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Research Article

Correlation of Perineural Invasion with Biochemical Recurrence and Negative Pathological Features in Prostate Adenocarcinoma

Seyma Ozkanli[1*], Oguz Ozkanli[1], Ebru Zemheri[1], Tulay Zenginkinet[1], Asif Yildirim[2] and Abdullah Aydin[1]

[1]Department of Pathology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey

[2]Department of Urology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey

[*]**Corresponding author:** Dr. Seyma Ozkanli, Tutuncu Mehmet Efendi Cad. Karanfil Sok. Ugur Apt: 16/3 Goztepe – Istanbul, Turkey, Tel: +9 0532 512 49 72; E-mail: seymaozkanli@gmail.com

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Abstract

Introduction: Perineural invasion is regarded as a significant pathological feature in many organ cancers and a poor prognosis symptom for most of these cancers. In this study, our aim is to analyze the significance of perineural invasion independently from factors such as preoperative Gleason score and clinical, and with regard to biochemical recurrence that occurs after radical prostatectomy.

Materials and Methods: The study analyzed 150 prostate cancer cases that underwent radical prostatectomy. The patients received postoperative follow-ups every 3 to 6 months during the first 2 years. The study employed univariate and multivariate analyses to identify any correlation between perineural invasion and surgical margin, Gleason score, extraprostatic extension, seminal vesicle invasion, and biochemical recurrence. The analysis also incorporated the Student T Test, ChiSquare Test, Logistic Regression Test, and SPSS.

Results: While the study identified biochemical recurrence in 60 (40.0%) patients, perineural invasion positivity was observed on 96 (64.0%) patients. When the univariate analysis examined the relation of variables to biochemical recurrence, the results indicated that biochemical recurrence was related to positive surgical margin, high Gleason score, seminal vesicle invasion, perineural invasion, high clinical stage, extraprostatic extension, and young age. The results of the logistic regression indicated that Gleason score and clinical stage were independent risk factors of biochemical recurrence. Analysis perineural invasion's relation with negative pathological features revealed perineural invasion as an independent risk factor for positive surgical margin and seminal vesicle invasion in multivariate analysis.

Conclusions: In the cases with perineural invasion, our study found that positive surgical margin, seminal vesicle invasion, extraprostatic extension, and biochemical recurrence occur more often, and that the Gleason score and clinical stage were higher.

Keywords: Prostate; Perineural invasion; Biochemical recurrence; Seminal vesicle invasion; Radical Prostatectomy

Introduction

Autonomic innervation plays a crucial role in the development and maturation of the prostate gland. In prostate cancer, perineural invasion (PNI) is the interference between the neural cells and epithelial cells. The peripheral nerve sheath is composed of three layers: the epineurium, perineurium, and endoneurium. PNI is identified as the incidence of tumor cells in any of these layers and their extension through neural tracts [1, 2]. PNI is an important pathological feature in many organ cancers such as pancreas out of prostate, colon, rectum, head and neck, biliary tracts, and stomach. PNI is considered to be a poor prognosis symptom in most of these cancer types. PNI is a differential pathologic entity that can exist in the cancer cases without lymphatic or vascular invasion [2]. Regarded as the most dominant mechanism that promotes the spreading of malignant cells into periprostatic tissue, PNI occurs on 5% of biopsy specimens from the patients with no lymph node metastasis, while it occurs on 75% of the specimens from the patients with radical prostatectomy [2,3]. The literature consists of varying results as to whether or not PNI is an independent determinant of poor prognosis. Some studies have identified PNI stabilization as a histopathologically independent risk factor in terms of high level, negative pathological features, and low survival rate [4,5]. In this type of cases, the removal of neurovascular tracts unilaterally or bilaterally may reduce the risk of a positive surgical margin (PSM) [6]. In this study, our aim is to analyze the significance of PNI independently from factors such as preoperative Gleason Score (GS) and clinical, and with regard to biochemical recurrence that occurs after radical prostatectomy.

Materials and Methods

This study retrospectively analyzed the records of 150 prostate cancer cases that were treated with radical prostatectomy between October 2002 and April 2011 in Istanbul Medeniyet University Goztepe Training and Research Hospital. The patients underwent routine evaluation and Prostate Specific Antigen (PSA) testing every 3 to 6 months within the first 2 years and annually thereafter in the postoperative period. The patients with lymph node metastases were excluded from the study. The study considered biochemical recurrence to have developed in the cases with PSA ≥ 0.20 ng/mL. The analysis included the evaluation of the radical prostatectomy specimens of the cases in terms of PNI, surgical margin, Gleason Score, extra prostatic extension, and seminal vesicle invasion (SVI). We defined PNI as tumor cell infiltration in, around, and through the nerves. Univariate and multivariate analyses determined the correlation between these variables and biochemical recurrence. While the univariate analysis used the Student T test for numeric variables and ChiSquare test for categorical variables; the multivariate analysis used a logistic regression test. SPSS packaged software performed the statistical analyses.

