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PROBLEMS AND OPPORTUNITIES OF EARLY DIAGNOSIS OF LOCALIZED PROSTATE CANCER

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ABSTRACT

Introduction. In most developed countries, prostate cancer takes a leading place among oncological diseases. In different countries frequency of early diagnosis varies. Unfortunately, nowadays in Uzbekistan the frequency of diagnosis of prostate cancer in the late stages prevails over the early.

Material and methods. We analyzed the results of 245 primary multifocal prostate core biopsies performed to patients who were examined in RSSPMCU in the period 2016-2019. Patients were divided into two groups: the first group included 203 patients who underwent primary prostate core biopsy; second group - 42 patients, whom performed mp-MRI and evaluated the risk by classification PI-RADS v2 before biopsy.

The procedure was performed TRUS guided, under local anesthesia, using lidocaine gel (Cathejel)+periprostatic nerve block with lidocaine). Material for the study was taken with a biopsy gun BIP-high speed multi, needle 18-20 g x 20 cm. from 10-12 areas of the prostate gland, with coverage of the peripheral and apical zones. In 42 patients of the second group, the same method was used to collect cores from 10-12 sites and, in addition from 2 to 6 cores were shot precisely from the zone of interest revealed by mp-MRI.

Results. Among 1st group of 203 primary biopsies in 145 (71.4%) patients was verified adenocarcinoma. In patient with PSA level up to 30 ng/ml indicator was 58.6%. In the 2nd group in patients with PSA up to 30 ng/ml cancer detecting indicator was 75%.

Conclusions. In the early diagnosis of prostate cancer in patients who have PSA level up to 30 ng/ml, without any suspicious according to DRE and TRUS of prostate, mp-MRI should be added to standard diagnostic scheme before primary biopsy.

Key words: Prostate Cancer, biopsy, mp-MRI, early diagnosis, cancer detecting rate, target.

Introduction. Prostate cancer (CaP) developing from the epithelium of its alveolar-cell elements is one of the most common malignant neoplasms in men in developed countries of the world and the second in a series of mortality in this population [1].

In most developed countries, prostate cancer takes a leading place among oncological diseases [2,3]. Every year, 1 million 100 thousand new cases of prostate cancer are registered in the world [4]. In Japan, 25% of the population is 75 years of age or older, i.e. almost in a third of patients prostate cancer is detected in old age [5]. In 1980 in Denmark 1297 patients with prostate cancer were registered, by 2012 the incidence rate increased several times - 4315 patients and mortality remains high, especially among people over 80 years of age [6].

In Belarus, about 60% of newly diagnosed cases of the disease are diagnosed in the late (III-IV) stages, in North America and Western Europe, this indicator is from 15 to 35% [7].
In Kazakhstan, the percentage of diagnosed patients with initial stages of prostate cancer is 42.7%, in Uzbekistan 29.2%, and rather lower in Kyrgyzstan 27.8% [8]. It is considered that the proportion of patients with stage I-II tumor process characterizes the timeliness of diagnosis, III-IV stages, respectively, about the late diagnosis.

High mortality from prostate cancer is due to the contingent of patients who were diagnosed in the late stages. It was found that up to 40% of men aged 60-70 years have microscopic prostate cancer that does not manifest certain symptoms. Due to the nature of the clinical course, the tumor may not affect the patient’s health for many years, or, if early symptoms appear, they are irritative and/or obstructive, which is not specific to prostate cancer. In this regard, in the success of treatment of many patients, early diagnosis of localized prostate cancer is of great importance, which is carried out exclusively by a biopsy of prostate.

In this regard, a prostate biopsy remains one of the most common urological procedure. In the United States, more than 500,000 prostate biopsies are performed annually [9]. Transperineal access was historically described first and has become the preferred method in several European and Asian countries [10]. In the USA and in many other countries of the world, at present, it is used less often than transrectal access [11]. The reason for this is that transperineal biopsy of the prostate is perceived as a more invasive and technically complex procedure [12].

