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Original Article / Оригинални рад

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Significance of the correlation between serum prostate specific antigen and percentage of volume prostate cancer in postoperative biochemical progression

Значај корелације серумских вредности простата специфичног антигена и процента волумена карцинома простате у постоперативној биохемијској прогресији

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SUMMARY

Introduction/Objective Radical prostatectomy (RP) is the best form of treatment of patients with locally confined prostate cancer (PC). In 27% to 53% of patients after RP occurs biochemical progression (BP) of disease.

Objective The aim of our analysis was to assess the significance of the correlation of preoperative prostate specific antigen (PSA) values and the percentage volume of PC in BP in patients with RP and the biopsy Gleason score 6 and 7.

Methods The analysis included results of treatment of 228 patients with the committed radical retropubic prostatectomy for localized PC in the period from 2007 to 2011. According to GGS values, three groups identifies - 6 (3 + 3), 7 (3 + 4) and 7 (4 + 3). According to the preoperative PSA values group ≤ 4 ng/ml, 4.1 to 10.0 ng/ml and values of ≥10.1 ng/ml. Biochemical progression was defined as two consecutive increase PSA values greater than 0.2 ng/ml after RP. The percentage of tumor volume (PTV) is determined by a visual assessment of the percentage of PC in each microscopic sample. Four groups were determined PTV 0–5%, 6–25%, 26–50% and 51–100%.

Results Biochemical progression was registered in 19 patients. Most frequent PTV in the group of patients with BP and from biopsy and from RP was for PTV 6-50%, an average of 30%.

Conclusion Our study showed the predictive significant connections of preoperative PSA values and the values of PTV after operational treatment and that these are independent parameters in the assessment of results of treatment.

Keywords: Prostate cancer, radical prostatectomy, prostate specific antigen, tumor volume, biochemical recurrence

САЖЕТАК

Увод/Циљ Радикална простатектомија (РП) представља најбољи облик лечења болесника са локално ограниченим крациномом простате (КП). Код 27% до 53% болесника након РП ипак долази до биохемијске прогресије (БП) болести.

Циљ Циљ наше анализе била је процена значаја корелације преоперативних вредности простата специфичног антигена (ПСА) и процента волумена КП у БП код болесника са учињеном РП и биопсијским Глисон градусом 6 и 7.

Методе У анализу су укључени 228 болесника са учињеном ретропубичном РП због локализованог КП у периоду од 2007. до 2011.године. Према ГГС вредностима издвојене су три групе - 6(3+3), ГГС 7(3+4) и 7 (4+3). Према преоперативним вредностима ПСА групе ≤ 4нг/мл, 4,1–10,0 нг/мл и ≥10,1 нг/мл. Биохемијску прогресију дефинисана је као два узастопна пораста вредности ПСА већа од 0,2 нг/мл након РП. Проценат тумор волумена (ПТВ) одређен је као визуелна процена процентуалне заступљености КП у сваком појединачном микроскопском узорку. Одређене су 4 групе ПТВ 0–5%, 6%-25%, 26–50% и 51–100%.

Резултати Биохемијска прогресија регистрована је код 19 болесника. Најзаступљенији ПТВ у групи болесника са БП и из ТРБП и из РП био је за ПТВ 6–50%, просечно 30%.

Закључак Наша студија је показала предиктивни значај везе преоперативних вредности ПСА и добијених вредности ПТВ након оперативног лечења те да су ово независни параметри у процени резултата лечења.

Кључне речи: карцином простате; радикална простатектомија: простата специфични антиген; волумен тумора; биохемијска прогресија

INTRODUCTION

Prostate cancer (PC) is the most common tumor of older men and one of the leading malignant tumor in the world.According to the results of epidemiological studies, diagnostics of PC in each year ranges from 26% to 28% of all malignant tumors [1].Thanks to early diagnosis and numerous therapeutic modalities mortality caused by PC annually declining and currently stands at 9% to 11%. Radical prostatectomy (RP) is the best form of treatment of patients with locally confined PC, expecting to survive longer than 10 years.In 27% to 53% of patients after PC occurs biochemical progression (BP) of disease [2]. Biochemical progression after PC is defined as the elevation of the value of prostate specific antigen (PSA) in the absence of diagnostic metastases [2-5].Together with

Gleason grade system (GGS) and the stage of the disease, serum PSA values represent the leading standard parameters PC for decades [1-4].The first results of work based on an estimate of the volume of PC in diagnostic biopsies and material from RP and its questionable character in assessing the progression of malignant disease have emerged in the nineties of the last century. The assessment of volumes PC depended on the implementation of the recommendations of the macroscopic treatment of prostate tissue, as well as computerized or other methods of its determination [6-12]. Despite the large number of positive correlations with tumor volume with BP, the volume PC analyzed through the significance of Gleason grade and stage of the disease, has not received the importance of an independent prognostic parameter [7-11].

