of the Alexandrovska University Multiprofile Hospital for Active Treatment over a period of nine years. All the patients gave their written informed consent to participate. The protocols conformed to the guidelines of the 1975 Helsinki Declaration. All the patients had renal transplantation and were at least 18 years of age. Patients with mental disturbances or proven oncological diseases, including pulmonary neoplasms, were excluded from the study. The exclusion criteria were chronic pulmonary diseases like asthma and chronic obstructive pulmonary disease or dysfunctional graft with developed terminal renal insufficiency, and chronic hemodialysis treatment. A history of pulmonary tuberculosis successfully treated in the past did form part of the eligibility criteria. In cases of a second or subsequent pulmonary complication, only the first complication, registered for the respective patient, was used for the needs of the study and the data analysis.

Methods

Detailed medical history was prepared for each patient, and all the patients underwent complete clinical examination. When the criteria responsible for the development of pneumonia were present, the patients were hospitalized for treatment at the clinic. During the hospitalization period, the pulmonary and cardiac statuses were followed-up on a daily basis, along with a control of the vital signs – arterial pressure, pulse and respiration rate, body temperature, and 24-hour quantity of urine. The following hematological and biochemical blood tests were performed: complete blood count with differential leukocyte count, erythrocytes sedimentation rate, C-reactive protein (CRP), creatinine, urea, aspartate aminotransferase, alanine aminotransferase, potassium, sodium, chlorides, blood glucose, fibrinogen. The tests of all the patients also included electrocardiography and arterial blood gases (ABGs) analysis (equipment used – RapidLab 248; Siemens Healthineers, Erlangen, Germany). Spirometry and in some cases diffusion capacity analysis (equipment used – Ganshorn Medizin Electronic GmbH, Niederlauer, Germany) were performed in accordance with the requirements of the American Thoracic Society / European Respiratory Society Guidelines (Miller 2005). Microbiological tests of sputum, pleural effusion liquid or broncho-alveolar lavage, and of blood for aerobic and anaerobic microorganisms, fungi, and *Mycobacterium tuberculosis* were done. We used Realquality RQ-CMV standard kits by AB Analitica s.r.l., Padova, Italy, for the identification and quantitative determination of the Cytomegalovirus deoxyribonucleic acid. Posteroanterior radiography of all the patients was performed. In cases of diagnostic difficulties, high resolution computer tomography of the thorax was performed (device used – Aquilion 64-multi-slice, Toshiba Medical Systems Corporation, Otawara, Japan; following Vitrea 2 protocol of Vital Images, Minnetonka, MN, USA). Some of the patients underwent fiberoptic bronchoscopy with bronchoalveolar lavage, catheter-biopsy, and – if necessary –fibre-clamp biopsy (BF 1T30, Olympus Corporation, Tokyo, Japan). Cytological or histological examinations of the material from the bronchial mucosa or the lung parenchyma were all examined.

Statistical analysis

The statistical data processing was carried out using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The adopted level of significance, eliminating the null hypothesis, was $p < 0.05$. The statistical analyses included a variational analysis of the quantitative variables – median, standard deviation, standard error of the median, and 95% confidence interval of the median, frequency analysis of qualitative variables, graphics. The χ^2 test and the Fisher's exact test were used for establishing the dependency between two qualitative variables, and the Kolmogorov–Smirnov and the Mann–Whitney methods for testing the normality of distribution of the quantitative variables. Quantitative indicators were assessed using a receiver operating characteristic (ROC) analysis. The probability ratio was calculated using logistic regression analysis, and the establishment of the effects of various factors and the risk estimation were carried out based on the Cox regression, using Kaplan–Meier survival curves.

RESULTS

A total of 124 kidney recipients with pneumonia were included in the study. The mean age of the patients was 41.23 ± 13.46 years. The male-to-female ratio was 78/46 (62.9% men and 37.1% women). According to the outcome of pneumonia, the patients were divided into two groups. In the first group, which was pneumonia (+), there were 83 patients recovered from pneumonia. The other 41 recipients in pneumonia (–) group died as a result of the pneumonia or related complications during their hospitalization. There was no significant difference between the two groups according to main demographic data – age, sex, smoking status, type and length of dialysis treatment before transplantation, immunosuppressive agents used in both patient groups, concomitant diseases ($p > 0.05$ for all).

In the pneumonia (+) group, three patients became ill during the first postoperative month, 36 patients between the first and sixth month after the transplantation, and 44 patients in the late post-transplantation period (more than six months after surgery). In the pneumonia (–) group, six patients became ill during the first postoperative period, 27 patients became ill between the first and sixth month after the transplantation, and eight patients in the late post-transplantation period. There is a statistically significant dependence between the period of development of pneumonia and the outcome of the disease ($p < 0.001$).

The effect of the period during which pneumonia occurs on the survival rate of the patients is shown in Figure 1.

