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## PROBLEMS AND OPPORTUNITIES OF EARLY DIAGNOSIS OF LOCALIZED PROSTATE CANCER

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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.

**Aim** of this study was to improve the results of early diagnosis of prostate cancer by optimizing the indications for performing a prostate biopsy.

**Material and methods.** We analyzed the results of 251 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 189 patients who underwent primary prostate core biopsy; second group - 62 patients, whom performed mp-MRI and evaluated the risk of PCa by classification PI-RADS v2 before biopsy.

The procedure was performed TRUS guided, under local anesthesia, using lidocaine gel (Cathjel)+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 in 189, with coverage of the peripheral and apical zones. In 62 patients of the second group, the same method was used to collect cores and, in addition from 2 to 4 cores were shot precisely from the zone of interest revealed by mp-MRI.

**Results.** Among 1<sup>st</sup> group of 189 primary biopsies in 124 (65.6%) patients was verified adenocarcinoma. In patient with total PSA level up to 20 ng/ml indicator was 35.3%. In the 2-nd group the cancer indicator was 17.9% for the 2-3 scores of PI-RADS v2, and 91.2% for those with 4-5 scores. In patients with PSA up to 20ng/ml cancer detecting was 75% (4-5 scores).

**Conclusions.** In the early diagnosis of prostate cancer in patients who have PSA level up to 20 ng/ml, without any suspicious according to DRE and TRUS of prostate, mp-MRI should be added to standard diagnostic scheme before primary biopsy.

Among them with a risk of 2-3 scores according to PI-RADS v2 it is advisable to follow up rather than do a biopsy.

**Key words:** Prostate Cancer (PCa), biopsy, mp-MRI, early diagnosis, cancer detecting rate.

**Introduction.** Prostate cancer (PCa) 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 aim 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 251 primary multifocal prostate core biopsies performed to patients who were examined in RSSPMCU because of LUTS in the period 2016-2019. Patients were divided into two groups based on the data of their preliminary clinical examination. The first group included 189 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/or 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 189 patients was  $68.54 \pm 0.54$  (years) (51-92), the volume of the prostate gland was  $72.36 \pm 2.29$  (cc), the total serum PSA level was  $75.21 \pm 9.88$  (ng/ml), in the range 1,4 – 893.5 (ng/ml). The second group included 62 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  $67.58 \pm 1.07$  years (47-88), PSA level  $86.90 \pm 18.65$  ng/ml, gland volume  $66.50 \pm 3.74$  cc, (17 – 174).

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 62 patients of the second group, the

same method was used to collect cores from 10-12 sites and, in addition from 2 to 4 cores were shot precisely from the zone of interest revealed by mpMRI.

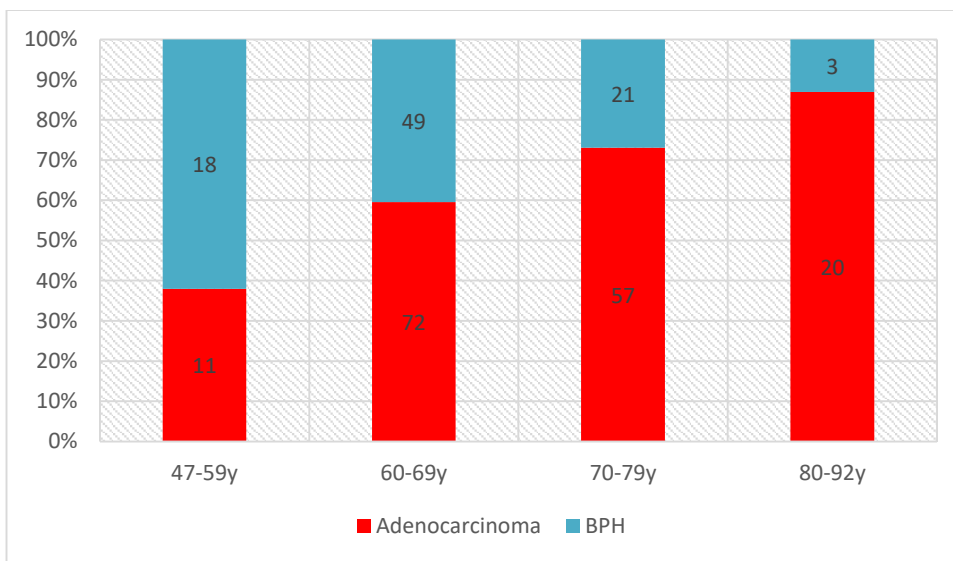
**Results.** Among 1<sup>st</sup>group of 189 primary biopsies in 124 (65.6%) patients was verified adenocarcinoma Analysis of biopsy results depending on the volume of the prostate showed the following picture (Table 1).