The aim of our analysis was to assess the significance of the correlation of preoperative PSA values and the percentage volume of PC in biochemical progression in patients with RP and the biopsy Gleason score 6 and 7.

METHODS

The analysis included results of treatment of 228 patients with the committed radical retropubic prostatectomy for localized PC in the period from 2007 to 2011.For this group for analyses, material from biopsies and RP for 113 patients with values GGS 6 and 7 was used.Status of the lymph nodes in all the patients was negative. Postoperative follow-up included the period from 29 to 77 months, an average of 56 months.Patients did not receive preoperative hormonal or radiation therapy.Diagnosis PC is determined according to standard clinical parameters, with ultrasound-guided transrectalbiopsy (TRBP). There were followed: preoperative and postoperative PSA values, clinical and pathological stage, Gleason score from biopsy and operational material, as well as the percentage of tumor volume.According to GGS values, three groups identifies: group 1 - GGS 6 (3 + 3) (Figure 1); group 2 - GGS 7 (3 + 4) (Figure 2) and group 3 - GGS7 (4 + 3) (Figure 3).

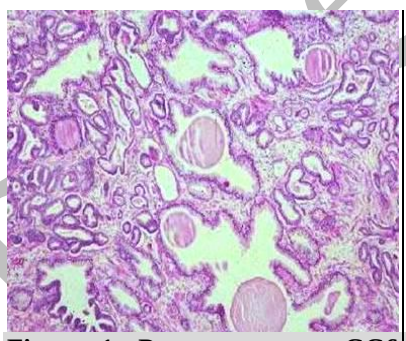

Figure 1. Prostate cancer GG6 (3+3), H&E, ×40.

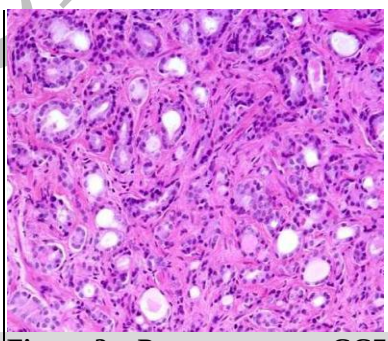

Figure 2. Prostate cancer GG7 (3+4), H&E, ×40.

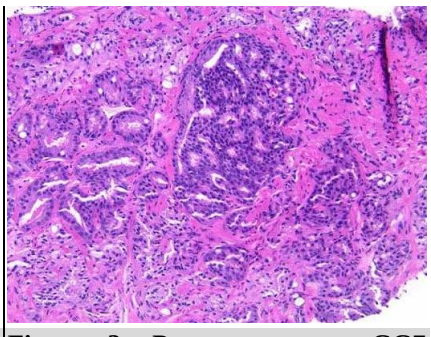

Figure 3. Prostate cancer GG7 (4+3), H&E, ×40.

Macroscopic treatment of the tissue of the prostate, seminal vesicles and groups of lymph nodes, was performed with the use of protocol labeled samples according to topography changes, including analysis of prostate apex and the status of the entire margin [11]. Volume of histologically processed tissue ranged from 70% to 100% of the total weight of the prostate. Prolonged tissue fixation in 10% formalin was applied, after which parasagittal sections width of 2-3 mm was