The main clinical symptoms are similar in both groups ($p > 0.05$). The only statistically significant difference in clinical features between the two groups is the presence of dyspnoea at admission ($p = 0.033$). This symptom occured more frequently in the pneumonia (–) group.

The major hematological and biochemical parameters are shown in Table 1. Statistical differences between their values in the groups of patients according to the outcome of pneumonia were observed for CRP and lymphocytes. The calculated ROC curve for CRP is shown in Figure 2. The area below the curve is 0.702 (95% CI, 0.584–0.819), p = 0.003.

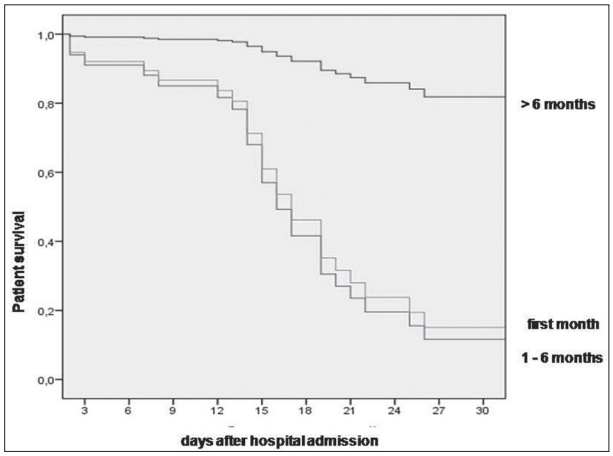

Figure 1. Kaplan–Meier plot – effect of the period after the transplant on the survival rate in patients with pneumonia

Table 1. Comparison of the hematological and biochemical parameters between the two groups

Laboratory indicator	Median ± SD Pneumonia (+)	Median ± SD Pneumonia (–)	p
CRP	54.60 ± 77.285	94.32 ± 94.100	0.026*
Erythrocytes	51.19 ± 31.688	55.30 ± 26.913	0.530
Leukocytes	9.175 ± 4.6359	9.656 ± 4.3531	0.583
Neutrophils	10.072 ± 11.8294	15.200 ± 21.3843	0.069
Lymphocytes	2.573 ± 3.8850	1.535 ± 2.5872	0.026*
Monocytes	0.965 ± 1.9900	0.777 ± 0.8372	0.301
Eosinophils	0.164 ± 0.4307	0.126 ± 0.1667	1.000
Basophils	1.02 ± 0.136	1.04 ± 0.192	1.000
Thrombocytes	266.59 ± 103.618	236.01 ± 132.407	0.062
Hemoglobin	117.00 ± 23.261	111.22 ± 18.331	0.442
Fibrinogen	5.1842 ± 1.66059	5.9019 ± 1.92601	0.559
Creatinine	205.94 ± 165.943	270.69 ± 210.343	0.321
Albumin	33.75 ± 1.03	32.00 ± 0.96	1.000

CRP – C-reactive protein
*Statistically significant

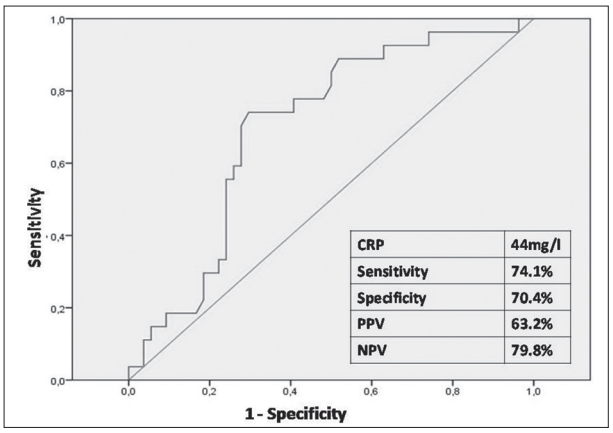

Figure 2. ROC curve of CRP as a predictor of the fatal outcome of pneumonia

The ABGs analysis shows that at admission 38 patients (45.78%) of those that subsequently recovered and 35 (85.37%) of the subsequently deceased patients had hypoxemia (p = 0.001). Figure 3 shows the ROC curve for PaO_2 in the ABGs at admission. The area below the curve is 0.703 (95% CI, 0.591–0.815), p = 0.003.

The ABGs analysis, performed on the third day of the treatment, revealed hypoxemia in 23 (27.71%) of the subsequently recovered and in 39 (95.12%) of the subsequently deceased patients (p < 0.001). Figure 4 shows the ROC analysis comparing both groups, based on the outcome of the disease and the PaO_2 values, obtained from the ABGs analysis on the third day of the treatment. The area below the curve is 0.884 (95% CI, 0.814–0.955), p < 0.001.

There was a statistically significant difference in the localization of the X-ray alterations between the two groups (p < 0.001). The predominant radiological findings in the pneumonia (–) group were bilateral changes. They increased the risk of fatal outcome (HR = 2.482; 95% CI, 1.439–4.279; p = 0.001).