**Table 1**

**Morphological results of a biopsy depending on the volume of the prostate, n = 189**

Results of biopsy	Amount of patients n (%)	Volume of prostate (cc) M±m	PSA (total)
PCa	124 (65.6)	67.47±2.79	101.69±14.48
BPH	65 (34.4)	81.68±3.78	24.71±2.06

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, Pic 1.



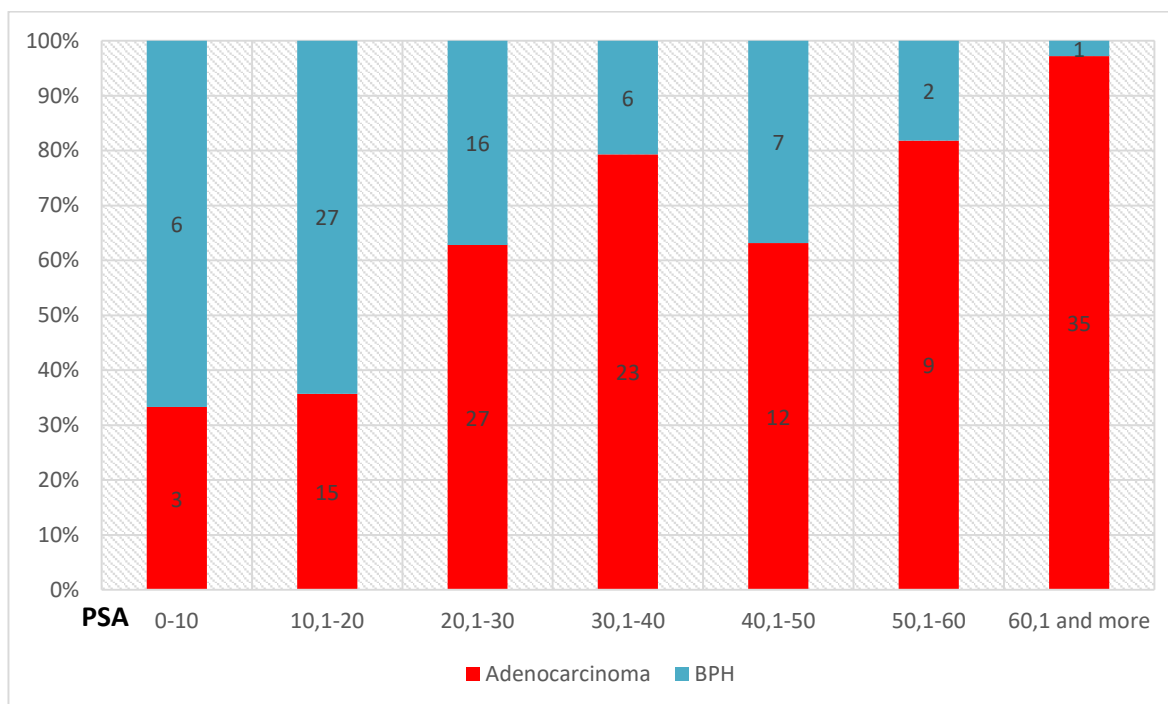
**Picture 1. Results of prostate biopsy taking into account the age of patients, n=251.**

The results of a morphological study of the prostate material, depending on the level of total PSA, showed that an increased level of total PSA significantly stipulates the detection of prostate cancer, pic. 2.

In order to determine the role of DRE and TRUS in the detection of the PCa, we performed the following analysis.

Our analysis clearly demonstrated that with a low PSA level (up to 10 ng/ml, n = 9), a negative result was at 67.0%, at a level of 10.1-20 ng / ml (n = 42) this indicator was 64.0%.

Pic.2 shows that the highest percentage of negative biopsy results was among patients with PSA level of less than 20 ng / ml (n = 51), where the rate was 33 (64.7%).



**Picture 2. Results of a prostate biopsy depending on the level of total PSA (n = 189)**

Considering the low detectability of PCa in patients with PSA level less than 20 ng / ml, the first group of patients (n = 189) was divided into two sub-groups - with PSA levels less than 20 ng / mL and a PSA level more than 20.1 ng / ml, table 2.

