Prostate Cancer Detection Rate and the Importance of Premalignant Lesion in Rebiopsy

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Objective: Establish the prostate cancer (PCa) detection rate and the premalignant lesion incidence, as well as their importance in cancer detection at the first rebiopsy. Materials and methods: In the period 2006-2008, at the CCUS Urology Clinic, there were 585 prostate biopsies performed in 515 patients. 12% of the patients underwent the first biopsy due to premalignant lesion findings. The main characteristics of the patients – age, prostate specific antigen (PSAt)-total and PSA ratio (PSAr), the number of needle biopsies, Gleason score and the role of premalignant lesions in diagnosis of PCa at the first rebiopsy were processed retrospectively. Results: Primarily detected PCa amounted to 32.4% (167/515), while the re-biopsy showed the detection rate of 35.7% (25/70). No statistically significant age or PSAt and PSAr difference was observed, while there was, however, a difference in the number of biopsy samples, 11 (6-18) vs. 12 (8-20) and in the Gleason score (6.5 vs. 5.9) among the observed groups (p< 0.05). Atypical small acinar proliferation (ASAP) and high grade intra epithelial neoplasia (HGPIN), were found in 4.95% and 7.2% of the cases, while the ASAP + HGPIN combination was found in 1.5% of the cases. The PCa detection rate at the first rebiopsy in patients with ASAP, HGPIN and ASAP + HGPIN lesions was 50%, 23.6% and 50%, respectively. The ANOVA test showed a statistically significant shorter time period for rebiopsy in ASAP+HGPIN patients than that of patients with ASAP and HGPIN lesions. Conclusion: A repeated positive biopsy establishes PCa in patients with lower PSAt values and the Gleason score, which is followed by an increased number of biopsy samples. ASAP and ASAP + HGPIN lesions carry a higher specificity of 75% and 91%, respectively, while the PPV in prostate cancer detection for HGPIN is low (24%). Key words: Prostate cancer, premalignant lesion, prostate rebiopsy

1. INTRODUCTION
Prostate cancer (PCa) is among the most frequent malignancies in male population with an increased risk of developing the disease over 50 years of age. Prostate cancer accounts for 14-17% and in some cases for even 21% of the total male cancer rate (1). Since the introduction of prostate specific antigen (PSA), trans rectal ultrasound (TRUS) guided biopsy of the prostate has become one of the most frequent urologic procedures. The post-biopsy diagnosis often shows only high grade intra epithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) in a biopsy specimen (2). HGPIN is related to architecturally benign prostatic acini and ducts covered by atypical cells. These atypical cells share morphological, histochemical and genetic changes with cancer (3). HGPIN is present in 1.5-24% of needle biopsy cases. ASAP, standing for the presence of suspect glands with insufficient cytological or architectural atypicalities with regard to definitive cancer diagnosing, is present in 0.5-23% of biopsies (4). Cancer detection at repeated biopsies amounts to approximately 30% and can even be as high as 75% when more of three fragments contain lesions as at the first biopsy (5). In cases when these changes (ASAP, HGPIN, ASAP+HGPIN) are verified through the primary biopsy, rebiopsy is strongly recommended, particularly extended biopsy if the first one was sextant biopsy. Although prostate cancer is usually multi focal, the use of extended biopsy techniques has resulted in an increased detection of uni focal and lesser cancers (6). In addition, they provide more reliable results with the cancer grade prediction possibility, thus facilitating the planned treatment. Therefore, schemes with 10 or 12 biopsy samples should be routinely used as early as in the initial evaluation of patients with suspect cancer prostate (7). It is known that adenocarcinoma diagnosis at repeated biopsies is not depen-
dent on the level of the serum PSA, even in patients with little or no increase in PSAt. These patients face the risk of 50% in terms of the adenocarcinoma presence at repeated biopsies performed within three years (8).

The aim of this study is to establish the prostate cancer detection rate at the primary and repeated trans rectal ultrasound-guided prostate biopsies, to identify the main differences between primarily and rebiopsy detected prostate cancer, as well as to establish the premalignant lesion incidence and its role in cancer detection at the first rebiopsy.