A failure of the antibiotic treatment administered and a need to re-evaluate it was determined in 21 (25.3%) recipients in the pneumonia (+) group and in 38 (92.68%) patients in the pneumonia (–) group. The two groups differ statistically (p < 0.001) (Figure 5).

In the pneumonia (–) group, three (7.31%) recipients were subjected to non-invasive ventilation (NIV) and 31 (75.61%) to invasive ventilation. In the pneumonia (+) group, seven (8.43%) patients were subjected to NIV, and two (2.41%) to invasive ventilation (p < 0.001). The effect of the need for intubation and mechanical ventilation

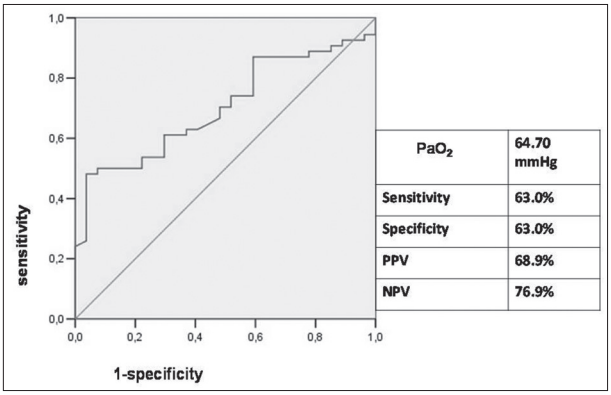

Figure 3. ROC curve of PaO_2 on the first day, as a lethality predictor

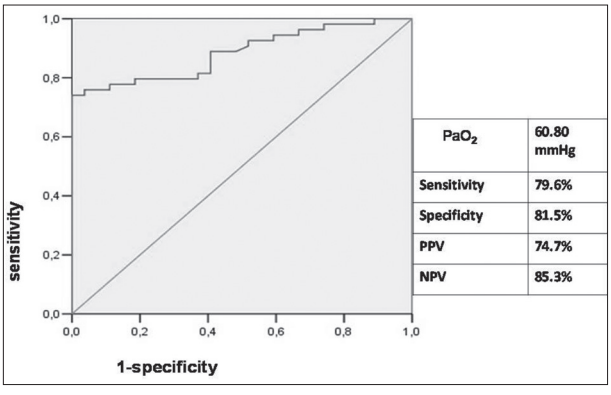

Figure 4. ROC curve of PaO_2 on the third day, as a lethality predictor

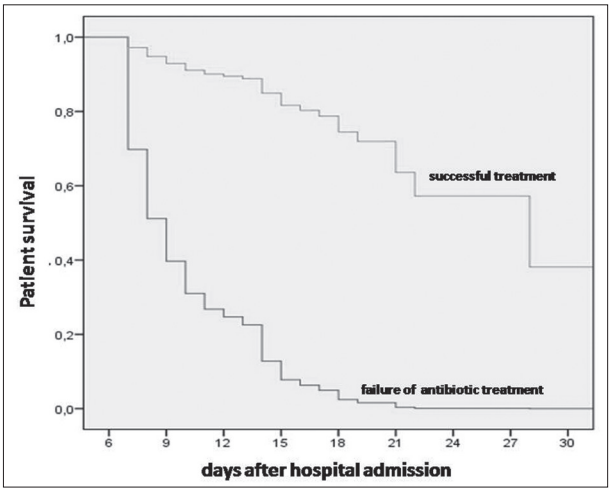

Figure 5. Effect of adjusting the antibiotics therapy on the survival rate of pneumonia patients

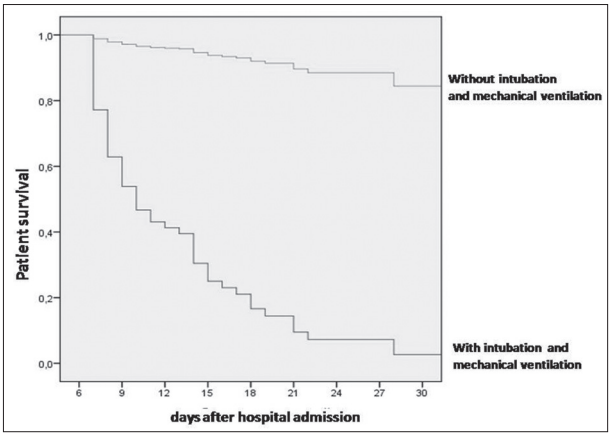

Figure 6. Effect of mechanical ventilation on the survival rate of pneumonia patients

Table 2. Indicators for the assessment of the fatal outcome risks

Indicator	HR	95% CI	p
1st month after renal transplantation	2.027	1.092–3.761	0.025
1–6 months after renal transplantation	2.303	1.104–4.803	0.026
Dyspnoea	2.184	1.239–3.849	0.007
Hypoxemia	2.261	1.314–3.890	0.003
Bilateral radiological changes	2.480	1.439–4.279	0.001
Failure of initial antibiotic therapy	3.548	2.418–5.205	< 0.001
Intubation and mechanical ventilation	4.635	2.276–9.437	< 0.001

HR – hazard ratio

on the survival rate of pneumonia patients is shown in Figure 6.