Among patients with a PSA level of less than 20 ng/ml, the detection of prostate cancer was low - 18 (35.3%), while among patients with a PSA level above 20.1 ng/ml, prostate cancer was statistically significantly more often, in 106 (76.8%) patients ( $P < 0.05$ ).

**Table 2**

**Distribution of patients by PSA level up to 20 ng/ml and more than 20.1 ng/ml**

Indicators	Overall n=189	Up to 20 ng/ml n=51	More than 20,1 ng/ml n=138
Age	68.54±0.54	67.84±1.02	68,8±0,64
Prostate volume (min-max)	72.36±2.29 (51-92)	68.39±3.85 (21-140)	73,80±2,8 (29-197)
PSA (min-max)	75.21±9.88 (1.4-893.5)	13.7±0.48 (1.4-20.0)	97.95±13.07 (20.1-893.5)
<b>Biopsy results</b>			
Adenocarcinoma	124 (65.6%)	18 (35.3%)	106 (76,8%)
PSA level (min-max)	101.69±14.48 6.37-893.5	13.32±0.8 6.37-19.68	116.7±16.51 20.14-893.5
BPH	65(34.4%)	33(64.7%)	32(23.2%)
PSA level (min-max)	24.71±2.06 1.42-111.3	13.9±0.60 1.42-20	35.8±3.10 20.66-111.3

Further, in each subgroup, we analyzed the significance and informational value of TRUS and DRE in the diagnosis of prostate cancer. In the table 3, we analyzed the correspondence of biopsy data with the information obtained during TRUS.

**Table 3**  
**The value of TRUS in the diagnosis of PCa depending on the PSA level, n = 189**

PSA	Yes suspicion in TRUS	Detection % PCa out of suspected patients	No suspicion in TRUS	Detection % PCa out of unsuspected patients
Up to 20 ng/ml n=51	2 (3.92%)	2 (100%)	49 (96.08%)	16 (32.7%)
More than 20.1 ng/ml n=138	23 (16.66%)	21 (91.3%)	115 (83.33%)	85 (73.9%)
Overall n=189	25 (13.2%)	23 (92.0%)	164 (86.8%)	101(61.6%)

The analysis showed that during TRUS examination out of 189 patients, suspicious lesions in the prostate gland were found only in 25 (13.2%) patients. The detection of prostate cancer among patients suspected in TRUS was high - 23 (92.0%) of 25 patients. But the calculation in relation to all patients showed that TRUS revealed the disease only in 23 (12.2%) of 189.

Moreover, among patients with a PSA level of less than 20 ng/ml, the role of TRUS in detection of suspicious hypo echoic area was low, i.e. at 3.92%. In this subgroup in vast majority of patients (96.08%), TRUS as a method did not play a diagnostic value in identifying the disease. The role of TRUS among patients with a PSA level of more than 20.1 ng/ml is slightly more 16.66%, but in this subgroup also a significantly larger number of patients underwent biopsy due to an increased PSA. Therefore, we concluded that the role of TRUS in the early diagnosis of PCa among patients with PSA level of less than 20 ng/ml was significantly less.

**Table 4.**  
**The value of DRE in the diagnosis of PCa depending on the PSA level, n=189**

PSA	Yes suspicion in DRE	Detection % PCa out of suspected patients	No suspicion in DRE	Detection % PCa out of unsuspected patients
Up to 20 ng/ml n=51	9 (17.6%)	6 (66.66%)	42 (82.4%)	12 (28.6%)
More than 20.1 ng/ml n=138	53 (38.4%)	49 (92.4%)	85 (61.59%)	57 (67.1%)
Overall n=189	62 (32.8%)	55 (88.7%)	127 (67.2%)	69 (54.3%)

The analysis regarding the role of DRE in the early diagnosis of PCa showed (see table 4.) that its value unfortunately increases only among patients with high PSA levels.

Of all 189 patients, in 62 (32.8%), the urologist found hardness and prostate cancer suspicion and out of the number of suspects, cancer detection after biopsy reached 55 (88.7%).

Results of analysis of 189 patients showed that DRE revealed the disease in 55 (29.1%) patients. Among patients with a PSA level of less than 20 ng/ml, only in 17.6% patients were suspected of cancer according to DRE and after a biopsy in 66.66% of the suspects, PCa was verified.

Thus, the analysis showed that the role of DRE in the early diagnosis of prostate cancer among patients with a PSA level of less than 20 ng/ml is also low 6 (11.76%) of 51.

Next, we analyzed the results of prostate biopsy in patients who suspected of prostate cancer according to both investigations DRE and TRUS (see table 5) and all 100% suspected patients' biopsy revealed PCa.

