



The Effect of Perineural Invasion on Biochemical Recurrence-free Survival Following Nerve-sparing Radical Prostatectomy

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Abstract

Objective: Perineural invasion (PNI) is a histopathological finding which represents invasion of the nerves and surroundings by cancer cells. Several studies have reported that PNI in prostate cancer (PCa) is a poor prognostic factor. However, there are insufficient data in literature related to the use of PNI status in the biopsy at the stage of making a decision for nerve-sparing surgery. This research aimed to investigate the impact of PNI identified in prostate biopsies on the biochemical recurrence-free survival (RFS) in individuals who underwent nerve-sparing radical prostatectomy (RP) for PCa.

Materials and Methods: The data of 972 patients who underwent nerve-sparing RP due to a clinically localized PCa diagnosis were retrospectively examined. Patients were divided into two groups as PNI (+) and PNI (-) according to PNI status in prostate biopsy pathology.

Results: Evaluation was made of 747 patients with suitable data for analysis. PNI was determined in the prostate biopsy of 162 patients and not in the biopsies of 585 patients. The 5-year biochemical RFS rates were 90% for PNI (+) patients and 89.6% for the PNI (-) group, and the difference between the two groups was not statistically significant. When the PNI positive and negative groups were compared in respect of surgical margin positivity, the surgical margin was determined as positive in 42 (25.9%) of the group with PNI and in 84 (14.4%) of the group without PNI. Surgical margin positivity was determined to be statistically significantly greater in the PNI (+) group. Biochemical RFS rates were compared according to the surgical margin positivity status, and 5-year biochemical RFS was found to be 81.5% in those with surgical margin positivity and 91.6% in those with surgical margin negativity, no statistically meaningful distinction was found between the groups.

Conclusions: The findings of this study indicated that PNI determined in prostate biopsy did not affect 5-year RFS following nerve-sparing RP.

Keywords: Prostate, prostate cancer, radical prostatectomy, perineural invasion, prostate specific antigen, survival, recurrence

Introduction

Prostate cancer (PCa) ranks as the second most commonly diagnosed cancer among males globally and stands as the sixth leading cause of cancer-related fatalities (1).

According to the results of many recent studies based on data series obtained from population-based records, the incidence and mortality rates of PCa seem to have fallen or be stable in several countries. This is thought to be due to prostate-specific antigen (PSA) screening being effective in reducing the incidence

of PCa and developments in treatment modalities reducing mortality rates (2). However, despite these developments, some PCa's have a more aggressive course and even if there is early diagnosis and definitive treatment, there is rapid recurrence.

Although there are several treatment alternatives available for localised PCa, biochemical recurrence (BCR) can be determined in approximately 18% of patients after treatment (3,4). Pathological grade, preoperative PSA levels, and Gleason score (GS) are known to be risk factors widely used for BCR (5).

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Perineural invasion (PNI) is a histopathological finding representing the invasion of nerves or the surroundings by cancer cells, and it is seen in 7-43% of needle biopsies in PCa (6,7).

PNI can be seen as a poor prognostic factor in many cancer types other than prostate, such as pancreas, rectum, and gastric cancers (8-10). There are many studies linking this interaction between tumor and nerve cells to separate perineural tumor spread, just as in lymphovascular invasion (11-13).

Although many studies have reported that PNI is a poor prognostic factor in PCa, there are insufficient data in literature about the use of PNI status in the biopsy at the stage of making a decision for nerve-sparing surgery (14-16).

The primary goal of this investigation is to appraise the significance of PNI and discern how it influences the decision-making for nerve-sparing radical prostatectomy (RP). The study aims to investigate the effects of PNI in prostate biopsy samples taken from patients with PCa, specifically examining its impact on BCR-free survival (RFS) after nerve-sparing RP.

