

HISTOPATHOLOGICAL OUTCOMES AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER BASED ON A NEW GRADING SYSTEM

Borislav Spajić^{1,2}, Sven Nikles¹, Igor Grubišić¹, Matej Knežević¹, Shoip Shoipi¹,
Monika Ulamec^{2,3}, Goran Štimac¹, Igor Tomašković^{1,4} and Boris Ružić^{1,2}

¹Department of Urology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;

²School of Medicine, University of Zagreb, Zagreb, Croatia;

³Ljudevit Jurak Department of Pathology, Sestre milosrdnice University Hospital Center;

⁴Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia

SUMMARY – One of the main reasons for the introduction of a new grading system was Gleason sum 7, which differed significantly in the prognosis of the disease depending on the primary Gleason. The aim of this study was to compare grade group 2 and grade group 3, and the impact of cancer percentages in final pathology reports after radical prostatectomy on the occurrence of T3 stage of the disease after radical prostatectomy of clinically localized prostate cancer. The study covered 365 patients with clinically localized prostate cancer who underwent radical retropubic prostatectomy (RRP) over the period of two years. The average percentage of carcinomas found in pathology reports after RRP was 20.1%. With the increase in the grade group, the average percentage of carcinomas in pathology reports increased significantly, $p < 0.001$. With regard to grade groups 2 and 3, irrespective of cancer percentages in pathology reports, more cases of T3 stage were found in grade group 3 when compared to grade group 2, which was statistically significant ($p < 0.001$). However, grade group 2 and grade group 3 patients with $\leq 10\%$ cancer occurrences in final pathology reports after RRP did not show any statistical significance in the occurrence of T3 stage, $p = 0.96$. Prognostic differences in grade group 2 and grade group 3 patients after RRP are significant, but not in all cases, because of their dependence on the percentage of cancer in the final pathology report after RRP of clinically localized prostate cancer.

Key words: *Gleason grade; Grade group; Prostate cancer; Pathology report; Radical prostatectomy*

Introduction

The Gleason score (GS) is the most commonly accepted and widely used parameter for the prediction of tumor biology and treatment outcomes. The Gleason grading system is the best independent predictor for prostate cancer progression after radical prostatectomy. Since its introduction¹, the Gleason grading system has undergone several revisions in order to im-

prove reproducibility and prognostic value^{2,3,4}. Most recently, a new grading system has been proposed by the International Society of Urological Pathology (ISUP) and has been integrated into the 2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs⁵.

The new grading system, ranging from 1 to 5, provides a simplified classification system for predicting the risk of disease progression after radical prostatectomy. One of the main reasons for the introduction of the new grading system was Gleason sum 7, which differed significantly in the prognosis of the disease depending on the primary Gleason^{5,6,7}.

Correspondence to: *Borislav Spajić, MD, PhD, Professor of Urology, Department of Urology, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia*
E-mail: borislav.spajic@kbcsm.hr

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Table 1. Age and PSA patient characteristic

	N	Mean	SD	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Age (years)	365	64.67	6.14	47.00	78.00	60.00	66.00	69.00
PSA level	365	11.61	10.36	1.70	88.92	6.37	8.51	12.75

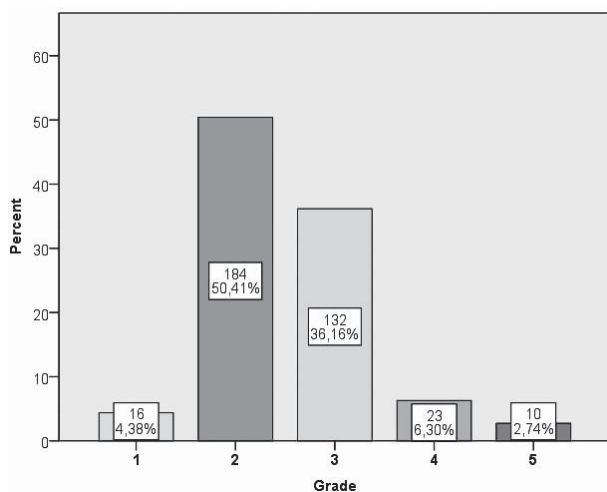


Fig. 1. Grade groups characteristic: The most common grade group was grade group 2 with 50.41% and grade group 3 with a share of 36.16%, while grade group 1 was represented by only 4.38% of the included patients.