**Table 5.**  
**The diagnostic value of DRE and TRUS in combination in the diagnosis of PCa depending on the level of PSA, n = 189**

PSA	Yes suspicion in both DRE and TRUS	Detection % PCa out of suspected patients	No suspicion in both DRE and TRUS	Detection % PCa out of unsuspected patients
Up to 20 ng/ml n=51	1 (1.96%)	1 (100%)	50 (98%)	17 (34.0%)
More than 20.1 ng/ml n=138	15 (10.87%)	15 (100%)	123 (89.13%)	91 (74.0%)
Overall n=189	16 (8.5%)	16 (100%)	173 (91.5%)	108 (62.4%)

But only one patient (1.96%) in the subgroup of those with a PSA level of less than 20 ng/ml had this positive combination of the investigation methods.

Therefore, our analysis showed that in the first subgroup patients the informative value of TRUS and DRE after biopsy was significantly lower (17.6%) than in the second subgroup (61.6%),  $p < 0.001$  (see table. 6).

Thus, among the majority of patients with a PSA level of less than 20 ng/ml, there are no characteristic changes in the prostate according to TRUS and DRE and the detection of prostate cancer in this subgroup was only 35.3%. In turn, 64.7% tested negative. Among the latter, there are patients with a truly negative and false negative result. Consequently, some of these patients, further according to indications will have to undergo a repeated, rather traumatic biopsy procedure.

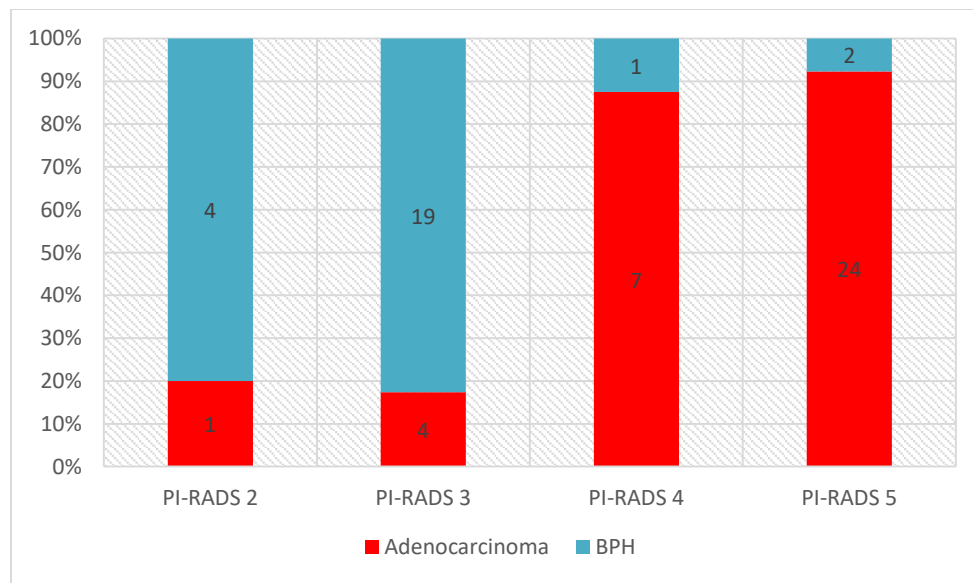


**Table 6.****Correspondence of TRUS and DRE data with prostate biopsy data in the diagnosis of prostate cancer**

Subgroups	Correspondence TRUS	Correspondence DRE	Correspondence TRUS+DRE	Informational value
Up to 20 ng/ml n=51	2 (3.9%)	6 (11.8%)	1 (1.96%)	9 (17.6%)
More than 20.1 ng/ml n=138	21(15.2%)	49 (35.50%)	15 (10.86%)	85 (61.6%)

Taking into consideration a similar picture, for rational selection of indications for biopsy, mp-MRI of the prostate was performed on 62 patients of the second group preoperatively. Patients were divided based on the risk of cancer detection according to Pirads-v2, and they all underwent a standard biopsy of 10-12 cores and simultaneously targeted biopsy, from the zones of interest in the amount of 2-4 cores (Pic. 3).

The analysis showed that, there were no patients with a 1st score PIRADS-v2 according to mp-MRI. With 2–3 scores according to PIRADS-v2, the detection of prostate cancer was no higher than 20%, with the 4–5 scores 87.5% and 92.3%, respectively (see pic. 3).

