

THE SIGNIFICANCE OF PERINEURAL INVASION AND PREOPERATIVE PROSTATE SPECIFIC ANTIGEN FOR RELAPSE AFTER RADICAL PROSTATECTOMY

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ISSN 0350-364X

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DOI: 10.5457/399

Introduction: Prognostic significance of prostate cancer perineural invasion after radical prostatectomy and preoperative prostate specific antigen (PSA) for recurrence or progression of the Disease is not completely understood.

Objective: To analyze the relation between prostate cancer perineural invasion after radical prostatectomy and preoperative PSA concentration in men with different stages of prostate cancer after radical prostatectomy.

Subjects and Methods: The study included 145 patients divided into two groups, the first (n=104) men, average age 64.59±6.12 years (50-75), with preoperative PSA≤10 ng / ml, and the second (n=41) men, average age 64.35 ± 6.39 years (49-77), with preoperative PSA>10 ng / ml. PSA concentration was measured with the appliance Architect ci 8200 at the Department of Laboratory Medicine, (range of normal values at our institution 0.5-4 ng/ml). Indication for operative treatment was biopsy confirmation of prostate cancer. Histopathological findings of prostate biopsy and radical prostatectomy specimens were made at the Department of Pathology, Clinical Center Tuzla, and the results presented by TNM 2002 classification.

Results: The average recorded values of PSA in two study groups were 5.40±1.93 ng/ml (1.54-9.4) and 13.19±11.2 ng / ml (10.05-18.2) (p=0.00023). Postoperative increase of PSA was recorded in 34 (23.5%) patients. The value of preoperative PSA had a significant impact on recurrence (p=0.001). Preoperative Gleason score of 5.68±0.98 (3-8) versus 5.95±0.99 (3-7) (p=0.10), postoperative Gleason score of 6:37±0.90 (4-9), vs. 6.85±0.96 (5-10) (p=0.074). Positive surgical margins are spotted in 29(20%) subjects and are a significant relapse predictor of the disease. Perineural prostate invasion was registered in 24 (16.6%) patients. The occurrence of prostate cancer perineural invasion was a significant predictor for recurrence (p=0.025). Patients with registered prostate cancer perineural invasion had significantly higher preoperative PSA compared to patients who did not (p=0.029).

Conclusion: Preoperative PSA value and perineural invasion are significant predictors for recurrence of prostate cancer after radical prostatectomy.

Keywords: prostate cancer, perineural invasion, prostate specific antigen

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Received:
26.01.2016.

Accepted:
04.05.2016.

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Competing interests:
The authors declare no competing interests.

INTRODUCTION

Prostate cancer is the most common malignant disease of men age over 50, and is present in 50% of cases of men older than 70 years. With over 12% of all deaths from cancer, it is the second most common cause of death in men, right next to lung cancer. Incidence of prostate cancer in the Federation of Bosnia and Herzegovina in 2010 was 11.6 per 100 000 people. Prostate carcinoma perineural invasion after radical prostatectomy is an important prognostic factor, solely or as a part of other prognostic factors, and it makes integral part of the postoperative histopathologic findings report.

Concentration of prostate specific antigen (PSA) can help determine patient treatment after radical prostatectomy.

Prostate cancer perineural invasion after radical prostatectomy is mainly found in samples taken from the peripheral zone of the prostate. Extracapsular spread of prostate cancer is often associated with disease progression.

SUBJECTS AND METHODS

The retrospective-prospective study conducted in the Clinical Center Tuzla analyzed 145 men, aged 49-77 years, who underwent radical retropubic prostatectomy for prostate cancer without nerve sparing.

According to preoperative PSA values, patients were divided into two groups: the first, 104 men, average age 64.59±6.12 years (50-75), with preoperative

PSA \leq 10 ng/ml, and the other, 41 males, average age 64.35 \pm 6.39 years (49-77), with the preoperative PSA $>$ 10 ng/ml. All subjects underwent two following urological examinations: urinary tract ultrasound examination, digital rectal examination, preoperative and postoperative histopathological findings and preoperative and postoperative PSA concentration. Postoperative PSA was done after 3, 6 and 12 months during the first year and every 6 months during the future monitoring. Confirmed postoperative PSA of \geq 0.4 ng/ml was used as a indicating value for biochemical relapse. In order to confirm the diagnosis of relapse patients were subjected to magnetic resonance imaging (MRI) of pelvis and static bone scintigraphy.