2. PATIENTS AND METHODOLOGY

In the three-year period (2006-2008) the CCUS Urological Clinic had 585 trans rectal ultrasound-guided prostate biopsies for the purpose of cancer detection. The introduction of trans rectal guided biopsy was initially based on taking six samples only, soon moving to the sextant extended peripheral biopsy scheme, then to the saturation biopsy and to cores sampling according to the Vienna nomogram. The number of biopsy samples increased with repeated prostate biopsies. All the patients underwent biopsy according to the standard protocol (preoperative antibiotic protection, NSAID suppository and local 2% lidocaine gel anaesthesia). Rebiopsy indications were basically findings of premalignant lesions, suspect digital rectal examination (DRE) or increased PSA over a short period (3-6 months). All the samples were examined by the same clinical pathologist.

3. RESULTS

The total of 515 patients were included in the analysis, with 585 biopsies; 70 patients had a repeated biopsy (12%), primarily due to premalignant lesion findings (ASAP, HGPIN) at the first biopsy. The total cancer detection for the observed group is 32.8% (192/585). The first biopsy detected 32.4% of prostate cancer (167/515), while the rebiopsy showed a detection rate of 35.7% (25/70). No statistically significant cancer detection rate increase was observed at the first rebiopsy (chi² 0.17, p 0.68). ASAP and HGPIN as premalignant lesions were detected in 12.1% (71/585) and 16.6% (97/585) of the cases, respectively. However, examination of pathohistologic findings established a high association of prostate cancer and premalignant lesions. Thus, ASAP and HGPIN are present with prostate cancer in 21.9% (42/192) and 28.5% (55/192) respectively, while the ASAP and HGPIN combination in 6.8% (13/192) of the cases. Therefore, isolated ASAP and HGPIN premalignant lesions without confirmed cancer were observed in 4.95% (29/585) and 7.2% (42/585) of the cases within the entire observed group. The ASAP and HGPIN combination was observed in 1.5% of the cases (9/585). Premalignant lesions in total are observed in 13.7% (80/585) of the cases. Finally, the total number of benign diagnoses (benign prostatic hyperplasia-BPH, atrophy or prostatitis) were found in 53.5% of the cases (313/585).

Table 1. Total biopsy findings in 585 biopsies. PCa–prostate carcinoma, ASAP- Atypical small acinar proliferation, HGPIN-high grade intraepithelial neoplasia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No (%) patients</th>
<th>Age Mean, median, range</th>
<th>No biopsy cores Mean, median, range</th>
<th>PSA (ng/ml) Mean, median, range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCa</td>
<td>192 (32.8%)</td>
<td>65.7 (66-52-79)</td>
<td>11.2 (12-6-20)</td>
<td>13.2 (8-1.5-100)</td>
</tr>
<tr>
<td>ASAP</td>
<td>29 (4.95%)</td>
<td>65.2 (67-43-79)</td>
<td>9.9 (12-6-14)</td>
<td>10 (6.7-16.3-46)</td>
</tr>
<tr>
<td>HGPIN</td>
<td>42 (7.2%)</td>
<td>66.3 (69-53-77)</td>
<td>11.5 (12-6-16)</td>
<td>8.9 (7.5-1.1-30.6)</td>
</tr>
<tr>
<td>ASAP +HGPIN</td>
<td>9 (1.5%)</td>
<td>69.1 (68-62-77)</td>
<td>11.7 (12-6-18)</td>
<td>8.1 (8.2-3.2-12.4)</td>
</tr>
<tr>
<td>Benign</td>
<td>313 (53.5%)</td>
<td>65.5 (66-40-79)</td>
<td>10.9 (12-6-18)</td>
<td>9.2 (8.8-1.2-70)</td>
</tr>
</tbody>
</table>

Table 2. Relationship among the main variables in patients with primary and rebiopsy diagnosed prostate cancer. PSA t: r prostate specific antigen ( PSA-total and ratio)

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>Mean (SD)</th>
<th>PSA t (ng/ml)</th>
<th>PSA r (ng/ml)</th>
<th>No biopsy cores Mean (SD)</th>
<th>Gleason score Mean (SD), range</th>
</tr>
</thead>
<tbody>
<tr>
<td>First biopsy PCa (No167)</td>
<td>68.7 (7)</td>
<td>62-79</td>
<td>13.6 (14)</td>
<td>1.16-100</td>
<td>0.14 (0.11)</td>
</tr>
<tr>
<td>Rebiopsy PCa (No25)</td>
<td>69.5 (5.6)</td>
<td>47-79</td>
<td>10.5 (10.45)</td>
<td>2.6-48</td>
<td>0.15 (0.16)</td>
</tr>
<tr>
<td>T test (p)</td>
<td>0.92</td>
<td>0.28</td>
<td>0.85</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 3. Gleason score differences in primary and rebiopsy diagnosed prostate cancer

