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Biochemical Recurrence Following Radical Prostatectomy in High-Risk Prostate Cancer Patients: A Retrospective Cohort Study

Biokemijski relaps nakon radikalne prostatektomije u bolesnika s karcinomom prostate visokog rizika – retrospektivna kohortna studija

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Abstract. ***Aim:*** Radical prostatectomy (RP) with extended pelvic lymphadenectomy (ePLND) is one of the treatment options for prostate cancer (PC). The aim of this study was to evaluate the impact of RP with ePLND on biochemical recurrence in „high-risk" PC patients. ***Patients and methods:*** This retrospective study included patients who initially presented with high-risk PC (Gleason score (GS) ≥ 8 and/or prostate-specific antigen (PSA) level > 20 ng/ml) and had at least 5 years of follow-up. A PSA value higher than 0,20 ng/ml was considered as biochemical recurrence. The hospital database was reviewed to identify patients with high-risk PC who underwent RP/ePLND between January 1, 2013 and December 31, 2017. After patient stratification, 69 patients who initially presented with high-risk prostate cancer (PC) classified as cN0 and cM0 remained. ***Results:*** During follow-up biochemical recurrence occurred in 47 patients (68.12%) while PSA remained below 0.20 ng/ml in 22 (31.88%) patients. Preoperative and postoperative PSA values were compared between the two groups, as well as pathohistological findings after prostate biopsy and surgery. A statistically significant difference was observed in postoperative PSA values, Gleason score (GS), and pathological T stage. ***Conclusion:*** Surgical treatment alone can lead to successful outcomes of high-risk PC in patients with pathological staging of pT3a or lower and in patients with GS 8 (3+5) or lower.

Keywords: pelvic lymphadenectomy; prostate cancer; radical prostatectomy

Sažetak. ***Cilj:*** Radikalna prostatektomija (RP) s proširenom zdjeličnom limfadenektomijom (ePLND) jedna je od terapijskih opcija za liječenje karcinoma prostate (PC). Cilj je ovog istraživanja procijeniti učinak radikalne prostatektomije s proširenom zdjeličnom limfadenektomijom na biokemijski relaps kod bolesnika s karcinomom prostate visokog rizika. ***Ispitanici i metode:*** U ovu retrospektivnu studiju uključeni su bolesnici koji su se inicijalno prezentirali s karcinomom prostate visokog rizika (Gleasonov zbroj (GS) ≥ 8 i/ili prostata-specifični antigen (PSA) > 20 ng/ml) i praćeni su minimalno pet godina. Vrijednost PSA iznad 0,20 ng/ml smatrana je graničnom za biokemijski relaps. Koristili smo bolničku bazu podataka kako bismo pronašli bolesnike s karcinomom prostate visokog rizika koji su liječeni radikalnom prostatektomijom s proširenom zdjeličnom limfadenektomijom između 1. siječnja 2013. i 31. prosinca 2017. Nakon provedenog probira pronađeno je 69 bolesnika koji su se inicijalno prezentirali kao cN0 i cM0 karcinoma prostate visokog rizika. ***Rezultati:*** Kod 47 bolesnika (68,12 %) došlo je do razvoja biokemijskog relapsa, dok je PSA ostao niži od 0,20 ng/ml kod 22 bolesnika (31,88 %). Usporedili smo prijeoperacijske i poslijeoperacijske vrijednosti PSA između dviju skupina bolesnika te patohistološki nalaz nakon biopsije prostate i nakon operacije. Pronašli smo statistički značajnu razliku kada su se uspoređivale poslijeoperacijske vrijednosti PSA i GS nakon operacije i patološki T-stadij bolesti. ***Zaključci:*** Kirurško liječenje može dovesti do definitivnog izlječenja karcinoma prostate visokog rizika kod bolesnika s patohistološkim stadijem pT3a ili nižim i s GS 8 (3+5) ili nižim.

Ključne riječi: radikalna prostatektomija; rak prostate; zdjelična limfadenektomija

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INTRODUCTION

Prostate cancer (PC) is the most common noncutaneous malignancy in men. In the European Union it's currently one of the biggest health problems due to its increasing incidence and mortality. Although since the introduction of prostate-specific antigen (PSA) screening, the number of patients with high-risk PC has decreased over the past 30 years, those patients still form a significant group of 20-30% of PC patients. According to the European Asscociation of Urology (EAU) since 2010 high-risk PC is defined as PC with PSA over 20 ng/ml, or Gleason score (GS) 8 or higher, or cT2c (tumor involves both lobes on digital rectal exam) or higher in localized disease. Any form of locally advanced disease is considered as high-risk prostate cancer[1].