A meta-analysis of literature data concerning of biopsies’ results showed that, in order to improve the diagnosis, the collection of material from 10-12 zones of the prostate by transrectal access under the control of TRUS is sufficient for primary and rebiopsies. These biopsy schemes should be carefully concentrate to the lateral and apical parts of the prostate gland in order to maximally cover the peripheral zone, as well as if there are suspicious areas [13].

It should be noted that timely biopsy plays a key role in the early diagnosis of localized prostate cancer. But, a high percentage of truly negative and false negative results of the primary biopsy, as well as a number of undesirable complications associated with the specificity of the procedure, raise the question of the need for researchers to develop optimal indications for this invasive procedure.

In this regard, the purpose of this study was to improve the results of early diagnosis of prostate cancer by improving the indications for performing a prostate biopsy.

MATERIAL AND METHODS

We analyzed the results of 245 primary multifocal prostate core biopsies performed to patients who were examined in RSSPMCU in the period 2016-2019. Patients were divided into two groups based on the data of their preliminary clinical examination. The first group included 203 patients who underwent primary prostate biopsy based on the detected elevated levels of serum total
prostatic specific antigen (PSA) and/or the presence of a suspicious lesion in the prostate according to digital rectal examination (DRE) and transrectal ultrasound examination (TRUS) of the prostate.

TRUS was performed in all patients using a rectal intracavitary probe with a frequency of 7.5 MHz (C9-4v, 42Hz, dynamic range) on a Philips Affinity 50G apparatus (Netherlands). Previously, patients were underwent a cleansing enema. Using this method, the sizes of the prostate were assessed - anteroposterior, transversal and sagittal, integrity and clarity of the capsule, and the volume in ml was calculated. In case of violation of the echostructure of the gland tissue, its nature and size were determined.

The age of the patients was 68.94 ± 0.54 (years), the volume of the prostate gland was 72.69 ± 2.13 (cc), the total serum PSA level was 61.95 ± 8.78 (ng/ml). The second group included 42 patients whom, in addition to the indicated studies, performed a multiparametric MRI of the prostate by using a Philips Ingenia 1.5 Tesla apparatus with evaluating with PI-RADS V2-v2 (Prostate imaging reporting and data system) scale before the biopsy procedure, i.e. determining the risk of detecting prostate cancer [14,15]. The age of this group of patients was 68.16 ± 1.32 years, PSA level 66.4 ± 18.56ng/ml, gland volume 67.21 ± 4.59 cc.

Preparing the patients for biopsy included: stopping intake antiplatelet agents 7 days before the procedure, starting ciprofloxacin 500 mg x 2 times a day before the procedure, and conducting cleansing enema for the patient 1 hour before the procedure.

The procedure was performed TRUS guided, under local anesthesia, using lidocaine gel (Cathejel) + periprostatic nerve block with lidocaine. Material for the study was taken with a biopsy gun BIP-high speed multi, needle 18-20 g x 20 cm. from 10-12 areas of the prostate gland, with coverage of the peripheral and apical zones. In 42 patients of the second group, the same method was used to collect cores from 10-12 sites and, in addition from 2 to 6 cores were shot precisely from the zone of interest revealed by mpMRI.

Results. Among 1st group of 203 primary biopsies in 145 (71.4%) patients was verified adenocarcinoma, in which the gland volume was 74.08 ± 2.12 (cc), in 58 (28.6%) - BPH adenomatous variant, volume 68.73 ± 2.14 (cubic cm)

<table>
<thead>
<tr>
<th>Results of biopsies</th>
<th>Number of patients, n (%)</th>
<th>Average prostate volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>145 (71.4)</td>
<td>74.08</td>
</tr>
</tbody>
</table>

Table 1.
We analyzed the biopsy results based on the age of the patients. According to our data, the detection rate of adenocarcinoma was higher at the age of 60 and more, Figure 1.