Materials and Methods

A retrospective analysis was conducted on the data of 972 patients with clinically localized PCa who underwent nerve-sparing RP without receiving adjuvant or neoadjuvant hormonal treatment or adjuvant radiotherapy, using the Urologic Cancer Database - Prostate of the Urooncology Association of Turkey.

The data for the study were gathered using the REDCap data collection software, a tool developed by Vanderbilt University and licensed by the Urooncology Association in Turkey (17,18).

The patients were subjected to assessment, considering demographic and clinical parameters such as age, body mass index, clinical information (PSA, and clinical T stage). Additionally, pathological data derived from transrectal ultrasound prostate biopsies were taken into account, including GS, International Society of Urological Pathology (ISUP) grade, PNI, and lymphovascular invasion.

Additional factors considered were the type of operation (open, laparoscopic RP, or robot-assisted laparoscopic RP), nerve-sparing RP side (single or bilateral), surgical margin status of the RP specimen, and follow-up BCR rates.

The criteria for BCR were met when two consecutive PSA values of 0.2 ng/mL or higher exhibited an increasing trend post RP. Patients were classified into two groups depending on whether PNI was present or absent, as determined during the pathology examination of the prostate biopsy.

Statistical Analysis

Statistical analysis was carried out using the SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). Each continuous variable underwent scrutiny for normality through both the Kolmogorov-Smirnov and Shapiro-Wilk tests. The one-way ANOVA test was implemented for normally distributed data, while the Kruskal-Wallis test was chosen for non-normally distributed data. Given the significance of the analysis of variance (ANOVA), post-hoc tests were conducted. When dealing with

non-normally distributed data, the Mann-Whitney U test was utilized for making comparisons.

ROC curves were constructed to evaluate the diagnostic performance of a binary classifier system. Areas under the curve, sensitivity, and specificity were computed.

A significance level of $p < 0.05$ was adopted, signifying that results with a p-value below 0.05 were deemed statistically significant.

Results

Evaluation was made of 747 patients who underwent nerve-sparing RP with suitable data for analysis. Of these, PNI was determined in the preoperative prostate biopsy of 162 patients and not in the biopsies of 585 patients.

The comparative analysis of clinical and pathological characteristics between the two groups is presented in Table 1. The mean age of patients in the PNI (+) group was 61.85 ± 6.90 years, while in the PNI (-) group, it was 61.58 ± 6.77 years, with no statistically significant difference observed between the groups ($p = 0.551$). Among the patients, 509 underwent open RP, 70 underwent laparoscopic RP, and 168 underwent robot-assisted RP. There was no statistically significant difference in the distribution of surgical types between the groups ($p = 0.443$).

Table 1. Clinical and pathological characteristics of the PNI negative and positive patients

Parameter	n	PNI (+)	PNI (-)	p-value
Patient	747	162	585	
Age		61.85 ± 6.90	61.58 ± 6.77	0.551
Surgery				
Open	509	127 (78.4%)	382 (65.3%)	0.443
Lap	70	15 (9.3%)	55 (9.4%)	
Rob	168	20 (12.3%)	148 (25.3%)	
NS side				
Single	82	23 (14.2%)	59 (10.1%)	0.155
Bilateral	665	139 (85.8%)	526 (89.9%)	
PSA (median)	6.79	7.37	6.60	0.050
IQR	(1.49-84.00)	(1.84-53.23)	(1.49-84.00)	
Clinical T stage				
T1c	350	82 (50.6%)	268 (45.9%)	0.182
T2a	162	34 (20.9%)	128 (21.9%)	
T2b	126	22 (13.6%)	104 (17.7%)	
T2c	109	24 (14.9%)	85 (14.5%)	
ISUP grade				
Grade 1	380	87 (53.7%)	293 (50.0%)	0.265
Grade 2	248	40 (24.6%)	208 (35.5%)	
Grade 3	69	19 (11.8%)	50 (8.6%)	
Grade 4	39	9 (5.6%)	30 (5.2%)	
Grade 5	11	7 (4.3%)	4 (0.7%)	
Surgical margin				
Negative	514	120 (74.1%)	501 (85.6%)	0.0001
Positive	233	42 (25.9%)	84 (14.4%)	

