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CLINICAL-MORPHOLOGICAL PROGNOSTIC CHARACTERISTICS OF PROSTATE CANCER

Abstract. *Among diagnostic clinical-morphological signs of prostate cancer (PC) the most significant ones are the level of prostate specific agent (PSA) of the blood, Gleason's pattern, and stage of the disease according to TNM (tumor, nodus, metastasis) system. Registration of these indices is essential for prognosis of the disease and choosing therapeutic tactics. Certain relations have been observed concerning an increased PSA level and T stage as Gleason's pattern increases (p<0,0001 and p<0,0001 respectively), as well as a tendency to higher Gleason's pattern among older people. Distribution of PC into the three groups of a low, intermediate and high risk considering PSA level, Gleason's pattern and invasive degree has shown the ratio 18,7%, 25,0% and 56,3% respectively. Risk groups were predominantly formed at the expense of extension of tumor process (T stage) and PSA level in the least.*
Key words: *prostate cancer, Gleason's pattern, T stage, PSA level, disease prognosis.*

Introduction. The study is a fragment of the scientific-research work of Kharkiv Medical Academy of Post-Graduate Education, the Ministry of Public Health of Ukraine "Nanotechnologies in Chemotherapy of Malignant Tumors in Adults and Children", 0113U000972 (2013–2017).

According to official statistical data in Ukraine [1] prostate cancer (PC) occupies the second position in the structure of ocnological diseases among manhood and the first one among men over 75. Annual 5,3 % increase of its sickness rate is registered [1]. The choice of therapeutic tactics of patients is based on consideration of prognostic criteria of the disease including the most significant ones: Gleason's pattern, tumor extension according to TNM classification, PSA level of the blood [2, 3]. According to the information of the European Association of Urology (EAU) [4] the issue of a prognostic value of certain clinical-morphological criteria remains unsolved, including lack of recommendations to apply immune-histochemical markers to prognosticate and manage PC patients. The objective of the study is to investigate the major prognostic PC signs and detect their interrelations with clinical-morphological characteristics and risk of recurrent disease.

Materials and methods. 886 patients diagnosed with PC were operated on at V.I. Shapovalov Kharkiv Regional Clinical Centre of Urology and Nephrology during the period of five years: from 2011 to 2015. In 280 cases open retropubic radical prostatectomy was performed. 168 patients were dropped out from the study due to incomplete data available, lack of microslides and paraffin blocks, or their low quality. Therefore, 112 cases of PC served as the material of the study.

PSA level of the blood, age of patients, Gleason's pattern according to the latest WHO classification [1], invasive degree according to TNM system [2] have been examined. In certain cases immune-histochemical examination to find basal cells markers – p63 and high molecular weight keratin (HMW) – was performed to confirm the diagnosis of PC.

The results of the study were statistically processed by means of the package «Statistica 6.0». The correlation between signs was evaluated according to non-parametric Pearson $\chi 2$ criterion. The results were considered reliable with $p<0,05$.

Results and discussion. An average age of PC patients was 69,5±7,9. The peak of morbidity was marked at the age of 60-79 with practically equal number of patients at the age of 60-69 and 70-79 (48 patients at the age of 60-69 and 46 at the age of 70-79, average 42,8% and 41,8% respectively).

PSA level in PC patients was 19,1±28,2 and ranged from 0 to 210 ng/ml. The most relative number of patients was with PSA level of 4-10 (34,8%) and 10-20 (25,0%). As it is evidenced from Table 1, PSA level under 4 ng/ml is not specific for

PC, although this PSA level could not be a criterion to exclude cancer as well as 0 PSA level which was found in 2 patients.

In PC group 18,7% of tumors were characterized by invasive growth within the borders of a half of the prostate one lobe, that is it corresponded to T1-2a stage according to the latest TNM system [5]. Those were tumors rarely bigger than 1 cm in size. Extension of PC more than a half of one lobe (T2b) and involving two lobes (T2c) was detected in 26,7% and 16,1% respectively. Among those tumors there were cases when several tumor nodes were found. Prostate capsule invasion was found in 38,4% (43 cases) including 16 ones with invasion into the seminal vesicles, and 3 with invasion into the muscular tissue and adjacent organs.