The risk factors for an in-hospital fatal outcome of pneumonia in patients after renal transplantation are shown in detail in Table 2.

DISCUSSION

The frequency of pneumonia, reported after RT varies 2.9–30%, as these are the lowest rates, compared to other organ transplantations [11, 12]. According to our results, the mortality rate resulting from pneumonia is 33.06%. The available literature provides inconsistent data on the mortality of pulmonary infections. Some authors report a rate of 15–20% [13]. Other studies show mortality rates of 21–35%, as there are certain differences between the mortality from pneumonia, acquired in public (8%), and Hospital-acquired (nosocomial) cases (58%) [14, 15].There is a statistically significant dependency between the period of the development of the pulmonary infection and the outcome of the disease ($p < 0.001$). The pneumonia outcome depends on the amount of time which passes after the transplantation before the infection develops [16]. The mortality rate is higher among patients who acquire pneumonia in the early post-transplantation period, i.e. between one and six months after surgery. The development of pneumonia during the early postoperative period (during the first month) increases the lethal outcome risk 2.027-fold (HR = 2.027; 95% CI, 1.092–3.761; p = 0.025). The development of pneumonia one to six months after surgery increases the risk of an unfavorable outcome 2.303-fold (HR = 2.303; 95% CI, 1.104–4.803; p = 0.026). At the same time, most of the successfully treated patients developed pneumonia in the late post-transplantation period.

Clinical symptoms of pneumonia do not differ from those in immunocompetent patients. The prevailing complaints of patients with the fatal outcome were dyspnoea. A statistically significant dependency between the outcome of pneumonia and the presence of dyspnoea at admission was determined (p = 0.033).The dyspnoea increases the risk of the unfavorable outcome 2.184-fold (HR = 2.184; 95% CI, 1.239–3.849; p = 0.007).

The analysis of the laboratory indicators revealed typical changes in infection markers, also observed in immunocompetent patients with pneumonia – increased CRP, leukocytosis with neutrophilia, lymphopenia, monocytosis. Also observed were slight anemic syndrome and increased levels of creatinine and fibrinogen. Statistically significant differences between the values of the laboratory results in the groups of patients, according to the pneumonia outcome, were observed only for CRP and lymphocytes. The analysis of the CRP ROC curve showed that CRP at 44mcg/L reveals the highest sensitivity (74.1%) and specificity (70.4%) as a fatal outcome predictor. In multivariate analysis, Diadar et al. [17] also found that high CRP is associated with significant risk for death from pneumonia.

Patients with post-RT pneumonia show increased rates of hypoxemia. At the same time, low levels of PaO_2 on admission or in the course of treatment are a risk factor for the fatal outcome of pneumonia [18]. Our results show that the ABGs analysis at admission revealed hypoxemia in 85.37% of the patients who subsequently died (p = 0.001). The PaO_2 values below the normal range increase the risk of the fatal outcome 2.261 times (HR = 2.261; 95% CI, 1.314–3.890; p = 0.003). According to the ROC analysis, the PaO_2 level of 64.7 mmHg has both the highest sensitivity and specificity (63%) as a predictor of the fatal outcome. If PaO_2 is observed dynamically, hypoxemia was determined in 95.12% of the deceased patients ($p < 0.001$) on the third day of the treatment. The analysis of the ROC

curve on the third day of the treatment showed the PaO_2 value of 60.8 mmHg with very high sensitivity (79.6%) and specificity (81.5%) as a predictor of the fatal outcome. These results coincide with the manuals prepared to date, in which PaO_2 values below 60 mmHg are considered a risk factor for the fatal outcome of pneumonia.

Several previous studies showed that multilobar radiographic pulmonary infiltrates were significantly associated with mortality [19, 20]. In our study, X-ray changes have diverse localization, as the presence of bilateral infiltrates increase the risk of the fatal outcome 2.482 times (HR = 2.482; 95% CI, 1.439–4.279; p = 0.001).

The early initiation of the treatment with appropriate antibiotics is of great importance for the outcome of pneumonia after RT. In the case of therapy failure, risk of mortality increases significantly [21, 22, 23].

According our results, a failure of the originally started antibiotics treatment and its subsequent re-evaluation in the course of treatment was observed in 92.68% of the patients in the pneumonia (–) group (p < 0.001).The need for adjusting the antibiotics therapy increases the risk of the fatal outcome 3.548-fold (HR = 3.548; 95% CI, 2.418–5.205; p < 0.001).