made.From paraffin embedded prostate tissue treated, obtained from RP to standard hematoxylin and eosin staining are determined: histologic type, tumor grade, and standard WHO grade (1 to 3 degrees) as GGS and pathological stage PC.The postoperative stage in all patients was revised and fully adapted to the seventh edition of the official protocol AJCC / UICC in 2009 [12]. Serum levels of PSA were determined by Hybritech monoclonal immunoassay method.According to the preoperative PSA values, 3 groups were determined and monitored: group 1 PSA ≤ 4 ng/ml, group 2-PSA 4.1 to 10.0 ng/ml, group 3 with PSA values of 10.1 or more ng/ml. The first postoperative result of serum PSA was made after three months. Biochemical progression was defined as two consecutive increase PSA values greater than 0.2 ng/ml after RP [2,3]. The percentage of tumor volume (PTV) is determined by a visual assessment of the percentage of PC in each microscopic sample. Data such as the status of the margin, the minimum and broad infiltration, transcapsular expansion, were analyzed as individual data by slides and customized folder.Total field of PC was estimated visually, according to the map. The percentage of tumor volume (PTV) [13] was determined from the weight of the prostate without seminal vesicles and according to assumed specific gravity of prostate for a little more than 1.0 g/cm3. Macroscopic and microscopic analyzes were made by one pathologist. Four groups were determined: group 1-PTV of 0–5%, Group 2-PTV of 6% -25%, group 3-PTV of 26–50% and a group of 4- PTV from 51–100%. The patients were monitored postoperatively and consultative considered from 21 to 83 months, 3 months during the first year of treatment and then every 6 months. Data are presented as count (percent) or mean±standard deviation, depending on data type. Group differences were analyzed using t test, Mann-Whitney U test and chi-square test (Pearson and test for trend). Cox regression was used to model relationship between independent variables and biochemical progression of prostate cancer. All data were analyzed using SPSS 20.0 (IBM corp.) statistical software. All *p* values less than 0.05 were considered significant.

RESULTS

The average age of patients with RP was 64 years (range 50 to 76 years) and the average value of preoperative PSA was 9.4 ng/ml (from 1.4 ng/ml to 20 ng/ml). In the analyzed group in 4 patients PSA levels were in the range to 4 ng/ml, PSA values from 4.1 to 10 ng/ml may be found in 71 (62.8%), and over 10 ng/ml in 38 (33.6%) patients. Only one patient or 5.2% with intermediate PSA values developed BP after RP, and 18(94.8%) with PSA values above 10 ng/ml BP developed after RP. Clinical stage T1 was determined in the 60 patients (53.1%), T2 in 47 patients (41.6%), and T3 in 6 patients (5.3%). After RP, pathologic stage T2 was diagnosed in 64 patients (56.6%), and T3 in 49 patients (43.4%).GGS valuein biopsy material were: GGS 6 (3 + 3) in 56 patients (49.6%), GGS 7 (3 + 4) in 52 patients (46%) and GS 7 (4 + 3) in 5 patients (4.4%). Finding GGSfrom RP was by the same groups: group 1 in 12 patients (10.6%), Group 2 in 75 patients (66.4%) and a group of 3 in 26 patients (23%). Table 1 shows the comparative values for the entire group and the group of patients with BP after RP.

Table 1. Comparative values for the entire group and the group of patients with BP after RP.

	Entire group n (%)	BP n (%)
Number of patients	113	19 (16,8)
Years of age		
Average	64	64
From To	50–76	54–74
Time monitoring (months)		
Average	47	56
From To	21–83	29–77
Preoperative PSA(ng/ml)		
Average	9.4	12.4
≤ 4.0	4	0
4,1–10	71	1 (5.2)
≥ 10,1	38	18 (94.8)
Clinical stage		
T1	60 (53.1)	5 (26.3)
T2	47 (41.6)	11 (57.9)
T3	6 (5.3)	3 (15.8)
Gleason score of TRBP		
6	56 (49.6)	6 (31.6)
7 (3+4)	52(46)	10 (52.6)
7 (4+3)	5 (4.4)	3 (15.8)
The percentage of tumor volume from TRBP (%)		
0–5	2 (1.8)	0
6–25	87 (77)	15 (79)
26–50	19 (16.8)	2 (10.5)
51–100	5 (4.4)	2 (10.5)
The pathological stages		
pT2	64 (56.6)	5 (26.3)
pT3	49 (43.4)	14(73.7)
Gleason score of RP		
6	12 (10.6)	1 (5.2)
7(3+4)	75 (66.4)	9 (47.4)
7(4+3)	26 (23)	9 (47.4)
The percentage of tumor volume from RP (%)		
0–5	1 (0,9)	0
6–25	82 (72.5)	10 (52.7)
26–50	28 (24.8)	7 (36.8)
51–100	2 (1.8)	2 (10.5)

The values of PTV in biopsy material within the group 1, were found in 2 patients (1.8%), from group 2 at 87 patients (77%), in 19 patients (16.8%) in group 3, while the biggest PTV was in 5 patients (4.4%). After RP, PVT in group 1 was found only in one patient (0.9%), while the largest number specified in group 2, even in 82 patients (72.5%).In 28 patients (24.8%), there was a group 3 of PTV and only 2 patients (1.8%) with PTV at intervals of 51-100%. With Cox regression analysis it was found that PSA and PTV from the RP have statistical significance in univariate analysis. In multivariate analysis, PSA is close to the very limits of statistical significance in correlation with the TV from RP (model 2) and PSA, TV from RP (model 4). Age of the patients was analyzed because of comorbidity that tracks and thus the life expectancy. Models of analysis of the parameters listed in table 2.