In general the data obtained correspond to those found in scientific literature. Thus, in 22-50% of patients with localized PC tumor process extended beyond the organ, and recurrent disease developed approximately in 15-44% of patients [6, 7]. Nowadays oncologists are facing the task to detect risk factors promoting relapse and progression of the disease enabling to prevent the onset of clinical signs of a local relapse or remote metastasis. A number of studies appear dealing with new pognostic factors of relapse in PC patients after prostatectomy, which would enable in clinical practice to isolate a high risk group of patients more accurately. Nowadays the most reliable independent prognostic system of PC is Gleason's pattern, which application is essential for choosing therapeutic tactics of patients [8].

In our material average Gleason's pattern was 6,8±1,35. The biggest group of PC was with Gleason's pattern 2-6 – 36,6% (41/112). According to the latest principles of PC gradation according to Gleason's pattern dated 2014 a great number of PC with Gleason's pattern ≤6 were classified into PC with Gleason's pattern 7, and all the forms of PC ≤6 were considered the least aggressive [9]. This group includes PC with microscopic manifestation in the form of dominated close adjacent glands located separately one from another, small and medium in their size, often branching and regular round shape. With the purpose to make highly specific differentiative diagnostics of PC with atrophic, hyperplastic processes, prostate intraepithelial neoplasm (PIN), and atypical adenosis immune-histochemical examination to find the markers of basal cells p63 and high molecular weight keratin (HMW) was carried out. Complete lack of basal cells was a criterion of cancer available. According to the latest changes of Gleason's pattern cribrous structures should be referred to 4 degree, although single cribrous glands available are allowed in case of 3 degree [8]. According to the modified system 4 degree according to Gleason's pattern is characterized by fusion or cribrous, or poorly formed glands, or glomerular structures [WHO, 2016].

In our material a prevailing number of cases – 65 (58,0%) were PC 4 degree according to Gleason's pattern. 5 degree is characterized by isolation of cancer cells, their solid location with possible unclear microacinar structure, formation of cords and rarely found glands, availability of comedonecrosis in solid nests and cribrous structures [9]. According to the latest recommendations of WHO and European Association of Urology [4, 8] PC should be distributed into groups with Gleason's pattern 2-6, 7 (3+4), 7 (4+3), 8, 9-10. It is that distribution into 5 groups with integration of PC with Gleason's pattern 2-4 and 4-6 into one group, and separation of PC with Gleason's pattern 7 into two groups which is of the greatest prognostic value. Thus, according to a mass-scale investigation involving 20 845 cases of PC after radical prostatectomy, 5-year relapse-free course of the disease was according to the distribution of PC into 5 groups – in 96%, 88%, 63%, 48% and 26% [10]. In our material PC with Gleason's pattern 2-6 constituted 36,6%, 7 (3+4) – 17,8%, 7 (4+3) – 13,4%, 8 – 16,9%, 9-10 – 15,1%. Scientific literature presents controversial information concerning the relation of patient's age and Gleason's pattern [11, 12]. In our study, as it is seen from Table 1, patients older than 70 were found more often among those with higher Gleason's pattern (8-10) than among the cases with Gleason's pattern 7 and less. All the patients with Gleason's pattern 9-10 were older than 60 (χ^2=1,9, p=0,1), and the age group of 50-59 included the biggest number (60%) of patients with Gleason's pattern ≤6 (χ^2=2,5, p=0,1). Therefore, higher Gleason's pattern was found among older patients. PSA level is one of the most

Table 1

Relation of age and PSA level of PC patients

Index	Gleason's pattern					Reliability, criterion χ^2
	≤6 n (%)	7 (3+4) n (%)	7 (4+3) n (%)	8 n (%)	9-10 n (%)	
Age						
50-59, n=10	6 (15)	2 (10)	0	2 (10)	0	
60-69, n=48	19 (46)	8 (40)	8 (53)	6 (32)	7 (41)	
70-79, n=46	14 (34)	9 (45)	6 (40)	9 (47)	8 (47)	χ^2=7,6, p=0,8
80-89, n=8	2 (5)	1 (5)	1 (6)	2 (10)	2 (12)	
PSA level						
0-4,0 (n=15)	7 (17)	4 (20)	3 (20)	1 (5)	0	
4,1-10,0 (n=39)	19 (46)	8 (40)	4 (26)	5 (26)	3 (17)	
10,1-20,0 (n=28)	12 (29)	5 (25)	4 (26)	3 (15)	4 (23)	
20,1-40,0 (n=17)	2 (4)	1 (5)	2 (13)	5 (26)	7 (41)	χ^2=30,1,
>40,1 (n=13)	1 (2)	2 (10)	2 (13)	5 (26)	3 (17)	p<0,03
Total	41	20	15	19	17	