Due to the occurring complications in the course of pneumonia, some patients had to undergo NIV or invasive ventilation. Mechanical ventilation increases the risk of the fatal outcome in patients with pneumonia. This fact has been confirmed by numerous studies carried out previously [15, 24, 25]. Prolonged mechanical ventilation is mentioned in a number of publications as the main risk factor for the development of nosocomial pneumonias [14, 15]. At the same time, in recent years, a significant volume of data has been accumulated on the role of the NIV in the treatment of acute respiratory insufficiency in immunosuppressed patients [26]. A randomized study by Antonelli et al. [27], involving 25 patients post RT, showed that NIV, due to hypoxemic respiratory failure, significantly reduced mortality rates (p = 0.05). Hilbert et al. [28] reported a lower rate of use of intubations (46% compared to 77%) and lower mortality rate (50% compared to 81%) (p ≤ 0.05 for both) among immunocompromised patients with acute respiratory failure and NIV, compared to those observed in conventional treatment [28].

The results of our study are similar to the previous publications. We have established a statistically significant correlation between the outcome of the disease and the type of ventilation administered (p < 0.001). The group of the recovered patients is dominated by those with non-invasive ventilation – seven kidney recipients (8.43%). In the pneumonia (–) group, 31 (75.61%) patients had been intubated and mechanical invasive ventilation had been administered to them. The need for intubation and mechanical ventilation increases the risk of the fatal outcome 4.635 times (HR = 4.635; 95% CI, 2.276–9.437; p < 0.001). Most patients on NIV recovered. At the same time, NIV is not statistically significant for the outcome of the disease. The results are probably due to the small number of patients treated with NIV.

The markers of inflammation, hypoxemia, and hypocapnea from the ABGs analysis, as well as the bilateral infiltration changes, shown by the radiological tests of the lungs, may be used as predictors for the outcome of the disease and the occurrence of complications. The need for re-evaluation of the antibiotics treatment in the course of the disease is an independent risk factor for the development of complications and the fatal outcome. That fact may be used when determining the high-risk groups of renal recipients with pneumonia, requiring increased attention and strict control in the course of treatment.

Our study has not determined any factors associated with increased risk of developing pneumonia. No comorbidities which may have an aggravating effect on the course of pneumonia have been taken into account. No long-term evaluation of the survival rate after pneumonia in this group of patients has been made. We studied only in-hospital death and did not analyze the mortality thereafter.

CONCLUSION

Based on the results that we have obtained, it is possible to prepare an algorithm with prognostic factors associated with a more severe course of pulmonary infections and an increased risk of the occurrence of complications and the fatal outcome. This makes it possible to differentiate a high-risk group of patients requiring early etiological diagnosis or strict control of the condition, in order to reduce the mortality from pneumonia after a renal transplantation.

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Упала плућа и болничка смртност после трансплантације бубрега

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САЖЕТАК

Увод/Циљ Пнеумоније су један од најчешћих разлога морбидитета и морталитета код прималаца бубрега.

Циљ овог рада је био да дефинише факторе повезане са већим ризиком од морталитета од упале плућа у болници после пресађивања бубрега.

Методе Анализирана су 124 болесника са пнеумонијом и пресађеним бубрегом хоспитализована у периоду од девет година. Коришћени су различити неинвазивни и инвазивни дијагностички тестови.

Резултати Због пнеумоније или сродних компликација умро је 41 болесник током боравка у болници. Фактори повезани са повећаним ризиком од морталитета у болници били су следећи: развој пнеумоније током раног постоперативног периода (до првог месеца) (*HR* = 2,027; *p* = 0,025) или од првог до шестог месеца после операције (*HR* = 2,303; *p* = 0,026), диспнеја (*HR* = 2,184; *p* = 0,007) и хипоксемија (*HR* = 2,261; *p* = 0,003). Присуство билатералних инфилтрата (*HR* = 2,482; *p* = 0,001), неуспех почетне антибиотске терапије (*HR* = 3,548; *p* < 0,001), трахеална интубација и механичка вентилација (*HR* = 4,635; *p* < 0,001) такође су повећавали ризик од смртног исхода.

Закључак Познавање прогностичких фактора повезаних са повећаним ризиком од смртног исхода од пнеумоније у болници после трансплантације бубрега пружа могућност одређивања групе болесника високог ризика, која захтева рану етиолошку дијагнозу и строгу контролу стања да би се смањила смртност од плућних инфекција код прималаца бубрега.

Кључне речи: пнеумонија; смртност; прималац; трансплантација, солидни орган, бубрег

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

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

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SUMMARY

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

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 biochemical progression in patients with RP and the biopsy Gleason score of 6 and 7.