Radical prostatectomy with extended pelvic lymphadenectomy can lead to successful treatment of high-risk prostate cancer in patients with pT3a disease or lower and GS 8 (3+5) disease or lower. Disease free surgical margins are also an important factor for biochemical recurrence free survival.

According to the EAU PC guidelines, options for initial treatment of high-risk PC include radical prostatectomy (RP) with extended pelvic lymphadenectomy (ePLND) or external beam radiation therapy (EBRT) with long-term androgen deprivation therapy (ADT). ePLND in PC patients is currently defined as removal of nodes overlying the external iliac artery and external iliac vein, nodes in the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. Historically, EBRT was the preferred method of treatment of high-risk PC but, due to surgical advances, RP with ePLND has become more popular over the past 15-20 years. Currently no large randomized control trials is comparing the efficacy of both treatment modalities. Most studies available are retrospective in nature and show similar oncological results with differences mostly in morbidity and quality of life parameters [2]. RP with ePLND is superior in that it provides the most accurate local staging of the disease, since small lymph node metastases are not visible on radiological and nuclear imaging, and downgrading of GS after surgery has been reported in multiple studies. Also, after RP there is a very low risk of local disease progression and development of local complications such as urinary retention or non-ischemic priapism. In case of residual tumor, salvage radiation therapy can be performed. As salvage radiation therapy can be used after RP, salvage RP can also be used after EBRT in case of treatment failure. Salvage RP is related to higher intraoperative and postoperative complications and morbidity[3]. In many cases, initial forms of treatment are only the first stage of multimodal therapy, since biochemical recurrence (BCR), marking disease progression will happen in a large number of cases. BCR in the case of PC means a rise in PSA values above a certain threshold after localized treatment. In our institution, PSA value of 0.20 ng/ml is considered as the threshold for BCR.

This study aimed to evaluate the impact of RP with ePLND on BCR in high-risk PC patients and to identify which patient subgroups may achieve successful outcomes with this treatment.

MATERIALS AND METHODS

In this retrospective study the hospital records of all patients who underwent radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND) at the University Hospital Center Rijeka between January 1, 2013, and December 31, 2017, were reviewed. Patients initially presented with high-risk prostate cancer (PC), according to the EAU guidelines on PC, and were required to have at least 5 years of follow-up to be included in the study. After patient stratification, 69 patients met the inclusion criteria. A prostate-specific antigen (PSA) value of 0.20 ng/mL was considered the threshold for biochemical recurrence (BCR). BCR occurred in 47 patients (68.12%), while PSA remained below 0.20 ng/mL in 22 patients (31.88%). Accordingly, patients were divided into BCR-positive and BCR-negative groups.

To identify potential factors influencing BCR-free survival, several parameters were compared between the two patient groups. These included in-

itial PSA values, Gleason score (GS) from the prostate biopsy, pathological staging (pT value) after surgery, postoperative GS on histopathological analysis, the presence of positive surgical margins, and the first PSA measurement at the initial follow-up, which occurred 4–6 weeks after surgery. It should be noted that the first postoperative PSA value in the BCR-positive group may be below the BCR threshold if recurrence occurred later during follow-up. The data were assessed for normality of distribution using the Shapiro-Wilk test. Differences in distribution were then analyzed using the Mann-Whitney U test or the chi-square test, depending on the normality of the data, with Stata 14 software[4].

A p-value of less than 0.05 was considered statistically significant.This study was approved by the Ethics Committee of the University Hospital Center Rijeka (Class: 003-05/23-1/119; Number: 2170-29-02/1-23-2) on November 23, 2023, and by the Ethical Council for Biomedical Research of the Faculty of Medicine, University of Rijeka (Class: 007-08/24-01/60; Number: 2170-1-42-04-3/1-24-8) on October 22, 2024.