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>≤6 No (%)</th>
<th>7 No (%)</th>
<th>4+3 No (%)</th>
<th>&gt;8 No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First biopsy Ca No167</td>
<td>78 (46.7%)</td>
<td>53 (31.7%)</td>
<td>18 (33.9%)</td>
<td>34 (20.6%)</td>
</tr>
<tr>
<td>Rebiopsy Ca No25</td>
<td>18 (72%)</td>
<td>4 (16%)</td>
<td>/</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Chi² (p)</td>
<td>4.6 (&lt;0.03)</td>
<td>1.9 (0.17)</td>
<td>/</td>
<td>0.6 (0.46)</td>
</tr>
</tbody>
</table>
Regression analysis of the group of patients with primarily detected PCa shows a positive correlation between PSA and the Gleason score ($r=0.35$, $p<0.000$), while a correlation between the Gleason score and PSA$\alpha$ and the Gleason score and age is not observed ($p=0.13$ and $p=0.6$, respectively). However, there is a positive correlation between the Gleason score and age in rebiopsy confirmed prostate cancer ($r=0.48$, $p=0.017$), while there is no observed correlation between the Gleason score and PSA$\alpha$ ($p=0.08$) or the Gleason score and PSA$\alpha$$\alpha$ ($p=0.6$).

Out of 29 ASAP cases, 82.8% (24/29) of them were subject to prostate rebiopsy, with the PCA detection rate of 50% (12/24). The HGPIN patients were subject to rebiopsy in 90% of the cases (38/42), with the cancer detection rate of 23.6% (9/38). Out of 9 ASAP + HGPIN cases, 89% of the patients (8/9) were subject to rebiopsy, with the PCA detection rate of 50%. The main features of rebiopsy diagnoses and the time period until biopsy of the observed groups are given in Table 4.

The mean time until rebiopsy in patients with ASAP lesions was 237.4 ± 106 days (90-414), while the mean rebiopsy time for HGPIN and ASAP + HGPIN lesions was 328.4 ± 10138 (90-644) and 164 ± 57 (88-274) days, respectively. The ANOVA test showed there was a significantly shorter rebiopsy period in patients with ASAP + HGPIN findings in relation to patients with other premalignant lesions ($F=8.2$, $p=0.0006$), but the rebiopsy time in patients with diagnosed PCA shows no differences among premalignant lesion groups ($F=2.1$, $p=0.14$).

Furthermore, the relationship between the values of PSA and age was analysed within the subgroups, in accordance with the type of premalignant lesion in rebiopsy findings (Table 5). The ANOVA test showed no significant difference in age and PSA among rebiopsy cases depending on the type of premalignant lesion, nor a difference in age and PSA in patients with rebiopsy diagnosed PCA. Upon rebiopsies, the further 32.9% (23/70) of the patients remained for following rebiopsies, while benign findings in 31.4% (22/70) of the patients included close monitoring and possible rebiopsies depending on the PSA kinetics and DRE.

With regard to an analysis of the relationship between age, PSA, PSA$\alpha$ and the number of biopsy samples among the subgroups with rebiopsy diagnosed PCa, repeated premalignant lesions and benign findings, a statistically significant difference is observed with regard to age, the mean PSA value and the number of biopsy samples (Table 6).

The 2x2 table test established the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of premalignant lesions in terms of PCa detection prediction at rebiopsy (Table 7). There is a high specificity for ASAP and ASAP+HGPIN lesions of 74% and 91%, while the positive predictive value in prostate cancer detection for HGPIN amounts to 24%.