Methods The analysis included the results of treatment of 228 patients with the committed radical retropubic prostatectomy for localized PC in the 2007–2011 period. According to the Gleason grade system values, three groups were identified – 6 (3 + 3), 7 (3 + 4) and 7 (4 + 3). According to the preoperative PSA values the following three groups were determined and monitored: ≤ 4 ng/ml, 4.1–10 ng/ml, and ≥ 10.1 ng/ml. Biochemical progression was defined as two consecutive increases of PSA values ≥ 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 PTV groups were determined: 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 RP was 6–50%, an average of 30%.

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

Keywords: prostate cancer; radical prostatectomy; prostate-specific antigen; tumor volume; biochemical recurrence

INTRODUCTION

Prostate cancer (PC) is the most common tumor in older men and one of the leading malignant tumors 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 declines each year and currently stands at 9–11%. Radical prostatectomy (RP) is the best form of treatment of patients with locally confined PC, who are expected to survive longer than 10 years. Biochemical progression (BP) of the disease occurs in 27–53% of patients after RP [2]. BP after RP is defined as the elevation of the value of prostate-specific antigen (PSA) in the absence of diagnostic metastases [2–5]. Together with the Gleason grade system (GGS) and the stage of the disease, serum PSA values have represented the leading standard PC parameters for decades [1–4]. The first results of work based on an estimate of the PC volume in diagnostic biopsies and material from RP and its questionable character in assessing the progression of the malignant disease have emerged in the 1990s. The assessment of PC volume 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, PC volume analyzed through GGS and the stage of the disease has not gained 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 PC percentage volume in biochemical progression in patients with RP and the biopsy GGS score of 6 and 7.

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METHODS

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

Macroscopic treatment of the prostate tissue, seminal vesicles, and groups of lymph nodes, was performed with the use of protocol-labeled samples according to topography changes, including the analysis of the prostate apex and the status of the entire margin [11]. The volume of histologically processed tissue ranged 70–100% of the total weight of the prostate. Prolonged tissue fixation in 10% formalin was applied, after which parasagittal sections 2–3 mm wide were made. Histologic type, tumor grade, and standard WHO grade (1 to 3 degrees) as GGS and pathological stage of the PC were determined from paraffin embedded prostate tissue obtained from RP, treated with standard hematoxylin and eosin staining. The postoperative stage in all the patients was revised and fully adapted to the seventh edition of the official AJCC/UICC protocol in 2009 [12]. Serum levels of PSA were determined by Hybritech monoclonal immunoassay method (Hybritech, Inc., San Diego, CA, USA). According to the preoperative PSA values, the following three groups were determined and monitored: group 1 – PSA values of ≤ 4 ng/ml; group 2 – PSA values of 4.1–10 ng/ml; group 3 – PSA values of ≥ 10.1 ng/ml. The first postoperative result of serum PSA was reached after three months. Biochemical progression was defined as two consecutive increases of 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, and transcapsular expansion were analyzed as individual data by slides and customized folder. The total field of PC was estimated visually, according to the map. The PTV was determined from the weight of the prostate without seminal vesicles and according to assumed specific gravity of the prostate for a little more than 1 g/cm^3 [13]. Macroscopic and microscopic analyses were made by a single pathologist. The following four groups were determined: group 1 – PTV of 0–5%; group 2 – PTV of 6–25%; group 3 – PTV of 26–50%; and group 4 – PTV of 51–100%. The patients were monitored postoperatively 21 to 83 months, three months during the first year of treatment and then every six months. Data are presented as number (percent) or mean ± standard deviation, depending on the data type. Group differences were analyzed using Student's t-test,