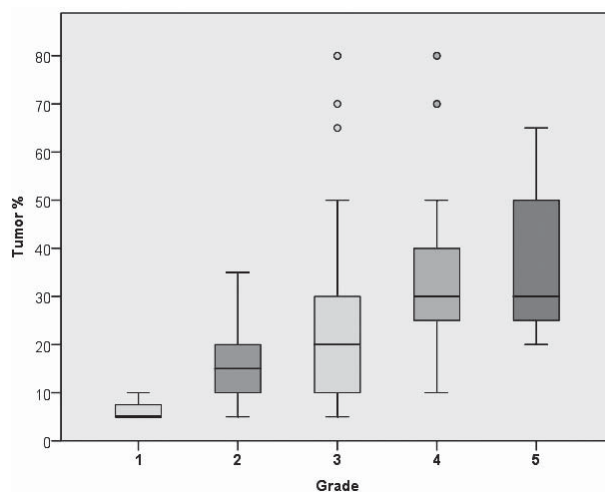


Fig. 2. Relationship between grade groups and cancer percentage: With the increase in the grade group, the average percentage of carcinomas in pathology report found after RRP also increased, $p < 0.001$.

The aim of the study was to compare grade group 2 (GS 3+4) with grade group 3 (GS 4+3) and the impact of cancer percentage in final pathology reports on the occurrence of T3 stage after radical prostatectomy in clinically localized prostate cancer.

Patients and methods

The study involved patients hospitalized in the Department of Urology at Sestre milosrdnice University Hospital Center who underwent RRP in the period between January 2015 and the end of 2016. We analyzed all patients who had undergone RRP using hospital records, operative protocols and pathology reports.

This retrospective study included 365 patients out of the total of 371 patients. One patient was excluded because of lacking pathology reports and 5 other patients due to missing PSA levels. All patients in the study had clinically localized prostate cancer and underwent RRP. The average age of patients who had undergone

surgery was 64.67 years. The youngest patient was 47 and the oldest 78 (Table 1). There was a large number of patients in the range of 66–70 years of age in our cohort ($n=123$, 33.79%). We also had a significant number of patients over the age of 70 ($n=60$, 16.48%). The lowest number of patients in the cohort was younger than 55, only 6.59%. PSA levels ranged from 1.70 ng/ml to 88.92 ng/ml, with the mean PSA value of 11.61 and median value of 8.51 ng/ml (Table 1). The minimum PSA level was 1.7 ng/ml and was found in grade group 2, while the highest PSA level was 88.9 ng/ml and was found in grade group 3. The highest median level of PSA, measuring 15.1 ng/ml, was, expectedly, found in grade group 5. The most common grade groups were grade group 2 with 50.41%, and grade group 3, with a share of 36.16%, while grade group 1 was represented by only 4.38% of the included patients (Fig. 1). We also had only 10 grade group 5 patients (2.74%). The average percentage of carcinomas found in pathology reports following RRP was 20.1%, ranging from 5 to 80% (Fig. 2). The minimum

of 5% was found in grade group 1, while the largest percentage of 80% was found in grade group 4. Out of the total number of 365 patients operated on within the selected period, T2 stage was found in 247, and T3 stage in 118 patients. In grade group 2, there were 153 patients with T2 stage of the disease and 31 patients with T3 stage in the final pathology report. In grade group 3, there were 72 patients with T2 stage and 60 patients with T3 stage in the final pathology report. When we observed patients with $\leq 10\%$ of carcinoma in the final pathology report, there were 68 patients with T2 stage in grade group 2 and 12 patients with T3 stage of the disease. In grade group 3, there were 50 patients with T2 stage and 9 patients with T3 stage.

