while Epstein and Potter identified HGPIN in 1.5–24% and ASAP in 0.5–23% of the examined biopsies [14].

Nowadays, it is generally agreed that the rebiopsy is mandatory if the sampled specimens contain ASAP or HGPIN. In these patients with a solid clinical suspicion of malignancy, PCa can be detected on the rebiopsy in 7–22% of cases [15].

There is no consensus about the optimal interval between the biopsies, some authors recommending a six months interval between the two [16].
The aim of this retrospective study is to evaluate the role of the rebiopsy in the diagnosis of PCa, in cases diagnosed with ASAP on the initial biopsy.

Materials and Methods

Our retrospective study included the results of TRUS-guided prostate biopsies performed over a period of four years (2009–2012) in two Romanian Clinics of Urology (Iassy and Tîrgu Mureș).

The initial study group included 1525 patients, 848 cases from the Department of Urology, Tîrgu Mureș County Hospital, and 677 patients from the Department of Urology, Iassy County Hospital, who underwent TRUS-guided prostate biopsy for a clinical suspicion of PCa. The inclusion criteria were: no prior diagnosis of PCa, elevated tPSA, suspicious DRE, or both.

PB was performed according to the standard protocol (preoperative antibiotherapy, continued five to seven days after the procedure, anti-inflammatory suppositories, local, intrarectal anesthesia with Lidocaine gel before the procedure, signed informed consent). The biopsy was performed using an endocavitary ultrasound probe with 7.5 MHz frequency and 18-gauge biopsy needle with an automatic biopsy gun. The patient position was in lithotomy/left-lateral decubitus.

Decision regarding the number of cores taken, according to the Vienna nomogram, was based on the following criteria: patient age, tPSA value, DRE findings, and prostate volume [17]. In other words, the younger the patient and the bigger the prostate, the more cores were taken.

The cores were placed in separate containers labeled according to their precise location in the prostate, processed using the standard technique (fixation in neutral buffered 10% formalin and paraffin embedding), and stained with Hematoxylin–Eosin (HE).

In cases with uncertain diagnosis on HE, IHC with p63 was performed in order to identify the presence of basal cells.

Antigen retrieval was performed in citrate buffer, pH 6 for 20 minutes. The slides were incubated with p63 antibody (1:400, LabVision) for 30 minutes at room temperature.

Ultra Vision LP Detection, System HRP Polymer (LabVision) and 3,3’-diaminobenzidine (DAB) chromogen substrate were used and the slides were counterstained with Hematoxylin.

In foci highly suspicious for cancer, a negative p63 IHC stain proved the absence of the basal cell layer and supported the diagnosis of cancer (Figure 1).

![Figure 1](image-url)

**Figure 1** – *Two cases classified as PCa after IHC: (a) suspicious aspect on HE staining (×100) and (b) p63 negative on serial sections (×100); (c) cribriform aspect on HE staining (×100) and (d) p63 negative on serial section (×100).*

All the samples were assessed by two teams of pathologists, and based on strict morphological features and IHC results, all cases were classified into four categories: (1) cancer, (2) ASAP, (3) HGPIN, and (4) benign, the latter including cases with normal histology, inflammatory lesions, and prostate atrophy.

A diagnosis of PCa was established in cases in which well-known criteria of malignancy [18, 19] were met,
and in cases in which negative immunostaining for p63 confirmed the malignancy. The tumor was graded according to the Gleason grading system [20]. Specimens which presented suspicious glands with insufficient cytological or architectural atypia to establish a definitive cancer diagnosis and inconclusive IHC results were included in ASAP category. The histopathological features favoring ASAP were: distortion of glands (Figure 2a), histological artifacts, tangential cutting, inadequate features of cancer (insufficient nucleomegaly or nucleolomegaly) or only 1–3 suspicious glands at the edge of the biopsy (Figure 2b) [21–24].

Medium-sized glands with benign architecture lined by atypical cells with nuclear stratification and prominent nucleoli on the biopsy specimen were diagnosed as HGPIN [24].