RESULTS

BCR occurred in 47 patients (68.12%) while PSA remained below 0.20 ng/ml in 22 (31.88%) patients. When initial PSA values at patient presentation were compared, the median PSA in the BCR-positive group was 21.09 ng/mL (IQR 8.95–30.79), compared to 21.015 ng/mL (IQR 6.94–27) in the BCR-negative group. The difference was not statistically significant (p = 0.216) (Table 1).

When analyzing Gleason score (GS) values from the histopathological analysis of prostate biopsies, we found that in the BCR-positive group, the majority of patients (38.3%) had a GS of 8 (4+4), followed by GS 7 (3+4) in 19.15% and GS 6 (3+3) in 14.89% of cases. In the BCR-negative group, most patients also had a GS of 8 (4+4) (27.27%), followed by GS 7 (3+4) and GS 6 (3+3) in 22.73% of cases each. The difference between the two groups was not statistically significant (p = 0.892) (Table 2). When comparing the first postoperative PSA values at the initial follow-up, one patient had to be excluded due to incomplete data. The median PSA in the BCR-positive group was 0.095 ng/mL (IQR 0.02–0.21), compared to 0.00 ng/mL (IQR 0.00–0.01) in the BCR-negative group. The difference between the two groups was statistically significant (p < 0.001) (Table 1). When analyzing Gleason score (GS) values from the histopathological analysis after RP with ePLND, one patient was excluded due to incomplete data. In the BCR-positive group, the majority of patients had a GS of 9 (4+5) in 30.43% of cases, followed by GS 7 (4+3) in 28.26% and GS 7 (3+4) in 17.39% of cases. In the BCR-negative group, most patients had a GS of 7 (4+3) in 50% of cases, followed by GS 7 (3+4) in 27.27% and GS 6 (3+3) in 13.64% of cases. The difference in GS distribution between the two groups was statistically significant, showing a lower incidence of BCR in patients with GS 6 (3+3), GS 7 (3+4), GS 7 (4+3), and GS 8 (3+5) (p = 0.017) (Table 2).

When analyzing pathological T (pT) values from the postoperative histopathological analysis, two patients were excluded due to incomplete data. In the BCR-positive group, the majority of patients had pT3b in 37.38% of cases, followed by

Table 1. Effect of PSA values on biochemical recurrence

	All patients			Biochemical recurrence = YES			Biochemical recurrence = NO			p-value
	N	MDN	IQR	N	MDN	IQR	N	MDN	IQR	
Age	69	73	69 – 76	47	74	71 – 76	22	72	66 – 78	0.3819
Initial PSA	69	21.09	8.71 – 29	47	21.09	8.95 – 30.79	22	21.015	6.94 – 27	0.2164
First postoperative PSA	68	0.03	0 – 0.13	46	0.095	0.02 – 0.21	22	0	0 – 0.01	**<0.0000**

Data are presented as medians and interquartile range IQR= Q1 to Q3 (representing the middle 50% of the data). N denotes number of patients in analysis, MDN the median. Significant values are given in bold (p<0.05).

Table 2. Effect of pathohistological findings on biochemical recurrence

	All patients		Biochemical recurrence = YES		Biochemical recurrence = NO		p-value
	N	%	N	%	N	%	
Initial GS (N = 69)							0.892
6 (3+3)	12	17.39	7	14.89	5	22.73	
7 (3+4)	14	20.29	9	19.15	5	22.73	
7 (4+3)	8	11.59	5	10.64	3	13.64	
8 (3+5)	1	1.45	1	2.13	0	0	
8 (4+4)	24	34.78	18	38.3	6	27.27	
8 (5+3)	2	2.9	2	4.26	2	9.09	
9 (4+5)	5	7.25	3	6.38	0	0	
9 (5+4)	1	1.45	1	2.13	0	0	
10 (5+5)	2	2.9	1	2.13	1	4.55	
Postoperative GS (N = 68)							**0.017**
6 (3+3)	3	4.41	0	0	3	13.64	
7 (3+4)	14	20.59	8	17.39	6	27.27	
7 (4+3)	24	35.29	13	28.26	11	50	
8 (3+5)	1	1.47	1	2.17	0	0	
8 (4+4)	4	5.88	4	8.7	0	0	
8 (5+3)	1	1.47	1	2.17	0	0	
9 (4+5)	16	23.53	14	30.43	2	9.09	
9 (5+4)	5	7.35	5	10.87	0	0	
Pathological staging (N = 67)							**0.037**
pT1a	1	1.49	0	0	1	4.55	
pT2	1	1.49	0	0	1	4.55	
pT2a	1	1.49	1	2.22	0	0	
pT2b	1	1.49	0	0	1	4.55	
pT2c	19	28.36	10	22.22	9	40.91	
pT3a	23	34.33	14	31.11	9	40.91	
pT3b	18	26.87	17	37.78	1	4.55	
pT3c	1	1.49	1	2.22	0	0	
pT4a	2	2.99	2	4.44	0	0	
Resection margins (N = 68)							**0.009**
R0	28	41.18	14	30.43	14	63.64	
R1	40	58.82	32	69.57	8	36.36	