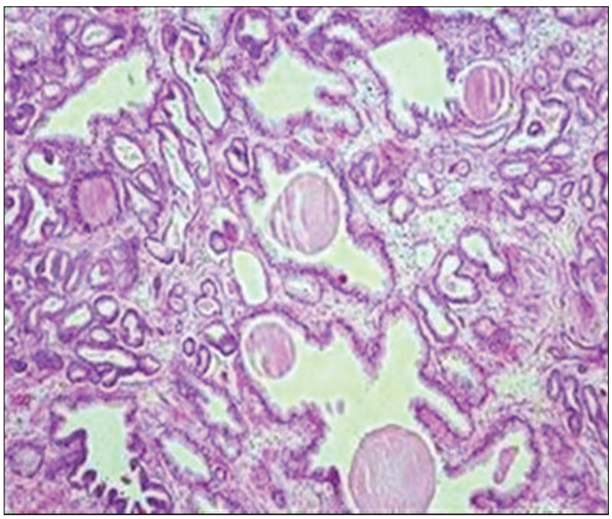

Figure 1. Prostate cancer GGS 6 3 + 3; H&E, ×40

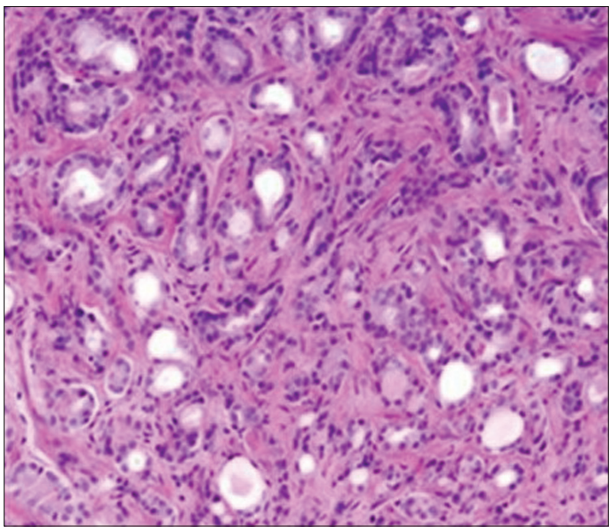

Figure 2. Prostate cancer GGS 7 3 + 4; H&E, ×40

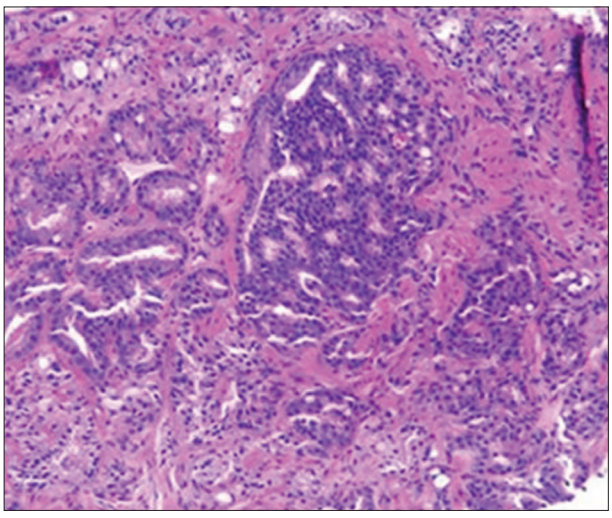

Figure 3. Prostate cancer GGS 7 4 + 3; H&E, ×40

Mann–Whitney U-test and χ^2 test (Pearson's and trend test). Cox regression was used to model the relationship between independent variables and biochemical progression of PC. All the data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) statistical software. All p-values less than 0.05 were considered statistically significant.

RESULTS

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

According to PTV values of the biopsy material, two patients (1.8%) were distributed into PTV group 1, 87 patients (77%) into PTV group 2, 19 patients (16.8%) into PTV group 3, while the highest PTV values (group 4) were found in five patients (4.4%). After RP, only one patient (0.9%) remained in PTV group 1, as much as 82 patients (72.5%) were in PTV group 2, 28 patients (24.8%) were in PTV group 3, and only two patients (1.8%) were in PTV group 4, with PTV in the range of 51–100%. With Cox regression analysis it was found that PSA and PTV with RP have statistical significance in the univariate analysis. In the multivariate analysis, PSA is close to the very limits of statistical significance in correlation with the tumor volume (TV) from RP (model 2) and PSA, TV from RP (model 4). The patients' age was analyzed because of associated comorbidities and subsequent life expectancy. Models of analysis of the parameters listed in Table 2.

BP was registered in 19 patients (16.8%). It was exhibited over a period of 24 months, with a median of 18 months. In one patient, BP was found 69 months after RP. The average age of patients in the group with BP was 64 years (54–74 years). In assessing BP, statistical significance existed in the clinical ($p < 0.001$) and in the pathological stage of prostate cancer ($p = 0.005$). 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 the levels were in the gray zone (4.1–10 ng/ml) in only one patient (5.2%). The average values of PSA at BP amounted to 12.4 ng/ml (the range being 5.7–19.9 ng/ml). Clinical stage T1 existed in five patients (26.3%) with BP, T2 in 11 patients (57.9%), and T3 in three patients (15.8%). In relation to the biopsy GGS scores, most of BP was registered in 10 (52.6%) patients with GGS 7 (3 + 4) score; six patients (31.6%) had GGS 6 (3 + 3) score, and three patients (15.8%) had GGS 7 (4 + 3) score. Regarding GGS score from RP, BP developed in only one patient (5.3%) with GGS 6 (3 + 3) score, in nine patients (47.4%) with GGS 7 (3 + 4) score, and in nine patients (47.4%) with GGS 7 (4 + 3) score. Postoperative stage T3 was determined in 14 (73.7%) patients with BP, and T2 stage was determined in five patients (26.3%).