RESULTS

Average value of PSA before surgery was 7.60 ng / ml (1.54-18.2 ng / ml). 5.40 \pm 1.93 ng/ml (1.54-9.4) in the first group and 13.19 \pm 11.2 ng/ml (10.05-18.2) in the second group (p=0.00023). Postoperative increase of PSA was recorded in 34 (23.4%) patients, with an average rise time of 19 months (2-68 months). Period of time, during which increase of postoperative PSA was recorded, is displayed by Kaplan Meier's curve in Figure 1.

Preoperative PSA had a significant effect on recurrence (OR=1.18, p=0.001), with each increase in preoperative PSA of 1 ng / ml, the risk of relapse increased by 1.18 times.

Preoperative Gleason score of 5.68 \pm 0.98 (3-8) versus 5.95 \pm 0.99 (3-7) (p=0.10), postoperative Gleason score of 6:37 \pm 0.90 (4-9), vs. 6.85 \pm 0.96 (5-10) (p=0.074) (Figure 2).

Statistical Analysis

Statistical analysis was performed in SPSS 19.0 statistical software package (SPSS Inc, Chicago, IL, USA), Medcalc 8.1, Statistica 7. All variables were presented with their corresponding measures of central tendency and dispersion, by using standard tests of descriptive statistics. Qualitative variables were compared by using Chi-square test. Quantitative variables were tested for normal distribution by using Student's t-test for comparison of 2 variables, while comparison of 3 variables we used Analysis of Variance (ANOVA) test with Turkey's post hoc analysis. Significant correlation between variables was tested by using Pearson's parametric correlation. All tests were performed with 95-percent statistical significance (p $<$ 0.05).

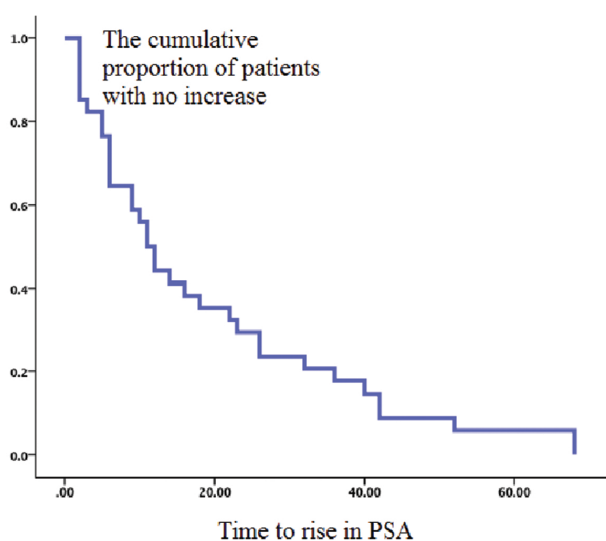


Figure 1. Kaplan-Meier curve rise in PSA after surgery

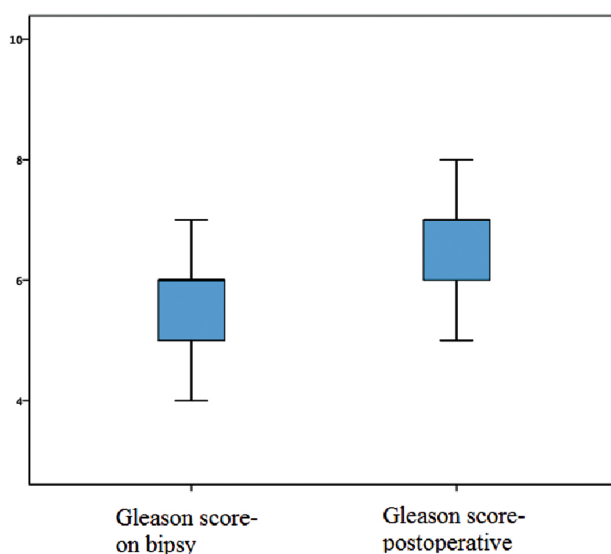


Figure 2. Relationship biopsy and postoperative Gleason score (Wilcox test)

Table 1. Prognostic parametar on histopatological finding

Parameter	Present		Absent	
	N	%	N	%
Positiv LN*	2	1.4	143	98.
Positive surgical margins	29	20.0	116	80.0
PNI*	24	16.6	121	83.4
Prostatic kapsule infiltration	31	21.4	114	78,6

* LN – limf node; *PNI- perineural invasion

Positive surgical margins are spotted in 29(20%) subjects. Positive surgical margins are also an predictor of a relapse apperaing in the disease with OR=6.70; p<0.001, or positive margins have increased a risk of relapse by 6.7 times. Individual features obtained intraoperative or on extirpated material are shown on Table 1.