PNI: Perineural invasion, PSA: Prostate-specific antigen, IQR: Interquartile range, ISUP: International Society of Urological Pathology

Regarding nerve-sparing procedures, unilateral surgery was performed in 82 patients, and bilateral surgery was performed in 665 patients. No significant difference was identified between the groups concerning the choice between unilateral or bilateral nerve-sparing surgery ($p=0.155$).

The median PSA value was 7.37 (range, 1.84-53.23) in the PNI (+) group and 6.60 (range, 1.49-84.00) in the PNI (-) group, with no significant difference determined between the groups in respect of the preoperative PSA values ($p=0.050$).

No significant difference was determined between the two groups in respect of the clinical T stages ($p=0.182$).

When the patients were grouped according to ISUP grades, 380 patients were ISUP grade 1, 248 were grade 2, 69 were grade 3, 39 were grade 4, and 11 were grade 5. No statistically significant difference was determined between the groups with and without PNI in respect of the ISUP grades ($p=0.265$).

Of the 747 patients who underwent nerve-sparing surgery, the surgical margin was determined as positive in 126 (16.8%) patients. When examining surgical margin positivity between the PNI (+) and PNI (-) groups, the PNI (+) group exhibited a statistically significant higher rate (25.9%) compared to the PNI (-) group (14.4%) with a p-value of 0.001.

The mean follow-up period was 58.6 months and the 5-year biochemical RFS was 89.7%. The 5-year biochemical RFS was 90% in the PNI (+) patients and 89.6% in the PNI (-) group, with no significant difference determined between the groups ($p=0.909$) (Figure 1).

Biochemical RFS rates were compared according to the surgical margin positivity status, and 5-year biochemical RFS was found to be 81.5% in those with surgical margin positivity and 91.6% in those with surgical margin negativity, with no statistically significant difference determined between the groups ($p=0.097$) (Figure 2).

Discussion

The relationship between the biopsy finding of PNI in PCa and the pathological characteristics in RP or progression after definitive treatment has been the subject of research in several

studies. Lee et al. (14) examined the relationship between PNI in biopsies and the pathological characteristics in RP, and showed that in all risk groups, the biopsy finding of PNI was valuable in predicting surgical margin positivity and pathological grade T3 disease.

Similarly, in a study by Kang et al. (19), PNI in PCa patients applied with RP was shown to be a negative pathological parameter and an independent predictor of BCR (20).

Yu et al. (21) reported that PNI was an independent risk factor associated with an increased risk of biochemical recurrence in PCa patients applied with radiotherapy.

Although there are also studies reporting the contrary, according to a recent meta-analysis, which included 19 studies and 13,412 patients, of which 4,197 (31.2%) had PNI, the determination of PNI in PCa patients who underwent RP or radiotherapy was associated with a higher risk of BCR (22-25).

Although many studies have shown that PNI in biopsy is a significant risk factor related to adverse events following RP, there is a limited amount of literature related to the role of PNI at the stage of decision-making for nerve-sparing surgery.

In a study published in 2010 by Loeb et al. (25), in which all the operations were performed by P. Walsh, it was reported that PNI positivity increased the rate of biochemical progression approximately 3-fold, but biochemical progression was not affected by PNI positivity in patients who underwent bilateral nerve-sparing surgery. With a mean follow-up period of 2.8 years in that study, which compared 113 PNI-positive patients with 956 PNI-negative patients who underwent bilateral nerve-sparing surgery, it was determined that nerve-sparing surgery reduced the risk of progression in PNI-positive patients (25).