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

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

Parameter	Entire group n (%)	BP n (%)
Number of patients	113	19 (16.8)
Years of age		
Average	64	64
From – To	50–76	54–74
Monitoring time (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)
GGS 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)
PTV 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)
Pathological stages		
pT2	64 (56.6)	5 (26.3)
pT3	49 (43.4)	14 (73.7)
GGS 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)
PTV 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)

BP – biochemical progression; PSA – prostate-specific antigen; TRBP – transrectal biopsy; PTV – percentage of tumor volume; RP – radical prostatectomy; GGS – Gleason grade system

Table 2. Models of parameter analysis

Models	p-value	HR	95% CI	
			Low	High
Model 1. Univariate analysis				
PSA	0.001	1.183	1.073	1.304
PTV from RP	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

HR – health risk; PSA – prostate-specific antigen; PTV – percentage of tumor volume; RP – radical prostatectomy; GGS – Gleason grade system

Table 3. Statistically significant parameters for the development of biochemical progression (BP) after radical prostatectomy (RP)

Parameters	BP		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%)	0.023
7 (3+4)	66 (88%)	9 (12%)	
7 (4+3)	17 (65.4%)	9 (34.6%)	
kT			
T1	5 (8.3%)	55 (91.7%)	0.002
T2	11 (22.9%)	37 (77.1%)	
T3	3 (60%)	2 (40%)	
pT			
T2	5 (7.8%)	59 (92.2%)	0.003
T3	14 (28.6%)	35 (71.4%)	

PSA – prostate-specific antigen; PTV – percentage of tumor volume; GGS – Gleason grade system

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

DISCUSSION

The first results of the TV aspect in localized PC in the 1990s pointed to its prognostic significance. However, it was lacking the monitoring of patients through the postoperative 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 PC is the absence of a unified position on the right time and manner of further treatment in case of BP manifestation. The expression of PSA progression represents a heterogeneous event of PC. The results of some studies show that PSA progression precedes clinical diagnostic dissemination of PC over a period of several months to several years. In some studies, there were no significant differences in the 10-year survival rate of patients either with or 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, PC is diagnosed in 33% of patients. Intermediate PSA values represent important information about the limitations of the tumor because, after RP, the diagnosis is reached in 53–81% of patients with localized PC. After RP, locally advanced PC can be diagnosed in more than 30% of patients [14, 15]. In our analyzed group of intermediate PSA values, out of the total number of patients, only one patient developed 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 of 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 being 6–25%. This result is in line with the threshold PTV values of prostate cancer > 20%, which is mentioned in several clinical studies. In a study by Hinkelammert et al. [19], the predictive value of PTV as an independent factor for the development of BP after RP, for the value of PTV > 20%, was demonstrated through a multivariate analysis. Song et al. [20] pointed out the significance of the results for a range of TV from 14% to 29%. However, for the same chosen method of determining TV, predictive significance in other studies is not determined [4, 7, 9].

The results of our analysis showed a positive correlation between preoperative PSA values, postoperative stage, and PTV. We found BP in 73% of patients with stage pT3 and PTV of about 30%. Similar results are found in a study by Blackwell et al. [21], 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. During the follow-up of patients after RP, there was no appearance of BP in 83.2% of patients during 29–77 months. The results of our analysis are similar to the results of a major study by Ramos et al. [22], derived from 1,850 RPs, which showed that BP does not present in 82% of patients with PTV > 20% during the five-year period of monitoring [22]. In a paper by Swanson and Basler [23], PTV greater than 25% appears as a significant predictor of BP in 57–88% of patients in the five-year follow-up period after RP, and in 25% of patients with PTV below 25%. BP is expressed in a lower percentage in 19 (16.8%) patients from our group, but over a period of two years. High statistical significance of GGS correlation with BP is presented in Table 3. There was an equal representation of GGS 7 (3 + 4) score and GGS 7 (4 + 3) score at 47.4%. This information is not common as, this is linked to a more aggressive behavior of PC with GGS 7 (4 + 3) score in most studies, which is diagnosed in more than 69% of patients with BP after RP [4].

CONCLUSION

This is a study made at a single institution, with a retrospective comparison of PTV with standard parameters, with a small group of patients. There were no deaths during the study period. The study showed the predictive significant connections between preoperative PSA values and the values of PTV after operational treatment. It also showed that these are independent parameters in the assessment of the results of treatment, in particular in the group of patients with with PTV values of 6–50%, which also carry the greatest risk for BP.

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

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САЖЕТАК

Увод/Циљ Радикална простатектомија (РП) представља најбољи облик лечења болесника са локално ограниченим карциномом простате (КП). Код 27% до 53% болесника након РП ипак долази до биохемијске прогресије (БП) болести. Циљ 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 је било укључено 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), 7 (3+4) и 7 (4+3). Према преоперативним вредностима ПСА групе установљене су и праћене следеће три групе: ≤ 4 *ng/ml*, 4,1–10 *ng/ml* и ≥10,1 *ng/ml*. Биохемијска прогресија дефинисана је као два узастопна пораста вредности ПСА већа од 0,2 *ng/ml* након РП. Проценат тумор волумена (ПТВ) одређен је као визуелна процена процентуалне заступљености КП у сваком појединачном микроскопском узорку. Одређене су четири 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 РП био је 6–50%, просечно 30%.

Закључак Наша студија је показала предиктивни значај везе преоперативних вредности ПСА и добијених вредности ПТВ после 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