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**Figure 1.**

*Results of prostate biopsy taking into account the age of patients, n=203.*

In order to determine the role of DRE and TRUS in the detection of the CaP, we performed the following analysis. According to DRE a suspicious area in the gland was detected in 6 (3%) patients before the biopsy; at the same time, the remaining 197 (97%) patients did not reveal any areas suspicious of malignancy. According to the results of a biopsy of 6 patients, 4 (66.7%) had prostate adenocarcinoma, and 2 (33.3%) had BPH. In 141 (71.6%) of the 197 patients who underwent a biopsy only because of elevated PSA level, but there were no suspicious areas according to the data of DRE, adenocarcinoma was detected, Figure 2.
The results of core biopsy based on DRE data, n=203

Of the 203 patients examined, in 12 (6%) according to TRUS in the prostate gland a hypoechoic lesion was detected, in 191 (94%) the enlargement of the prostate gland was regarded as due to BPH. The biopsy result showed that both DRE and TRUS play a complementary role in the diagnosis of prostate cancer, but their diagnostic value is lower than the definition of total serum PSA (figure 3).

The results of core biopsy based on TRUS data (TRUS), n = 203

The results of a morphological study of prostate biopsy samples, depending on the level of total PSA, showed that the higher the level of total PSA, the higher the detection rate of cancer, Table 5. Therefore, our analysis clearly demonstrated that with PSA level up to 10 ng/ml, a negative result
was at 88.8%, with the level up to 20 ng/ml (n=69), this indicator amounted to 53.6%. There were 116 patients with a PSA level below 30 ng/ml, a negative result was 58 (41.4%), Table 2.

### Table 2

**Distribution of primary prostate biopsy results depending on the level of total PSA (n = 203)**

<table>
<thead>
<tr>
<th>PSA level, (ng / ml)</th>
<th>Number of patients, n</th>
<th>Number of identified adenocarcinomas (%)</th>
<th>Number of patients with G1-2 (% of identified)</th>
<th>Number of patients with G3-4 (% of identified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 10</td>
<td>17</td>
<td>2 (11.2)</td>
<td>-</td>
<td>2 (100)</td>
</tr>
<tr>
<td>11-20</td>
<td>52</td>
<td>30 (57.7)</td>
<td>13 (43.3)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>21-30</td>
<td>47</td>
<td>36 (76.6)</td>
<td>7 (19.4)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>31-40</td>
<td>41</td>
<td>37 (90.2)</td>
<td>7 (18.9)</td>
<td>30 (81.1)</td>
</tr>
<tr>
<td>41-50</td>
<td>25</td>
<td>22 (88.0)</td>
<td>2 (9.1)</td>
<td>20 (90.1)</td>
</tr>
<tr>
<td>51-60</td>
<td>11</td>
<td>9 (81.8)</td>
<td>1 (11.1)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>61-100</td>
<td>10</td>
<td>9 (90.0)</td>
<td>-</td>
<td>9 (100)</td>
</tr>
</tbody>
</table>

Considering the rather high negative result of the primary biopsy, as well as to determine the rational choice for determining the indications for biopsy, to 42 patients who had an elevated level of serum total PSA while their appeal, we performed prostate multiparametric MRI. As a result, patients were distributed based on a certain risk of detecting cancer according to PI-RADS V2-v2 subsequently performed a standard transrectal multifocal biopsy of 10-12 cores and a targeted (targeted) biopsy from the zones of interest in the amount of 2-6 cores, Table 3.