GS=GSscore. Significant values are given in bold ($p<0.05$).

pT3a in 31.11% and pT2c in 22.22% of cases. In the BCR-negative group, most patients had pT2c or pT3a, each in 40.91% of cases. The remaining patients in the BCR-negative group were equally distributed among pT1a, pT2, pT2b, and pT3b. The difference in pT distribution between the two groups was statistically significant, indicating a lower BCR incidence in patients with pT3a or lower ($p = 0.037$) (Table 2).

When comparing patients according to surgical margin status, 69.57% of patients in the BCR-positive group had positive surgical margins (presence of tumor at the resection edge), while surgical margins were positive in 36.36% of cases in the BCR-negative group. One patient was excluded from this analysis due to incomplete data. The difference was statistically significant ($p = 0.009$) (Table 2).

DISCUSSION

The study demonstrates that RP with ePLND alone can result in successful treatment of high-risk PC in a selected group of patients, particularly those with a GS of (3+5) or with pT3a or lower stage tumors on pathohistological analysis. This does not imply that RP with ePLND should not be considered a treatment option for other high-risk PC patients. The management of high-risk PC is often multimodal, and surgery can represent the first step in therapy. Alternatively, patients may be offered EBRT.

There are no large randomized controlled trials comparing these two treatment options; however, the available—mostly retrospective—data suggest that oncological outcomes are comparable. In certain cases, when one treatment modality fails, the other typically serves as the next line of treatment. It is important to note that salvage RP with ePLND is a complex surgical procedure associated with high morbidity, in contrast to salvage radiotherapy following RP with ePLND[3].

The choice between treatment modalities usually depends on the institutional preferences where they are performed. At our institution, we favor a surgical approach as the initial treatment for patients suitable for surgery, while also considering each patient's personal preferences.

A key challenge lies in identifying patients with favorable pathological staging who, according to our findings, would benefit most from surgery. Currently, multiparametric magnetic resonance (mpMR) imaging represents the best available option for local staging, especially with the advent of more powerful, high-resolution scanners. Research indicates that mpMR provides high sensitivity and specificity in detecting extracapsular extension (ECE) and seminal vesicle invasion (SVI)—both of which are criteria for T staging according to the AJCC TNM system, where ECE corresponds to T3a and SVI to T3b disease[5, 6].

Recently, the use of biparametric magnetic resonance (bpMR) for local PC staging has been evaluated, with results showing comparable specificity and sensitivity to mpMR for detecting ECE and SVI[7]. The combination of PSMA PET/CT with mpMR may further enhance the sensitivity and specificity of local staging in PC, although data on this topic remain limited[8].

Based on the available evidence and the results of our study, patients who would benefit most from RP with ePLND can be identified with high accuracy.

Use of modern imaging techniques such as mpMR or bpMR of the prostate and PSMA PET/CT can help us to better differentiate which patients will benefit most from radical surgical treatment of prostate cancer.

Currently, all high-risk PC patients are generally managed using the same treatment modalities and follow-up protocols. However, our findings suggest that postoperative pathohistological analysis could serve as a prognostic indicator and may help tailor postoperative follow-up strategies. Further research is needed before firm recommendations can be made. Accurate staging remains of paramount importance in oncology, as it significantly influences treatment planning and decision-making. Surgery continues to provide the most precise means of determining the local stage of disease.

CONCLUSION

In conclusion, our data indicate that surgery alone can achieve successful treatment outcomes in high-risk prostate cancer (PC) patients with pathological stage pT3a or lower and a Gleason score (GS) of 8 (3+5) or lower, provided that surgical margins are negative.

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