Statistics

The Kolmogorov–Smirnov tests were used to test the hypothesis of normal distribution. Normally distributed continuous data were reported as mean (standard deviation, SD), while interval data and ordinal data without normal distribution were reported as median (interquartile range) and evaluated using the Kruskal–Wallis test. Categorical variables were presented as count (percentages) and were evaluated using chi-square and Fisher tests where appropriate. Spearman's correlation coefficients were calculated to assess the correlation between PSA levels and tumor clinical characteristics. All P levels < 0.05 were considered significant. All statistical procedures were performed using IBM SPSS Statistics version 24.

Results

The average age of patients who had undergone surgery was 64.67 years. The youngest patient was 47 and the oldest 78 years old (Table 1). Patient age did not increase with the increase of the grade group, $p = 0.48$. PSA levels ranged from 1.70 ng/ml to 88.92 ng/ml, with the mean PSA value of 11.61, and the median value of 8.51 ng/ml (Table 1). PSA levels increased significantly with the increase of the grade group, $p < 0.001$. The most common grade groups were grade group 2, with 50.41%, and grade group 3, with a share of 36.16%, while grade group 1 was represented by only 4.38% of the included patients (Fig. 1). The average percentage of carcinoma found in pathology reports after RRP was 20.1%, ranging from 5 to 80%.

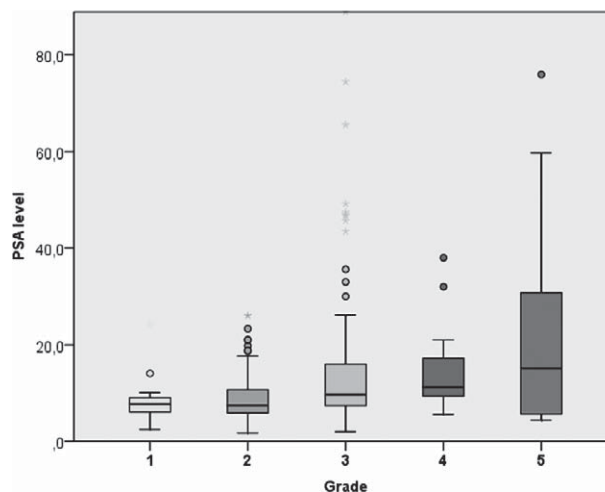


Fig. 3. Relationship between grade groups and PSA levels: With the increase of grade group PSA increased significantly, $p < 0.001$.

The average percentage of carcinoma in pathology reports found after RRP also increased with the increase in the grade group, $p < 0.001$ (Fig. 2). Furthermore, the increase in tumor percentage per group was accompanied by an increase in PSA values, $p < 0.001$ (Fig. 3). Out of the total number of 365 patients operated on within the selected period, T2 stage was found in 247, and T3 stage in 118 patients. In grade groups 2 and 3, irrespective of cancer percentages in pathology reports, more T3 stage cases were found in grade group 3 when compared to grade group 2, which was statistically significant, $p < 0.001$ (Table 2, Fig. 4). However, grade group 2 and grade group 3 patients with $\leq 10\%$ cancer occurrences in final pathology reports after RRP did not show any disparity in the occurrence of T3 stage, $p = 0.96$ (Table 3, Fig. 5). Out of the total number of 80 grade group 2 patients with a percentage of cancer $\leq 10\%$, T2 stage was found in 68 patients (85%) and T3 stage in 12 patients (15%). Out of the total number of 59 grade group 3 patients with a percentage of cancer $\leq 10\%$, T2 stage was found in 50 patients (84.7%). T3 stage was found in 9 patients (15.3%), $p = 0.96$.

Discussion

Gleason's assessment was made in 1966 by the pathologist Dr. Donald F Gleason⁸. Since 1966, the rating system has undergone several revisions to improve the prognostic value. The most significant changes

Table 2. Relationship between cancer percentage, grade groups 2 and 3, and T stage on final pathology report

			T grade		Total
			2	3	
Grade group	2	Count	153	31	184
		% within grade group	83.2%	16.8%	100.0%
	3	Count	67	65	132
		% within grade group	50.8%	49.2%	100.0%
Total		Count	220	96	316
		% within grade group	69.6%	30.4%	100.0%