Perineural invasion of prostate after radical prostatectomy for prostate cancer was recorded in 24 (16.6%) patients and was a significant predictor for disease recurrence (OR=2.89, p=0.025), and it increased risk of relapse by 2.89 times. In the first group PNI was recorded in 12 (11.5%) patients, in the second group it was recorded in 12 (29.2%) patients, as shown in Figure 3.

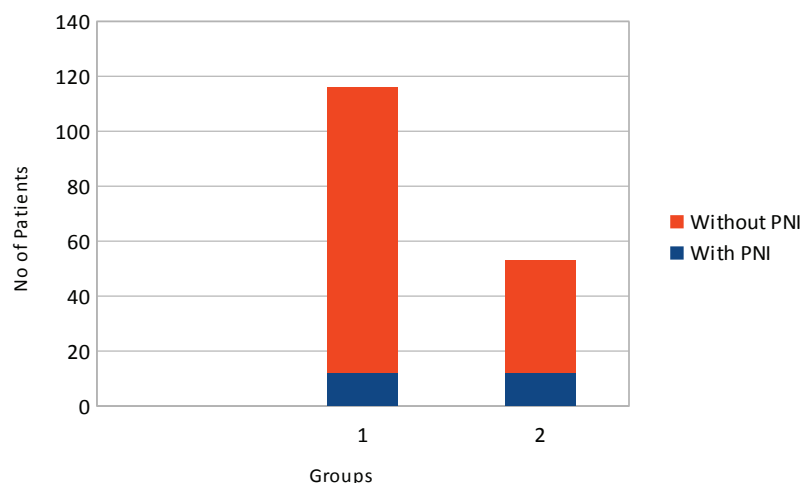


Figure 3. Groups of patients according to preoperative PSA and PNI

Preoperative PSA value was compared between patients with recorded and those without recorded invasion of prostate cancer after radical prostatectomy. PSA was significantly higher in patients with recorded perineural invasion of prostate cancer after radical prostatectomy (p=0.029)(Figure 4).

Organ-confined disease,- stage pT2, was recorded in 98 (67.6%) patients, while biochemical relapse was recorded in 18 (18.2%) patients. Patients with stage pT2a had no registered biochemical relapse. Biochemical relapse was recorded in four (4%) patients stage pT2b and 14 (14.2%) patients stage pT2c. Biochemical relapse of patients with stage T3 was recorded in 58% of cases as shown in Table 2.

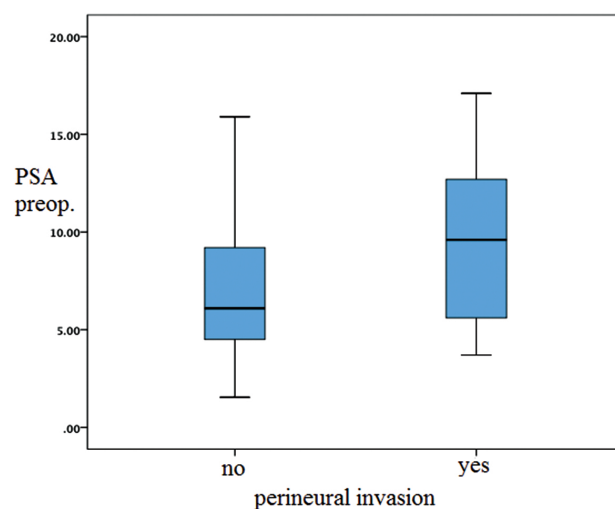


Figure 3. Relationship preoperative PSA and perineural invasion

Table 2. Relationship perineural invasion to pT stage of tumor

		T stage						
		pT 2a	pT 2b	pT 2c	pT 3a	pT 3b	pT 4	
Perineural invasion	No	n	22	17	63	15	3	1
		%	91.7%	89.5%	86.3%	62.5%	75.0%	100.0%
	Yes	n	2	2	10	9	1	0
		%	8.3%	10.5%	13.7%	37.5%	25.0%	0.0%
Total	n	24	19	73	24	4	1	
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	

DISCUSSION

The increase of PSA in serum is often used as a criterion for determination of clinical disease progression after treatment for prostate cancer. It provides valuable information if there's a need for future therapy. Because of PSA half-life of 15.3 days in the serum, it is considered that it reaches undetectable levels within 21 to 30 days after radical prostatectomy. For most patients, the first sign of disease recurrence after radical prostatectomy is increase of PSA level, without clinical or radiographic signs of disease progression. The reason for the increase of PSA after radical prostatectomy may be due to local recurrence in the prostatic lodge, the appearance of distant metastases or a combination of these two.