required prognostic criteria, although with Gleason's pattern less than 6 this index is not of a prognostic value [13]. The experts from the College of American Pathologists suggest that PSA level should be referred only to the third prognostic category due to controversial data [14].

Comparing PSA level with Gleason's pattern statistically significant dependence was found in the form of increased PSA level as Gleason's pattern increases (χ^2=75,0, p<0,0001). As Table 2 presents PSA level of PC with Gleason's pattern ≤6 and 7 was predominantly 4-10 ng/ml, a high relative number of cases among them was with PSA level lower 4 and 10-20. PC with Gleason's pattern ≤6 is not characterized by PSA level of 20-40 (χ^2=5,3, p<0,03) and more than 40 (χ^2=5,2, p<0,03). PC with Gleason's pattern 8 and more demonstrated an opposite dependence: there was none of the case with PSA level lower than 4 among PC with Gleason's pattern 9-10, the biggest relative number of cases was with PSA level 20-40 and a great relative number of cases with PSA level >40. PC with Gleason's pattern 8 was found to be associated with PSA level > 40,1 (χ^2=4,8, p<0,03), and PC with Gleason's pattern 9-10 — with PSA level 20,1-40,0 (χ^2=10,5, p<0,003).

The dependence between Gleason's pattern and degree of PC invasion was found in the form of Gleason's pattern increase as the indices of pathomorphological stage T (χ^2=72,1, p<0,0001) increase as well. Among PC with Gleason's pattern ≤6 the most relative number of tumors were localized in one lobe (41%) or its half (39%), there were no cases with invasion into the seminal vesicles and adjacent organs. In its turn, among PC with Gleason's pattern 8 and 9-10 there were none case of tumors localized in the half of one lobe, and they included all the three cases of PC of T4 stage. PC of the groups 7 (3+4) and 7 (4+3) were rather close by the level of invasion, although among PC with Gleason's pattern 7 (4+3) less relative number of tumors localized in the half of one lobe was found (6,6% and 20% respectively). Apparently, in case a dominating by its volume part of tumor is of a lower differentiation, such kind of cancer is more invasive (Table 2).

Considering association of PC in every group with T stages it was found that PC with Gleason's pattern ≤6 was characterized by its localization within the borders of a half of one lobe, that is T1-2a stage, (χ^2=17,4, p<0,0001) and the whole lobe, T2b stage (χ^2=7,4, p<0,01). It is not characterized by invasion of prostate capsule, T3a stage (χ^2=13,8, p<0,0003) and invasion into the seminal vesicles, T3b stage (χ^2=10,7, p<0,003). PC with Gleason's pattern 7 (3+4) and 7 (4+3) was characterized by lack of dependence considering the level of invasion of the process. PC with Gleason's pattern 8 was associated with T3a stage, that is, it was characterized by invasion of

Table 2

T stage and Gleason's pattern of PC

Age	Gleason's pattern					Reliability, criterion χ^2
	≤6 n (%)	7 (3+4) n (%)	7 (4+3) n (%)	8 n (%)	9-10 n (%)	
T1-2a	16 (39)	4 (20)	1 (6,6)	0	0	χ^2=72,1, p<0,0001
T2b	17 (41)	4 (20)	4 (26,6)	4 (21)	1 (6)	
T2c	7 (17)	4 (20)	4 (26,6)	1 (5)	2 (12)	
T3a	1 (2,4)	5 (25)	3 (20)	11 (58)	4 (23)	
T3b	0	3 (15)	3 (20)	2 (10)	8 (47)	
T4	0	0	0	1 (5)	2 (12)	
Total	41	20	15	19	17	

the organ capsule into the paraprostate cellular tissue (χ^2=18,0, p<0,0001). It was not characterized by its localization within the borders of one half of prostate lobe (χ^2=5,2, p<0,03). PC with Gleason's pattern 9-10 was associated with T3b and T4 stages, that is, it was characterized by pronounced extra-organic invasion with infiltration of the seminal (χ^2=17,5, p<0,0001) and adjacent organs (χ^2=6,4, p<0,03). At the same time, PC with Gleason's pattern 9-10 is not characterized by localization within the half (χ^2=4,6, p<0,05) and one prostate lobe (χ^2=4,4, p<0,05).