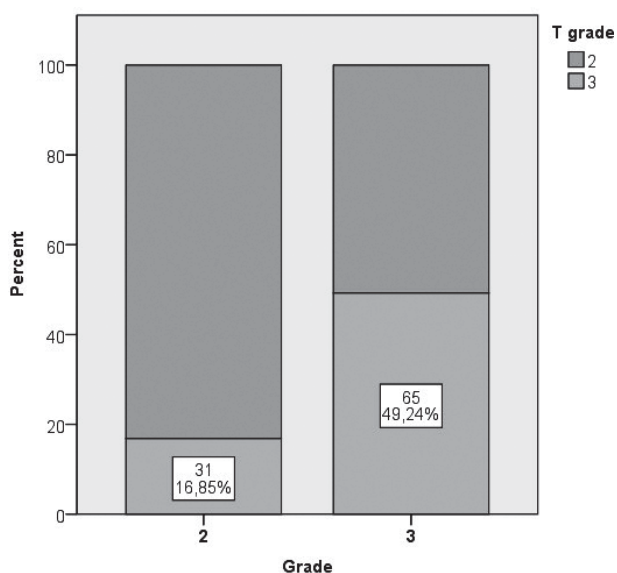


Fig. 4. Relationship between cancer percentage, grade groups 2 and 3, and T stage on final pathology report: Irrespective of cancer percentage in pathology reports, more T3 stage cases were found in grade group 3 when compared to grade group 2, which was statistically significant, $p < 0.001$.

were made in 1997, 2005 and the last, and current one, in 2016^{2,3,4}.

The modifications of the Gleason grading system made by the International Society of Urological Pathology (ISUP) had a significant effect on the clinical practice of developing prostate cancer, with the Gleason score still positioned as a key factor for patient management. The 2005 ISUP Gleason grading system has been greatly appreciated, which is a significant step in establishing more repetitive classifications of prostate cancer. The Gleason score assigned to prostate

cancer in radical prostatectomy specimens is strongly predictive of postoperative progression. Gleason score 7 tumors are heterogeneous in their biologic behavior. The differences in the prognoses of tumors with Gleason scores 3+4 and 4+3 after radical prostatectomy are significant. However, the prognosis of Gleason score 7 tumors is not uniformly poor. The majority of studies performed as yet has shown that Gleason score 7 differs significantly in the progression of the disease or unfavorable pathology reports depending on the dominant Gleason.

In the last 15 years, many researches have dealt with the question whether the dominant sample in Gleason score 7 tumor results (score 3+4 to 4+3) is an independent predictor of the progression following RRP^{9, 10, 11, 12,13}. They have concluded that Gleason scores 3+4 and 4+3 do not have the same malignant potential. Gleason sum 4+3 in the final pathology analysis following RRP has a worse prognosis for a more significant progression of the disease¹⁰. This is very important, as Gleason score 7 is one of the most important factors in the introduction of the new grading system (grade group system).

However, more research at the beginning of this century has shown that the percentage of cancer is a very important factor in unfavorable histopathology analysis and postoperative progression of the disease¹⁴. In their research, Freedland *et al.* have demonstrated that the percentage of carcinogenic tissue in biopsy specimens after RRP was a better indicator of biochemical relapse and final pathological stage than preoperative PSA and GS¹⁵. For this reason, cancer percentages in pathology reports after RRP must be taken as an essential factor in the occurrence of the T3 stage of the disease.

Table 3. Relationship between cancer percentage of $\leq 10\%$, grade groups 2 and 3, and T stage on final pathology report

			T grade		Total
			2	3	
Grade group	2	Count	68	12	80
		% within grade group	85.0%	15.0%	100.0%
	3	Count	50	9	59
		% within grade group	84.7%	15.3%	100.0%
Total		Count	118	21	139
		% within grade group	84.9%	15.1%	100.0%