The analyzed parameters for all patients at the moment of the first biopsy were: histopathological diagnosis, age, prostate volume, tPSA serum level, and the number of positive cores and Gleason score in PCa cases.

In the cases classified as ASAP a second biopsy was performed. Since there is no convention regarding the interval between the first and the second biopsy, we carried out the latter one at time intervals ranging from three months to one year. These second biopsies were histopathologically examined according to the criteria described above.

The data were analyzed statistically using SPSS Statistics software version 17.0.

## Results

### Initial biopsy

#### Types of lesions

More than two-thirds of the 1525 cases were diagnosed as PCa on the first biopsy, while the other cases were subdivided into ASAP, HGPIN, and benign. This latter category included normal tissue, inflammatory lesions, and prostate atrophy. The distribution is presented in Figure 3.

It should be mentioned that the features of ASAP or HGPIN were observed in 11 other cases but in association with a malignant proliferation, so these cases were included in the (1) cancer group.

#### Age distribution

There was little variations in the mean age of patients diagnosed with benign, ASAP, HGPIN or PCa. Results are presented in Table 1.

### Prostate volume

There were no significant differences among the four main subgroups of lesions regarding the mean value of the prostate volume (Table 1).

#### tPSA levels

tPSA levels were generally higher than normal. However, it can be noticed that benign lesions and ASAP had a mean value around 10 ng/mL whereas HGPIN and PCa had mean values over 15 ng/mL, with higher levels in PCa (Table 1).

#### Number of positive cores

The analysis of the number of positive cores revealed that the suspicious foci or the preneoplastic glands are observed on one or two cores while in PCa cases a mean number of 6.4 cores are involved (Table 1).
**Gleason score in PCa cases**

One-third of the 1053 cases with a certain diagnosis of malignancy were well-differentiated tumors (Gleason score 6), another third were moderately differentiated (Gleason score 7), and the other third represented poorly differentiated tumors with a Gleason score equal to or higher than 8 (Figure 4 and Table 2).

**Figure 4 – Distribution of PCa cases according to Gleason score.**

**Table 2 – Mean values of the main assessed parameters in Gleason subgroups**

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Age [years]</th>
<th>tPSA [ng/mL]</th>
<th>Positive biopsy cores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl 6</td>
<td>69.14</td>
<td>43.12</td>
<td>8.98</td>
</tr>
<tr>
<td>Gl 7</td>
<td>71.88</td>
<td>71.32</td>
<td>7.32</td>
</tr>
<tr>
<td>Gl 8</td>
<td>71</td>
<td>146.16</td>
<td>6.47</td>
</tr>
<tr>
<td>Gl 9</td>
<td>70.77</td>
<td>137.33</td>
<td>6.34</td>
</tr>
<tr>
<td>Gl 10</td>
<td>67.94</td>
<td>90.11</td>
<td>6.05</td>
</tr>
</tbody>
</table>

The age of patients was slightly lower in cases with well- and moderately differentiated tumors (Gleason scores 6 and 7) than in poorly differentiated cases (Gleason scores ≥8) (Table 2).

The general trend of tPSA levels was an increasing one from well- to poorly differentiated cancers, with the exception of the Gleason score 10 subgroup which did not have any statistical significance because of the low number of cases (2%).

Finally, in all cases with malignant proliferation, the number of positive cores was significant (Table 2).

**Rebiopsy**

For the 52 cases classified in ASAP category, a second biopsy became mandatory in order to clarify the diagnosis. Thirty-five patients did not present for follow-up examinations, despite telephone or written invitation. Thus, rebiopsy was performed in 17 cases.

PCa was detected on the second biopsy specimens stained with HE in seven cases. In two of these, the Gleason score was 6 (3+3) (Figure 5a), four other cases had Gleason score 7 (3+4 or 4+3) (Figure 5b) and, in the last case, a high-grade PCa, with Gleason score 9, composed of pattern 4 and 5 was observed (Figure 5c).

In the remaining 10 cases, the second biopsy specimens displayed normal histological aspect.