Results

The average age of the patients in the cases was 64.7±7.6. The average length of the follow-up was 59.8 months (24-92 months) following surgery. While the study identified biochemical recurrence in 60 (40.0%) patients, PNI positivity was observed on 96 (64.0%) patients. There was a positive surgical margin in 52 (34.7%) cases, seminal vesicle invasion in 25 (16.8%) cases, and extra prostatic extension in 13 (8.7%) cases. The median value of Gleason Score was 6.0; in 98 (65.3%) cases Gleason Score was ≤6, in 33 (22.0%) cases it was 7, and in 19 (12.7%) cases it was ≥8. Clinically, 32 (21.3%) patients were categorized as Stage 1, 105 (70.0%) as Stage 2, and 13 (8.7%) as Stage 3. Among the cases with and without PNI, there was significant difference in terms of PSM, GS, seminal vesicle invasion, clinical stage, extra prostatic extension, and biochemical recurrence (Table 1). When the univariate analysis examined the relation of variables to biochemical recurrence, the results indicated that biochemical recurrence was related to positive surgical margin, high GS, SVI, PNI, high clinical stage, extra prostatic extension, and young age (Table 2).

		Perineural Invasion		P value
		Negative	Positive	
PSM* (%)		11.1	47.9	<0.0001
GS* (%)	6 and less	75.9	59.4	
	7	20.4	22.9	0.032
	8 and more	3.7	17.7	
SVI* (%)		3.8	24.0	0.002
PSA Recurrence* (%)		25.9	47.9	0.008
Clinical Stage* (%)	T1	33.3	14.6	
	T2	64.8	72.9	0.005
	T3	1.9	12.5	
EPE** (%)		0	13.5	0.004
Age*** (year)		65.9	64	0.128
Pearson Chi-Square Test; **Fisher's Exact Test; ***Student T Test; PSA, Prostat Specific Antigen				

Table 1: The features of the cases with/without PNI.

		PSA		P value
		0.2 and less	0.2 and more	
PSM* (%)		22.2	53.3	P<0.0001
GS* (%)	6 and less	83.3	38.3	
	7	16.7	30.0	P<0.0001
	8 and more	0	31.7	
SVI* (%)		1.1	40.0	P<0.0001
PNI* (%)		55.6	76.7	0.008
Clinical Stage* (%)	T1	32.2	5.0	
	T2	67.8	73.3	P<0.0001
	T3	0	21.7	
EPE** (%)		2.2	18.3	0.001
Age*** (year)		65.6	63.1	0.031
Pearson Chi-Square Test; **Fisher's Exact Test; ***Student T Test; PSA, Prostate Specific Antigen; PNI, Perineural Invasion				

Table 2: The features of the cases with/without biochemical recurrence.

The multivariate analysis used the logistic regression model to examine, positive surgical margin, GS, PNI, clinical stage, and age. As seminal vesicle invasion and extra prostatic extension directly affected the clinical stage, they were omitted from the multivariate analysis. The results of the logistic regression indicated that Gleason Score and clinical stage were independent risk factors of biochemical recurrence. Our findings suggested that the correlation between biochemical recurrence and PNI, age and positive surgical margin would lose its significance in multivariate analysis (Table 3). Analysis PNI's relation with negative pathological features revealed PNI as an independent risk factor for positive surgical margin (odds ratio 5.439 p=0.001) and seminal vesicle invasion (odds ratio 5.091 p=0.048) in multivariate analysis. The correlation between PNI and the high stage of the disease (Stage 3) was not significant (Table 4).

	Odds Ratio (%95 CI)	P value*
GS	3.366 (1.786-6.344)	0
PNI	1.150 (0.463-2.858)	0.763
Clinical Stage	3.088 (1.186-8.039	0.021
Age	0.969 (0.916-1.026)	0.282
PSM	1.802 (0.732-4.431)	0.200
*Logistic Regression; PNI, Perineural Invasion		

Table 3: The factors affecting biochemical recurrence in multivariate analysis.