The mean follow-up duration for the participants in this study was 58.6 months, revealing a 5-year biochemical RFS rate of 89.7%. The 5-year biochemical RFS rates were found to be 90% in patients with PNI (+) and 89.6% in those with PNI (-), showing no statistically significant difference between the two groups.

In the above-mentioned study by Loeb et al. (25), no significant difference was determined in respect of surgical margin positivity

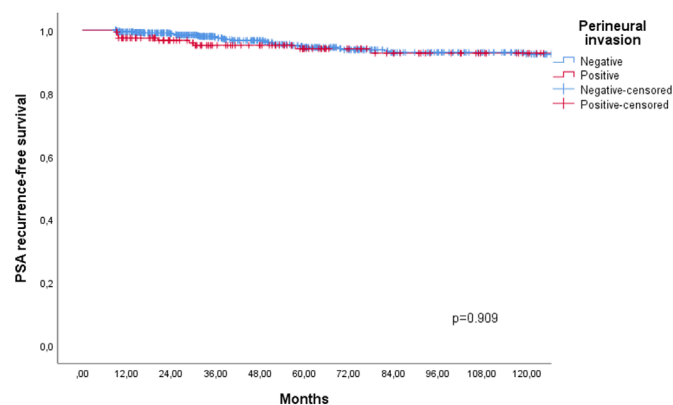


Figure 1. Probability estimates of biochemical RFS in perineural invasion negative and positive patients

RFS: Recurrence-free survival, PSA: Prostate-specific antigen

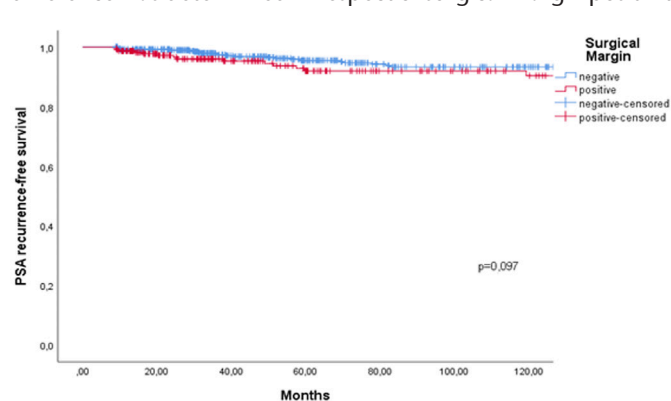


Figure 2. Probability estimates of biochemical RFS in surgical margin negative and positive patients

RFS: Recurrence-free survival, PSA: Prostate-specific antigen

in the patients with PNI who underwent nerve-sparing surgery. However, in the current study, surgical margin positivity was determined as 25% in PNI (+) patients who underwent nerve-sparing RP and 14.4% in the PNI (-) patients, and the difference was statistically significant.

Despite a seemingly shorter RFS in individuals with surgical margin positivity, the analysis showed no statistically significant difference in 5-year biochemical RFS between the groups in this patient cohort.

Study Limitations

Our study has notable limitations, primarily stemming from its retrospective design and analysis.

Additionally, there was no centralized pathological examination. Another significant limitation is the absence of data on pathological examination of patients regarding unilateral or bilateral PNI in the prostatic biopsy specimens.

Conclusion

The findings from this study indicated that the presence of PNI identified in the prostate biopsy did not have an impact on the 5-year biochemical RFS after nerve-sparing RP. Nevertheless, there is a need for further more comprehensive prospective and retrospective studies with longer follow-up periods to confirm these findings.

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Ethics

Ethics Committee Approval: Since this study is designed as a database report ethics committee approval was not obtained.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ş.K., G.A., E.S., B.A., S.S., M.G., S.Y., Concept: Ş.K., G.A., Design: Ş.K., S.S., Data Collection or Processing: Ş.K., G.A., E.S., B.A., S.S., M.G., S.Y., Analysis or Interpretation: Ş.K., S.S., M.G., Literature Search: Ş.K., Writing: Ş.K.

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