**Discussion**

TRUS-guided needle biopsy is currently the most reliable method to ensure accurate sampling of prostate tissue in men for harboring prostate cancer based on DRE and tPSA findings [6].

In our study, the TRUS-guided needle biopsy was performed according to the 2013 European Association of Urology Guidelines, i.e.: increased or rising PSA level, abnormal DRE findings. The first elevated PSA level should not prompt an immediate biopsy; it should be verified after a few weeks by the same assay under standardized conditions, in the same diagnostic laboratory, using the same method [2]. Our results confirm the general agreement that, on one hand, the cancer can be present in cases with low tPSA values and, on the other hand, a high PSA value does not necessarily indicate the presence of PCa.

Concerning the technique, there is no consensus about the optimal number of cores that should be taken [1, 6], the general idea being, as we mentioned above, “the younger the patient and the bigger the prostate, more cores are needed”, meaning that even more than 12 cores can be performed at the initial biopsy. According to the recommendations of Vienna nomogram, we performed between six and 24 biopsies.

Regarding the efficiency of the PCa detection rate at the first biopsy, our value of 69.77% is within the range reported in the literature [17, 25].
The ASAP incidence at the first biopsy was of 3% in our series, values similar to those in the literature, which range between 0.7–23.4% [13, 26, 27]. Our findings revealed 1% HGPIN, lower than described by other authors (2.7–14.2%) [28].

A question arises in connection to the definition of ASAP and its clinical significance.

Bostwick et al. used the term “atypical small acinar proliferation of uncertain significance” for the first time to name a lesion that is not characterized by distinctive morphologic criteria [29].

ASAP can be assessed in many cases: distortion of acini, atrophic features, insufficient nucleomegaly or nucleolomegaly, small acini with foamy cytoplasm, histological artefacts, tangential cutting, small foci present at biopsy edge, loss of focus in deeper level, and inconclusive immunohistochemical findings [21–24].

In other words, the architectural and cytological findings in ASAP are insufficient for final diagnosis, so it is recognized as a diagnostic category, not a specific histological diagnosis [8].

In difficult cases, IHC can help, but the final diagnosis must always be based on the morphological aspect, IHC stains being used only for confirmation.

In cases in which ASAP or extensive HGPIN are present, besides the rising or/and persistently high tPSA levels and suspicious DRE, the recommendations of 2013 European Association of Urology Guidelines are for repeating prostate biopsy [2, 25].

In this respect, the next step in our study in cases classified as ASAP was rebiopsy.

Bostwick and Meiers’ recommendations in line with the findings of Iczkowski et al. for the rebiopsy are performing them in the entire prostate; by sampling only the side or sextant site initially diagnosed as ASAP may lead to missed cancer in 39% of patients [16, 23].

The predictive value of ASAP and/or HGPIN concerning the risk of cancer in the second biopsy has wide ranges, between 34% and 60% of the cases with ASAP and up to 29.5% of the cases with HGPIN depending on the authors and the number of cores involved, the rest representing reactive lesions (most often atrophic acini) [23, 30–37].

In our series, the PCa detection rate at the second biopsy was of 41.17%, value in concordance with the above-mentioned literature data.

Finally, the overall detection rate of prostate malignancy, going through the complete diagnosis algorithm, was of 71.01% in our series.

Our study has some limitations because only 17 patients attended rebiopsy, although we had 52 cases of ASAP.

Used prudently ASAP is a valid diagnostic category, and the cooperation between the pathologist and clinician has a decisive role in the impact of ASAP and in patient care.

🔍 Conclusions

PCa diagnosis is the result of a complex algorithm including DRE, tPSA, TRUS and TRUS-guided prostate biopsy. TRUS-guided prostate biopsy is the key step of this algorithm because it is the only examination which confirms the diagnosis of PCa. ASAP in a biopsy specimen is a significant predictor for PCa. Rebiopsy is indicated in these cases especially when there is a solid clinical suspicion of PCa.

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Author contribution

All authors had equal contribution in realizing this study and preparing and writing this article.

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