Our study has recorded increase of PSA after surgery in 34 (23.4%) patients, 20 (13.7%) in the first group, and 14 (9.6%) in the second group. It was found that preoperative PSA has a significant impact on the recurrence of prostate cancer after radical prostatectomy (OR = 1.18, $p = 0.001$), and that each increase of preoperative PSA value by 1 ng / ml, increases the risk of recurrence of prostate cancer by 1.18 times.

In our study there were 29(20%) patients with a positive surgical margins. Patients were mostly treated with additional radiotherapy and hormone therapy. Nine patients were observed which of four had a biochemical relapse and were treated with radiotherapy. Five patients are observed and are without the progress of the disease. Positive surgical margins are in our study a significant relapse predictor of the disease and have increased the risk of the disease relapse by 6.7 times. There was no correlation between the height of the preoperative PSA and positive surgical margins.

Prognostic significance of perineural invasion after radical prostatectomy (PNI) on the outcome of prostate cancer disease is still under discussion because there is a large number of works in which the PNI is considered as a powerful prognostic factor for recurrence of the disease, while in many other works it is still questionable. The presence of PNI and its significance as a prognostic factor was compared with biochemical disease recurrence indicators and other prognostic factors. In a study of 131 patients Endrizzi and Seay

found that PNI is an important prognostic factor for biochemical recurrence, with a sensitivity of 82% and specificity of 57%. Miyake and colleagues showed that the PNI is significant predictor for biochemical relapse in single-variable, but not in multi-variable analysis. Similarly, in our study, in single-variable analysis, 16% of patients had PNI, which proved itself as a significant predictor of relapse and increased number of relapses by 2.8 times.

The Maya Institute's five-year long study of organ-confined disease showed that patients with the pT2a disease stage are without biochemical relapse in 83% of cases, and patients with the pT2c disease stage in 81% and 62% of cases. During the ten-year long study Sung, out of 85 - 89% of patients with organ-confined disease, 67-69% of patients had recorded biochemical relapse with focal extra-prostatic expansion (pT3a), and 36-58% of patients had large extra-prostatic expansion (pT3b). Similar results were recorded in our study.

CONCLUSION

This study has shown that preoperative PSA had a significant impact on the recurrence of prostate cancer, i.e., with each increase of the preoperative value of PSA by 1 ng / ml, the risk of recurrence increases by 1.18 times. The appearance of perineural invasion of prostate cancer after radical prostatectomy increases the occurrence of relapse by 2.8 times.

REFERENCES

1. Walsh PC, Retik AB, Vaughan ED. Campbell's Urology, 8th Edition. Philadelphia: WB Saunders Company 2003; 3003-3223.
2. Anonimous, Zdravstveno statistički godišnjak Federacije Bosne i Hercegovine 2010, Zavod za javno zdravstvo Federacije Bosne i Hercegovine, Sarajevo, 2011; 27-28.
3. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974; 111(1): 58-64.

4. Sobin LH, Ch. Wittekind (eds.): UICC International Union Against Cancer TNM Classification of Malignant Tumors, Sixth Edition. Wiley-Liss, New York, 2002;310
5. Endrizzi J, Seay T. The relationship between early biochemical failure and perineural invasion in pathological T prostate cancer. *BJU Int* 2000; 85: 696–698.
6. Bostwick DG, Grignon DJ, Hammond ME. Prognostic factors in prostate cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 2000; 124:995–1000.
7. Partin AW, Oesterling JE. The clinical usefulness of prostate-specific antigen: update 1994. *J Urol* 1993; 152: 1358-1368.
8. Pound CR, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281: 1591-1597.
9. Endrizzi J, Seay T. The relationship between early biochemical failure and perineural invasion in pathological T prostate cancer. *BJU Int* 2000; 85: 696–698.
10. Miyake H, Sakai I, Harada KI, Eto H, Hara I. Limited value of perineural invasion in radical prostatectomy specimens as a predictor of biochemical recurrence in Japanese men with clinically localized prostate cancer. *Acta Urologica Japonica* 2005; 51(4): 241–246.
11. May F, Hartung R, Breul J. The ability of the American Joint-Committee on Cancer staging system to predict progression-free survival after radical prostatectomy. *BJU Int* 2001; 88:702–707.
12. Sung MT, Lin H, Koch MO. Radial distance of extraprostatic extension measured by ocular micrometer is an independent predictor of prostate specific antigen recurrence: a new protocol for the substaging of p prostate cancer. *Am J Surg Pathol* 2007; 31: 311-318.



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