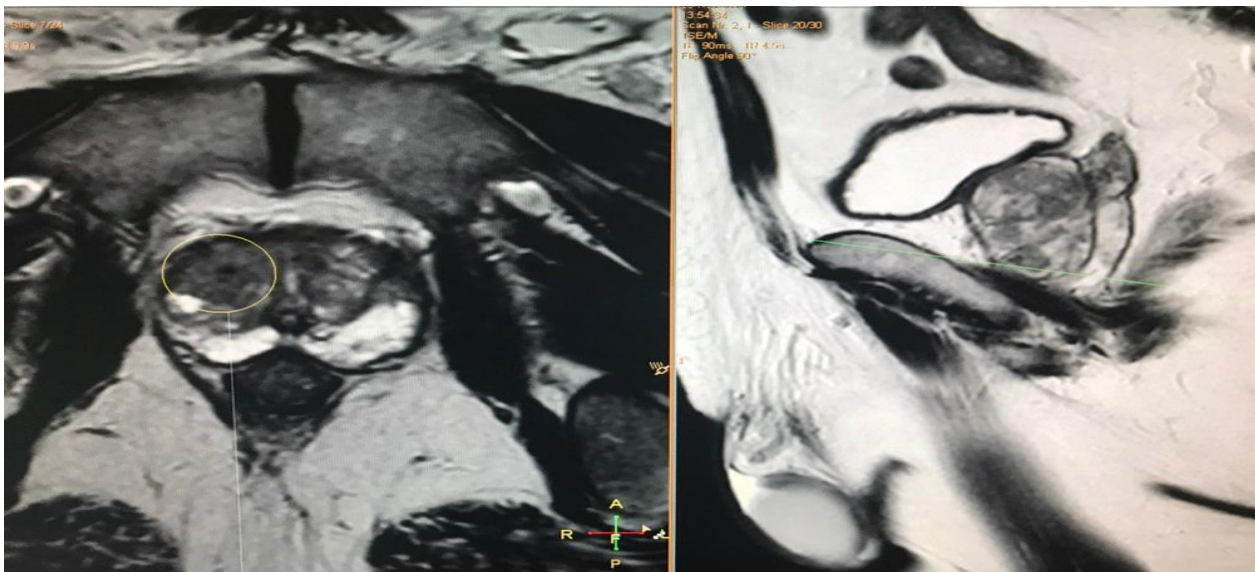
**Picture 3. Patient distribution according to Pirads-v2 and biopsy result**

Next, we analyzed the biopsy results based on the PSA level, dividing the patients into two subgroups, as we previously conducted among the patients of the first group, table 7.

Table 7.

**Results of primary transrectal prostate biopsies performed using  
mp-MRI data, n=62**

PSA	PIRADS-v2	Total		Adenocarcinoma		HGPIN		BPH	
		n	%	n	%	n	%	n	%
Up to 20 ng/ml	2	3	100.00	0	0,00	0	0.00	3	100.00
	3	15	100.00	1	6.67	2	13.33	12	80.00
	4	3	100.00	2	66.70	0	0.00	1	33.30
	5	5	100.00	4	80	0	0.00	1	20
	Total	26	100.00	7	26.92	2	7.69	17	65.38
More than 20,1 ng/ml	2	2	100.00	1	50.00	0	0.00	1	50.00
	3	8	100.00	3	37.50	0	0.00	5	62.50
	4	5	100.00	5	100.00	0	0.00	0	0.00
	5	21	100.00	20	95.23	0	0.00	1	4.77
	Total	36	100.00	29	80.55	0	0.00	7	19.45



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

### 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 PCa. 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 PCa 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 PCa 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 to 62 patients prostate mp-MRI, who had not had a biopsy before, who has suspicion to PCa with an increase in the level of total PSA. We were more interested in the group of patients with a PSA level up to 20 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 in patients who have PSA level up to 20 ng/ml, without any suspicious according to DRE and TRUS of prostate, mp-MRI should be added to standard diagnostic scheme before primary biopsy.

3. The identical risk of prostate cancer by PI-RADS-v2 in different patients differs based on the PSA level. At 2 and 3 PI-RADS-v2 scores among patients with a PSA level of less than 20 ng/ml and no suspicion in TRUS and DRE, follow-up may be recommend without a biopsy. At the similar risk level by PIRADS-v2 in patients with a PSA level of more than 20.1 ng/ml, a biopsy is preferable. At 4–5 degrees of risk for PIRADS-v2, a prostate biopsy should be performed regardless of PSA level.

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