Biochemical progression (BP) was registered in 19 patients (16.8%). It was exhibited in the context of 24 months, with a median of 18 months. In one patient, 69 months after RP was founded BP. The average age of patients in the group with BP was 64 years (54–74 years). In assessing the BP statistical significance existed in the clinical ($p<0.001$) and in pathological stage KP ($p=0.005$). According to the PSA group, in the majority of patients with BP, a total of 18 patients (94.8%), preoperative PSA levels were higher than 10 ng/ml and only in one patient (5.2%) were in the gray zone (4.1–10 ng/ml). Average values of PSA at BP amounted to 12.4 ng/mL (5.7–19.9). Clinical stage T1 existed in 5 patients (26.3%) with BP, T2 in 11 patients (57.9%) and T3 in 3 patients (15.8%). In relation to the value of the biopsy GGS, most BP is registered in patients with GGS 7 (3+4) of 10 (52.6%). According to the others GGS groups that number was 6 patients (31.6%) for GS 6 (3+3) and 3 patients (15.8%) with GGS 7 (4+3). Within GGS from RP only one patient (5.3%) with GGS 6 (3+3) BP developed, with GGS 7 (3+4) in 9 patients (47.4%) and with GGS 7 (4+3) in 9 patients

Table 2. Models of analysis of the parameters.

	p value	HR	95% IP	
			Lower	The top
Models 1. Univariate analysis				
PSA	0.001	1.183	1.073	1.304
PTVfromRP	0.002	1.051	1.019	1.084
Age	0.694	1.016	0.938	1.100
GGS from RP	0.012	2.814	1.258	6.298
Model 2. PSA and PTV from RP				
PSA	0.014	1.145	1.028	1.274
PTV from RP	0.081	1.031	0.996	1.067
Model 3. PSA and GGS from RP				
PSA	0.011	1.150	1.032	1.281
GGS from RP	0.182	1.790	0.762	4.207
Model 4. Age, PSA, PTV from RP				
PSA	0.006	1.171	1.046	1.310
PTV from RP	0.060	1.034	0.999	1.071
Age	0.176	1.061	0.974	1.155
Model 5. Age, PTV from RP and GGS from RP				
Age	0.393	1.037	0.954	1.126
PTV from RP	0.086	1.036	0.995	1.078
GGS from RP	0.171	1.988	0.743	5.315
Model 6. PSA, PTV from RP, GGS from RP				
PSA	0.027	1.134	1.015	1.268
PTV from RP	0.244	1.024	0.984	1.066
GGS from RP	0.501	1.399	0.526	3.721
Model 7. PSA, PTV from RP, GGS from RP				
Age	0.172	1.062	0.974	1.158
PSA	0.013	1.159	1.031	1.303
PTV from RP	0.209	1.027	0.985	1.069
GGS from RP	0.487	1.414	0.533	3.752

Table 3. Statistically significant parameters for the development of BP after RP.

	Biochemical progression		*p* value
	Yes	No	
Age	64.2±6.4	63.9±5.7	0.881
PSA	12.5±3.9	8.8±3.7	<0.001
PTV from BP	23.4±18.7	19.8±13.6	0.024
PTV from RP	29.7±11.4	21.7±9.7	0.001
GGS from RP			
6 (3+3)	11 (91.7%)	1 (8.3%)	
7 (3+4)	66 (88.0%)	9 (12.0%)	0.023
7 (4+3)	17 (65.4%)	9 (34.6%)	
kT			
T1	5 (8.3%)	55 (91.7%)	
T2	11 (22.9%)	37 (77.1%)	0.002
T3	3 (60.0%)	2 (40.0%)	
pT			
T2	5 (7.8%)	59 (92.2%)	0.003
T3	14 (28.6%)	35 (71.4%)	

(47.4%). In 14 patients (73.7%) with BP, T3 postoperative stage was determined and T2 stage was determined in 5 patients (26.3%).