PSA in rebiopsy diagnosed cancer up to 4 ng/ml was found in 3 (12%) patients, there were 15 patients (60%) with 4-10, there were 5 patients in the range of 10-20 PSA (20%), and 2 patients (8%) with over 20 (up to 48 ng/ml). The chi$^2$ test showed no statistically significant difference in percentage with regard to the range of PSA at the first and second detection.
4. DISCUSSION
The prostate biopsy is indicated in all males with increased PSA at or sus- pect DRE prostate findings, or a combination of the two (9). The prostate bi- opsy is best performed under the TRUS control. The optimum solution is to systematically take samples from the prostate periphery, not only from the suspect areas (10). There was no statisti- cally significant increase in the cancer detection rate at the first biopsy. It should be noted that, in early 2006, there were standard sextant biopsies performed at our Clinic, with a soon shift to extended schemes with 10-12 prostate biopsy samples and biopsy ac- cording to the Vienna nomogram (11), all the way to saturation biopsy (20 samples where, on the basis of PSA and DRE findings and premalignant lesions, there were a considerable suspicion of prostate cancer, which was not con- firmed through biopsy) (12). In the initial period, the rate of cancer detected through sextant biopsy was 20.95% (13). By means of introducing the extended schemes with 10-12 and up to 20 biopsy samples, the rate increased by 11.4%.

Examination of pathohistologic findings revealed a high association of prostate cancer and premalignant lesions. Thus, ASAP and HGPIN are present with prostate cancer in 21.9% and 28.5% respectively, while the combi- nation of ASAP and HGPIN in 6.8% of the cases. Isolated premalignant les- ions are present in the total of 13.7% of the cases. ASAP and HGPIN, with- out diagnosed cancer in the entire ob- served group, was established in 4.95% and 7.2% of the cases, respectively. The ASAP and HGPIN combination is found in 1.5% of the cases. According to the results presented by Leite et al. (14), ASAP is diagnosed in 1.8%, HGPIN in 10%, while ASAP and HGPIN in 2.8% of the cases. At biopsies, cancer was present together with ASAP in 43.8% of the cases, while in 41.4% of the prosta- tite cancer cases it was present together with ASAP+HGPIN. The cancer detect- tion percentage might have been higher the study used α-methylacyl-CoA racemase (AMACR). This is an enzyme involved in peroxisomal oxidation of dietary branched-chain fatty acids and C27-bile acid intermediates. It is pres- ent in large quantities in most prostate cancers. Since AMACR is also present with HGPIN cancer detection, it is not of great help in the case of this lesion with AMACR (15). The total of 13.2% of the cancers coexisted with HGPIN. Out of 29 ASAP cases, 82.8% of them were subject to prostate biopsy, with the PCA detection rate of 50%. HGPIN patients were subjected to biopsy in 90% of the cases, with the cancer de- tection rate of 23.6%. Out of 9 ASAP +HGPIN cases, 89% of the patients were subject to biopsy, with the PCA detection rate of 50%. These results ap- proximate the results of the American Urological Association, where in 98% of the patients rebiopsy is mandatory with ASAP diagnosis (16). In addition, there is the research by Fadare et al. re- porting the ASAP incidence in 2.8% of the cases, rebiopsy in 67% of the cases, and adenocarcinoma diagnosis in 38% of the cases (17). Leite et al. report that as much as 38.5% of the patients with ASAP diagnosis were not subjected to rebiopsy (14). The practice at our Clinic, therefore, is in line with the main prin- ciples relating to the need of perform- ing biopsy. Moreover, a substantially shorter biopsy period is observed in patients with premalignant ASAP les- ions in comparison with HGPIN.

There is a positive correlation between the Gleason score and age in biopsies diagnosed prostate cancer, while there is no observed correlation between the Gleason score and PSA, or the Gleason score and PSAr. There- fore, the rebiopsy level of the Gleason score shows a positive correlation with age, involving elderly patients with a lower Gleason score (and presumably less invasive PCa as well). Upon rebi- opsies, premalignant lesions were re- peated in 32.9% of the patients, deter- mined for further biopsies. ASAP and ASAP+HGPIN lesions showed a high specificity of 74% and 91%, while the positive predictive value in prostate cancer detection for ASAP is 24%.

5. CONCLUSION
Through the use of extended biopsy sampling, the HGPIN diagnosis is less associated with the risk of developing cancer prostate. Such patients are rec- ommended to undergo biopsies once a year, depending on their clinical picture, DRE findings and PSA kinetics determination, and the absence of clinical can- cer indicators raises the issue of whether rebiopsy is justified at all. The presence of ASAP and ASAP+HGPIN combina- tion indicates the high risk of false neg- ative biopsies, so that rebiopsies in cases where these premalignant lesions are found are indicated for at least 6 months. In addition, the use of α-methylacyl-CoA racemase (AMACR) is highly recom- mended in order to convert atypical di- agnoses into cancer in cases with highly suspected malignant lesions.

REFERENCES