### Table 3.

**Results of primary transrectal prostate biopsies performed after mp-MRI data, n=42**

<table>
<thead>
<tr>
<th>PI-RADS v2</th>
<th>Amount, (%)</th>
<th>PSA (M±m)</th>
<th>Volume of prostate</th>
<th>Age</th>
<th>Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5(11.9)</td>
<td>21.5±3.46</td>
<td>49.4±8.72</td>
<td>62.8±2.39</td>
<td>1(20)</td>
</tr>
<tr>
<td>3</td>
<td>14(33.3)</td>
<td>20.96±2.98</td>
<td>88.28±9.71</td>
<td>64.4±1.57</td>
<td>3(21)</td>
</tr>
<tr>
<td>4</td>
<td>7(16.7)</td>
<td>48.4±15.9</td>
<td>55.5±6.19</td>
<td>68.14±3.04</td>
<td>6(86)</td>
</tr>
<tr>
<td>5</td>
<td>16(38.1)</td>
<td>128.12±44.67</td>
<td>59.4±5.13</td>
<td>73.1±2.36</td>
<td>14(87.5)</td>
</tr>
<tr>
<td>Total</td>
<td>42(100)</td>
<td>66.4±18.56</td>
<td>67.21±4.59</td>
<td>68.16±1.32</td>
<td>24(57)</td>
</tr>
</tbody>
</table>
Patient 58y.o. In the right lobe a suspicious lesion. PIRADS 3.

Patient 64y.o, PI-RADS 5. There is a suspicious lesion in both lobes

This analysis showed that the detectibility of prostate cancer at a risk of PI-RADS V2 of 2–3 grade was significantly lower than PI-RADS V2 4–5g., as we expected. But we were interested in the results of a group of patients in whom the PSA level was below 30 ng/ml without any suspicious areas according to DRE and TRUS of the prostate, as especially in this group of patients in a primary biopsy without mRIdetection rate of prostate cancer was 58.6% out of 116 patients, table 4.
Table 4
Distribution of patients with a PSA level of less than 30 ng/ml depending on the degree of risk according to PI-RADS, n =30

<table>
<thead>
<tr>
<th>PI-RADS v2</th>
<th>Amount, (%)</th>
<th>PSA. (M±m)</th>
<th>Volume of prostate</th>
<th>Age</th>
<th>Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>5(16,7)</td>
<td>21,5±3,46</td>
<td>49.4±8,72</td>
<td>62.8±2.39</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>13(43,3)</td>
<td>18,59±1,96</td>
<td>91,38±9,94</td>
<td>63,7±1,50</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>3(10,0)</td>
<td>12,9±3,2</td>
<td>58,0±14,36</td>
<td>69,74±5.7</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>9(30,0)</td>
<td>19,2±2,81</td>
<td>56,0±6,5</td>
<td>68,5±2.92</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>30(100)</td>
<td>18,7±1,36</td>
<td>70,43±6,02</td>
<td>65,6±1.31</td>
</tr>
</tbody>
</table>

As it can be seen from the table 7, in patients with a total PSA level up to 30 ng/ml and with a high risk of detecting cancer according to PI-RADS 4g, the detection rate of prostate cancer was 67%, among PI-RADS 5g - 78.0%, i.e of 12 patients with PI-RADS 4-5g, in 9 (75.0%) patients detected PCa. Therefore, we can conclude that among patients whose early diagnosis of a localized form of prostate cancer is difficult, cancer detecting rate indicator increased from 58.6%(in patients without MRI) to 75% (in patients who underwent preoperatively mp-MRI) due to targeted biopsy.

DISCUSSION.
A key event in the laboratory differential diagnosis of prostate diseases in 70s and 80s of 20th century was the detection of the PSA and the determination of its role in the recognition of prostate cancer [16-18]. Twenty years later, by researchers determined a very high differential diagnostic value of the PSA in detection CaP. So, according to the results of numerous studies on the information content of PSA in the early diagnosis of prostate cancer, according to meta-analyzes, it was found that the sensitivity, specificity and positive predictive value of PSA are, respectively, 72.1%, 93.2% and 25.1% [19,20].

Several studies have shown that the introduction of the PSA marker as a screening technique doubled the detection of prostate cancer in the early stages of the disease (T1-T2), while DRE revealed prostate cancer in only 30% of histologically confirmed cases [21]. Of the three methods accepted in the literature as the “gold standard” for prostate examinations (determination of PSA, DRE, and TRUS of prostate) [22], the level of PSA has the least false negative results.