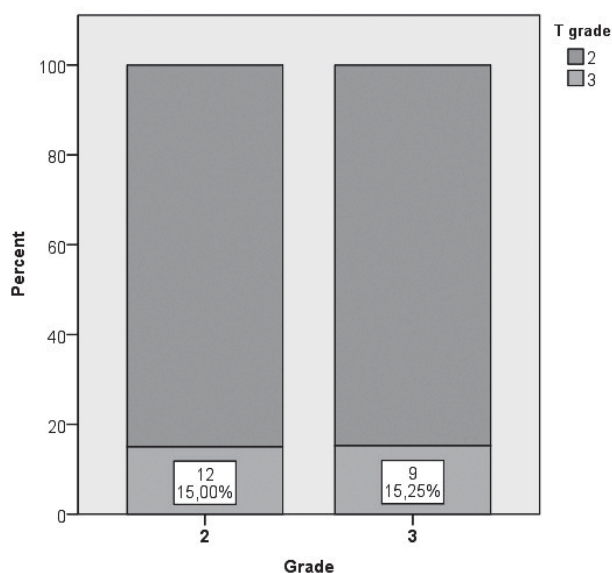


Fig. 5. Relationship between cancer percentage of $\leq 10\%$, grade groups 2 and 3 and T stage on the final pathology report: Patients with both grade group 2 and 3 and with the percentage of $\leq 10\%$ cancer in the final pathology report after RRP did not show any difference in the occurrence of T3 stage, $p = 0,96$.

Conclusion

Gleason sum 7 is heterogeneous in its biologic behavior. The differences in prognoses for grade group 2 and grade 3 patients after RRP are significant, but not always. The relevance of the percentage of prostate cancer after RRP must be considered in the risk assessment process, i.e. lower carcinoma percentage ($\leq 10\%$) in this study.

But what about patients with $\geq 50\%$ of cancer in the final pathology report after RRP? In this study, the to-

tal of 20 patients with the percentage of cancer $\geq 50\%$ and only 8 patients in grade groups 2 and 3 were reported, which is insufficient for any further investigation.

Seeing that this is only a part of the study conducted in the period between 1 January 2005 and 31 December 2016, and covering the total of 1.800 patients who had undergone surgery, a sufficient number of patients with a high percentage of cancer are expected to answer the above question.

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Sažetak

PATOHISTOLOŠKI NALAZ NAKON RADIKALNE PROSTATEKTOMIJE TEMELJENE NA NOVOM SUSTAVU OCJENJIVANJA

B. Spajić, S. Nikles, I. Grubišić, M. Knežević, S. Šhoipi, M. Ulamec, G. Štimac, I. Tomašković i B. Ružić

Kao jedan od glavnih uzroka uvođenja novih gradus skupina bio je Gleasonov zbroj 7, koji se bitno razlikovao u prognozi bolesti ovisno o primarnom Gleasonu. U ovom istraživanju usporedili smo gradus skupinu 2 (GZ 3+4) i gradus skupinu 3 (GZ 4+3) u pojavnosti T3 stadija kod pacijenata s $\leq 10\%$ karcinoma u patohistološkom nalazu nakon retropubične radikalne prostatektomije, klinički lokaliziranog karcinoma prostate. Studijom je obuhvaćeno 365 pacijenata s klinički lokaliziranim karcinomom prostate koji su podvrgnuti radikanoj retropubičnoj prostatektomiji između 1. siječnja 2015. i 31. prosinca 2016. godine. Najzastupljenije gradus skupine bile su gradus skupina 2 s 50,41% i gradus skupina 3, s udjelom od 36,16%. Postotak karcinoma u PHD nalazu nakon RRP bio je u rasponu od 5 do 80%, prosjek 20,1%. Kod gradus skupina 2 i 3, neovisno o postotku karcinoma prostate u konačnom PHD nalazu, bilo je statistički značajno više T3 stadija u gradus skupini 3 u odnosu na gradus skupinu 2, $p=0,001$. Međutim, pacijenti gradus skupina 2 i 3 s postotkom karcinoma $\leq 10\%$ u konačnom PHD nalazu nakon RRP nisu pokazali razliku u pojavnosti T3 stadija, $p=0,96$. Razlike u prognozi za pacijente gradus skupine 2 i gradus skupine 3 nakon RRP su značajne, ali ne uvijek. Svakako pri procjeni rizika moramo uzeti u obzir i značajnost postotka karcinoma prostate nakon RRP, u ovom istraživanju niži postotak karcinoma ($\leq 10\%$).

Ključne riječi: *Gleason ocjena; Gradus skupine; Karcinom prostate; Patohistološki nalaz; Radikalna prostatektomija*