Most frequent PTV in the group of patients with BP and from TRBP from RP was in groups 1 and 2 (for PTV 6–50%), an average of 30%.

Determined according TRBP,the most common PTV existed in 15 patients (79%), and determined from RP in 10 patients (52.7%). In the group with BP, high statistical significance was found for preoperative PSA levels ($p<0.001$), PTV from biopsy material ($p=0.024$) and the PTV from the RP ($p=0.001$). It was observed statistical significance in the group with BP and according to GGS from biopsy ($p=0.016$) and from operating materials ($p=0.023$). Table 3 are parameters were statistically significant for the development of BP after RP.

DISCUSSION

The first results of character tumor volume (TV) in localized PC, in nineties pointed to its prognostic significance. However, it was lacking the monitoring of patients through the post-operative PSA levels that have not yet been widely applied in the world [9,13]. At the same time there were recommendations that TV should not be a routine part of the pathologist report, because it has no predictive value, particularly in relation to the benefits of GGS [8]. One of the reasons for the prognostic significance of TV in the PC IS the absence of a unified position on the right time and manner of further treatment in case of manifestation of BP. Expression of PSA

progression represents a heterogeneous event of PC. The results of some studies show that PSA progression precedes clinical diagnostic dissemination PC over a period of several months to several years. In some studies there were no significant differences in 10-year survival of patients with and without PSA progression after RP [14].

Maintenance of the differences in the assessment of the real limitations of PC in the selection of patients for the treatment of RP, assessed through serum PSA values is the lack of studies in the 21st century.Within the intermediate levels of serum PSA, in 33% of patients PC is diagnosed. Intermediate PSA values represent important information about the limitations of the tumor because, after RP, diagnose in 53% -81% of patients with localized PC.After RP and in the range of PSA values in more than 30% of patients can be diagnosed locally advanced PC [14,15]. In our analyzed group of intermediate PSA values,we determined in 71 patients (62.8%), of whom only one from BP in the postoperative pT3 stage.

Divided opinions on the importance of PTV are the result of the application of various methods of its determination. These methods include the maximum diameter or multiple fields of tumor growth calculated through a sophisticated computerized method or method of visualization on a certain block sections [16-19]. In our work, we applied imaging method for the percentage of PC.The most frequent PTV in patients with BP, determined in TRBP and RP, was in group 1 with the distribution of PTV 6-25%. This result is in line with the limit PTV values KP > 20%, which is mentioned in several clinical studies. In the work of Hinkelammert and associates [19], with multivariate analysis was demonstrated the predictive value PTV, as an independent factor, for the development of BP after RP and that for the value of PTV> 20%. Song and authors [20] have pointed out the significance of the results for a range of tumor volume from 14% to 29%. However, for the same chosen method of determining tumor volume predictive significance in other works is not determined [4,7,9].

The results of our analysis showed a positive correlation between preoperative PSA values, postoperative stage and PTV. In 73% of patients with stage pT3 and PTV about 30% we have found BP. Similar results are found in the study of Bleckwell and assistant, where it is demonstrated that the preoperative value of PSA is significant in predicting not only TV, but also pathological stage and the risk of spread of the disease [21]. During follow-up of patients after RP from 29-77 months in 83.2% of patients there was no appearance of BP. The results of our analysis are similar to the results of major studies of Ramos and authors derived from 1850 RP which showed that the five-year period of monitoring BP does not present in 82% of patients with PTV> 20% [22]. In the magazine work of Swanson and Basler [23] PT greater than 25% appears as significant predictor of biochemical progression in 57% -88% of patients in the five-year follow-up period after the RP, and in 25% of patients with PT below 25%. In 19 patients (16.8%) from our group BP is expressed in a lower percentage, but over a period of two years.The high statistical significance in the group with BP, we have found from correlation with the GGS. There was equal representation of GG7 (3 + 4) and GGS7 (4 + 3) at 47.4%. This information is not common because in the most studies, this is linked to more

aggressive behavior of PC with GGS7 (4 + 3), which is diagnosed in more than 69% of patients with BP after RP [4].

CONCLUSION

This is a study of an institution, with a retrospective comparison of PTV with standard parameters in a small group of patients. During the study there were no deaths. Our study showed the predictive significantconnections of preoperative PSA values and the values of PTV after operational treatment and that these are independent parameters in the assessment of results of treatment, in particular in the group with the values of patients with PTV 6-50%, which also carries the greatest risk of BP.

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