In our study, we also evaluated the informational content of DRE, TRUS of prostate and PSA level in determining biopsy indications for early diagnosis of a localized form of prostate cancer and made sure that all these methods have their value, but a greater extent - PSA level, and we confirmed the data of literature.
Every year, the development of new diagnostic methods for prostate cancer occurs. The use of standard diagnostic methods for the diagnosis of prostate cancer, TRUS, MRI, and changes in PSA levels are currently insufficient [23]. A reliable method is a core biopsy of the prostate, however, there is a possibility of negative results of the procedure, especially among people with a low level of PSA.

Nowadays, radiological method of diagnosis of prostate diseases has stepped forward thankfully to the introduction of clinical imaging techniques such as CT and MRI. These research methods have high diagnostic capabilities in determining the locally advanced forms of prostate cancer. At the same time, there are problems in the differential diagnosis of adenocarcinoma forms, with minimal spread of the tumor out of prostate capsule, especially localized forms.

Magnetic- resonance imaging is increasingly being put into practice as an objective, highly effective research method. This diagnostic method continues to evolve and improve. According to many authors, MRI, which has high soft tissue contrast, should be included as a mandatory method in the diagnostic complex of studies of the prostate gland [24–28]. According to the literature, a multiparametric magnetic resonance imaging study in patients with prostate cancer has a great advantage over other clinical and radiation diagnostic methods in determining the location, true size of a tumor, and its degree of aggressiveness [28]. These mentioned authors believe that prostate mp-MRI should be performed in patients with negative biopsy results (both primary and repeated) and/or with suspicious PSA levels, low and/or in the gray zone (4-10 ng / ml). Although it should be noted that when performing the mp-MRI of the prostate after a negative result of a primary or secondary biopsy in the early post-biopsy period, difficulties arise in the qualitative diagnosis of prostate cancer, because the signal from hemorrhage in the gland is similar to the signal from a contrast agent. In this regard, to conduct a study with contrasting impractical in this group of patients. In some oncological centers were developed standards for CT and MRI studies with intravenous contrast [29].

In 2007, by the international working group consisting of experts in prostatic MRI, together with the European Society of Urogenital Radiology (ESUR), were published the fundamental principles for interpreting prostatic MRI studies in the form of PI-RADS v.1 system [30]. Due to its widespread use, in 2015 a second version of the PI-RADS v.2 system was suggested [31], where the disadvantages of the first version were corrected and improved. PI-RADS v.2 improves the primary diagnostic process, allows to assess the risks and prognosis of the disease [32]. Due to the CaP segmentation map [30], the PI-RADS v.2 concept is based on the understanding of the anatomical and histological structure of the prostate[33]. This map allows to visually localize the revealed pathological changes in the structure of the prostate according to the mp-MRI and to provide visual support for the planned targeted biopsy [34].
We also for the first time in Uzbekistan, began to introduce prostate mp-MRI in the diagnosis of both advanced CaP and in order to determine the risk of the disease for early diagnosis. Unfortunately, today in Uzbekistan the frequency of diagnosis of prostate cancer in the late stages prevails over the early [8]. Because of this, the main goal of our work was to improve the early diagnosis of prostate cancer. To do this, initially in Uzbekistan we performed on 42 patients prostate mp-MRI, who had not had a biopsy before, who have suspicion to CaP with an increase in the level of total PSA. We were more interested in the group of patients with a PSA level up to 30 ng/ml, in whom DRE and prostate TRUS were not informative regarding the detection of prostate cancer. We confirmed in our study that a multifocal core biopsy in combination with a targeted, using PI-RADS v.2-classification improves the detection of the disease and saves patients from additional repeated interventions.

Conclusions.
1. In determining the indications for a biopsy for the early diagnosis of localized prostate cancer, the information value of DRE and TRUS of prostate is significantly lower than the level of total serum PSA.
2. In the early diagnosis of localized prostate cancer, the priority for biopsy indications is increased level of serum total PSA.
3. In the early diagnosis of localized prostate cancer in patients who have PSA level up to 30 ng/ml, without any suspicious according to DRE and TRUS of prostate, mp-MRI should be added to standard diagnostic scheme before primary biopsy.

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