	Odds Ratio	%95 Confidence Interval	P value*
PSM			
GS	2.414	(1.544-3.775)	0
PNI	5.439	(2.017-14.665)	0.001
Age	0.983	(0.934-1.035)	0.522
SMI			
GS	3.519	(2.082-5.947)	0
PNI	5.091	(1.011-25.638)	0.048
Age	0.982	(0.918-1.050)	0.593
High Stage (Stage 3)			
GS	3.371	(1.892-6.006)	0

PNI	3.189	(0.353-28.847)	0.302
Age	0.896	(0.818-0.981)	0.017
*Logistic Regression; PNI, Perineural invasion			

Table 4: Multivariant analysis of PNI, GS, and age in predicting negative pathological features.

Discussion

The literature reported that the rate of PNI in radical prostatectomy specimens was 75%, but our study determined it to be 64%. PNI is an important factor for malignancy but not accepted pathognomonicly. The occurrence of PNI in the benign prostate glands was a defined condition, and the occurrence of PNI without neoplasia symptoms was not diagnostic for prostate cancer [2,13].

Our study found that positive surgical margin, seminal vesicle invasion, extra prostatic extension, and biochemical recurrence occur more often in cases with PNI, and that Gleason Score and clinical stage were higher in PNI cases. Our findings indicate that PNI positivity might be related to poor prognosis. Most of the studies on PNI in prostate cancer focus on its effects on prognosis. Many studies observed that PNI had a significant relation with biochemical recurrence and survival in univariate analysis. Moreover, many studies found that when multivariate analysis was used with other factors, the significance of PNI in predicting biochemical recurrence became null [2,4,9,10,12]. In the study by Anderson et al. on 266 patients with prostate cancer who underwent external radiotherapy showed that in multivariate analysis, the occurrence of PNI on biopsy with GS and palpation phase is an independent predictor in terms of the controls without biochemical disease symptom [7]. The study by Bonin et al. conducted on 484 patients who were diagnosed by transrectal needle biopsy, in a group whose pre-treatment PSA value was under 20ng/mL, PNI had an independently significant relation with survival without biochemical disease symptom [8]. The study by DeLancey et al. on 3226 patients exposed to radical prostatectomy showed that the occurrence of PNI on prostate biopsies was an independent prognostic factor related to negative pathologic features and worse survival outcomes [5]. It was determined that in a study analyzing the prognostic values of perineural invasion, Gleason Score, and Ki-97 expression; all three factors were independent indicators of local and systemic progression and they were significantly related to cancer-specific death [14]. The study by O'Malley et al. found no significant differences of PSA recurrence between the groups of patients who underwent radical prostatectomy with and without PNI [11]. The study by Beard et al. conducted on 381 patients in both low and high-risk groups, found that the existence of PNI on biopsy was a significant predictor in univariate analysis, while in multivariate analysis, this significance was lost in the high-risk patient group. Researchers said that the existence of PNI in the biopsies of patients in the low-risk group showed a possibility of an occult high-grade disease and the biopsy might have been performed from a wrong localization [9]. All of the variables (PSM, GS, SVI, PNI, clinical stage, extra prostatic extension, and young age) that we examined in our study are indicators of biochemical recurrence in univariate analysis. However, only Gleason Score [odds ratio 3.366 (1.786-6.344) p<0.0001] and clinical stage [odds ratio 3.088 (1.186-8.039 p=0.021] were presented as independent risk factors for PSA recurrence. The significance of PNI in univariate analysis was not present in multivariate analysis. Our findings, which were related to the correlation of PNI with negative pathologic features, indicated that the existence of PNI was an independent risk factor for positive surgical margin and seminal vesicle invasion. The study by DeLancey et al. observed similar results [5]. However, the study by De la Taille et al. determined that the occurrence of PNI was an independent risk factor for high-grade prostatic adenocarcinoma, while the findings suggested no significant correlation for positive surgical margin and seminal vesicle invasion [4]. Although PNI bears no importance on radical prostatectomy materials, in the cases that exhibit PNI during the needle biopsy or TUR materials, the disease's aggressiveness must be taken into consideration and the treatment strategies should be evaluated accordingly. The data acquired from our study showed that PNI is related to biochemical recurrence but not an independent risk factor. Moreover, our study observed that PNI was an independent risk factor for negative pathological features such as positive surgical margin and seminal vesicle invasion.

We believed that if supported with further large scale and prospective studies with longer follow- up; presence or absence of PNI in the radical prostatectomy material may be used in developing models to estimate the risk of biochemical recurrence or regional and distant metastasis and rationalize any adjuvant treatment.

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