According to the recommendations of the WHO and EAU [4, 8] to prognosticate the risk of relapse, repeated therapy and lethal outcome, PC should be divided into three groups considering PSA level, T stages and Gleason's pattern.

High risk group included 56,3% (63/112) of tumors including 96,8% (61/63) of cases with T2c-T4 stages, two more cases were on T2b stage of tumor process; 57,1% (36/63) PC from the high risk group was characterized by Gleason's pattern 8-10, other 27 cases were characterized by Gleason's pattern 7 — in 36,5% (23/63) and Gleason's pattern ≤6 — in 6,3 % (4/63). PSA level more than 20 ng/ml was found only in 47,6% (30/63) of cases, other PC cases from this group were with PSA level of 0-4 ng/ml — in 1,5% (1/63), 4-10ng/ml – in 22,2% (14/63) and 10-20 ng/ml – in 28,5% (18/63) (Table 3).

Distribution of PC into low and intermediate risk groups constituted 18,7% (21/112) and 25% (28/112) respectively. All 28 PC cases from the intermediate risk group were in T2b stage and with Gleason's pattern 7 in 42,8% (12/28) and Gleason's pattern ≤6 in 57,1% (16/28); PSA level 10-20 was found in 35,7% (10/28) of cases, 4-10 — in 46,4% (13/28), 0-4 — in 17,8% (5/28). All 21 cases of PC from the low risk group were localized within the borders of the half of the prostate lobe, with Gleason's pattern 2-6 and PSA level up to 10 ng/ml (0-4 ng/ml — in 42,8% (9/21), 4-10 ng/ml — in 57,1% (12/21)).

Conclusions: 1. An average age of PC patients was 69,5±7,9. The peak of morbidity was marked at the age of 60-79 with practically equal number of patients at the age of 60-69 and 70-79 (42,8% and 41,8% respectively). An average PSA level was 19,1±28,2 and ranged from 0 to 210 ng/ml.

2. The comparison of patients' age, PSA level, T stage of tumor process with Gleason's pattern has

Table 3

Risk groups of PC

	I (low risk group)	II (intermediate risk group)	III (high risk group)
Definition	PSA up to 10 ng/ml, T1-2a stages, Gleason's pattern 2-6.	PSA 10-20 ng/ml, or T2b stage, or Gleason's pattern 7.	PSA more than 20, or T2c stage, or Gleason's pattern 8-10.
Number of cases (%)	21 (18,7%)	28 (25,0%)	63 (56,3%)

found dependence between increased PSA level and T stage as Gleason's pattern increases (p<0,0001 and p<0,0001 respectively). Patients of older age had a tendency to higher Gleason's pattern.

3. PC with Gleason's pattern ≤6 was associated with its localization of tumor process within the borders of a half of one lobe (T1-2a and T2b stages), (p<0,0001). It is not characterized by PSA level more than 20 (p<0,03), invasion of prostate capsule (T3a stage) (p<0,0003), and invasion into the seminal vesicles (T3b stage) (p<0,003). PC with Gleason's pattern 8 was associated with PSA level>40 (p<0,03), invasion of the organ capsule (T3a stage) (p<0,0001), localization within the borders of the half of the prostate gland (T1-2a stage) (p<0,03). PC with Gleason's pattern 9-10 was associated with PSA level 20-40 (p<0,003), invasion of the seminal vesicles (T3b stage) (p<0,0001) and adjacent organs (T4 stage) (p<0,03), but it is not characterized by localization within one prostate lobe (T1-2b stage) (p<0,05).

4. Distribution of PC into the three groups of a low, intermediate and high risk considering PSA level, Gleason's pattern and degree of invasion has found the ratio of 18,7%, 25,0% and 56,3% respectively. Risk groups were mainly formed at the expense of extension of tumor process (T stage) and at the expense of PSA level at the least.

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