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ORIGINAL ARTICLE

The Impact of Perineural Invasion on Prognosis in Patients Undergoing Robot-Assisted Radical Prostatectomy

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What is already known on this topic?

- *Perineural invasion (PNI) is a recognized histopathological feature in prostate cancer and is commonly associated with aggressive tumor biology.*
- *The PNI can be detected in both biopsy (PNIb) and prostatectomy (PNIp) specimens; however, its prognostic significance—particularly in predicting biochemical prostate-specific antigen (PSA) recurrence—remains controversial.*
- *Previous studies have yielded inconsistent findings regarding the prognostic utility of PNI, especially in patients treated with radical prostatectomy.*

What does this study add to the literature?

- *This study demonstrates that the presence of PNI in biopsy specimens (PNIb) significantly predicts its detection in radical prostatectomy specimens (PNIp).*
- *PNIp is significantly associated with adverse pathological features, including higher Gleason scores, greater tumor involvement, and increased rates of positive surgical margins.*
- *While PNIp was not found to be an independent predictor of biochemical PSA recurrence, the earlier recurrence observed in PNIp-positive patients may carry clinical implications, warranting further investigation.*

Abstract

Objective: This study aimed to investigate the clinical relevance of perineural invasion (PNI) detected in prostate needle biopsy specimens (PNIb) and radical prostatectomy specimens (PNIp) and to evaluate its associations with clinical characteristics, histopathological features, biochemical recurrence, and prognostic outcomes in patients undergoing nerve-sparing robot-assisted radical prostatectomy (RARP).

Methods: A retrospective analysis was conducted on 106 patients who underwent RARP for prostate cancer between September 2016 and December 2021 at the institution. Clinical data, including prostate-specific antigen (PSA) levels, multiparametric magnetic resonance imaging findings, biopsy results, and postoperative pathology reports, were reviewed. Patients were stratified based on the presence of PNI in prostatectomy specimens (PNIp), and oncological outcomes were compared accordingly.

Results: The presence of PNIp was significantly associated with higher PSA density ($P = .031$), a greater frequency of PIRADS ≥3 lesions ($P = .048$), and a higher percentage of tumor involvement in biopsy cores ($P = .001$). Gleason scores ≥7 ($P = .028$) and positive surgical margins ($P = .009$) were also more prevalent in the PNIp group. Although biochemical recurrence occurred more frequently in PNIp-positive patients (21.1%) compared to PNIp-negative patients (6.7%), this difference did not reach statistical significance ($P = .076$). The mean time to biochemical recurrence was shorter in the PNIp-positive group (69.6 months) compared to the PNIp-negative group (78.6 months). Multivariate logistic regression analysis did not identify any independent predictor of recurrence (Nagelkerke $R^2 = 0.155$, $P < .001$).

Conclusion: While PNIp was significantly associated with adverse pathological features, it did not independently predict biochemical recurrence. Nevertheless, the earlier onset of recurrence in PNIp-positive patients—despite the lack of statistical significance—may suggest potential clinical relevance that warrants further investigation.

Keywords: Perineural invasion, prostatectomy, prostatic neoplasms, radical, robotics

Introduction

Several histopathological features are recognized as characteristic of prostatic adenocarcinoma, including perineural invasion (PNI) and lymphovascular invasion. While lymphovascular invasion is infrequently identified in needle biopsy specimens, it is observed in 5%-53% of radical prostatectomy samples and is associated with greater tumor volume, higher grade and stage, as well as increased risks of biochemical recurrence, distant metastasis, and reduced survival.[1]

The PNI is defined as the infiltration of malignant cells into the neural sheath or the circumferential encasement of nerve fibers by tumor cells, involving up to 33% of the nerve's perimeter.[2] Initially described in head and neck cancers—tumors known for their propensity for neural invasion[3]—PNI has since been studied in various malignancies, including those of the pancreas, prostate, bile duct, stomach, and colon.[4]

The PNI is widely acknowledged as a pathological feature indicative of an elevated risk for local recurrence, unfavorable prognosis, and increased likelihood of metastatic dissemination.[5]

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It was originally hypothesized that tumor cells reached nerve fibers via lymphatic spread. However, subsequent studies demonstrated the absence of lymphatic vessels within the neural sheath, distinguishing PNI from lymphatic metastasis.[6] Later, the "low-resistance pathway" hypothesis suggested that the neural sheath enables tumor dissemination due to its limited mechanical resistance.[7] More recent research has shown that PNI results from complex molecular, cellular, and metabolic interactions between tumor cells and nerves. Nerve-derived factors can promote tumor proliferation and invasion, while tumor-secreted molecules can induce axonal growth and nerve elongation toward malignant tissues, creating a bidirectional dynamic of tumor-nerve interaction.[8]

Prostate cancer is notably neurotropic and is characterized by dense perineural innervation, which facilitates PNI and contributes to extracapsular extension of the tumor. A deeper understanding of PNI may help refine nerve-sparing prostatectomy techniques and enhance oncologic outcomes in prostate cancer treatment.[9]

This study aimed to evaluate the relationship between PNI identified in prostate needle biopsy specimens (PNIb) and in radical prostatectomy specimens (PNIp) and to examine the associations of PNI with clinical, histopathological, biochemical recurrence, and prognostic parameters.

Methods

This retrospective study included patients diagnosed with prostate cancer via transrectal ultrasound-guided prostate biopsy performed due to elevated prostate-specific antigen (PSA) levels or clinical suspicion. All patients subsequently underwent robot-assisted radical prostatectomy (RARP) as definitive treatment. The study cohort consisted of individuals who were evaluated and treated at the Urology Clinic of Gülhane Training and Research Hospital, University of Health Sciences, between September 2016 and December 2021.

Ethical approval for the study was granted by the Scientific Research Ethics Committee of the University of University of Health Sciences, Gülhane Scientific Research Ethics Board on March 14, 2023 (Decision No. 2023-86). Additionally, approval was obtained from the Medical Specialty Training Committee (TUEK) of the University of Health Sciences, Health Practice and Research Center on December 1, 2022 (Decision No. 2022/23).

The data collected included demographic information, preoperative and postoperative serum PSA levels, prostate biopsy results, staging data from multiparametric magnetic resonance imaging (mpMRI) and positron emission tomography-computed tomography (PET-CT), as well as final pathological findings from radical prostatectomy specimens.

Inclusion criteria were (i) histopathological confirmation of prostate cancer via biopsy, (ii) subsequent treatment with RARP, and (iii) availability of follow-up data regarding oncological outcomes. A total of 204 patient records were initially reviewed through the institutional electronic medical records system and supplemented by follow-up telephone interviews. Patients were excluded if they were deceased, lacked accessible preoperative data (particularly if evaluated at external centers), or were lost to follow-up. After applying these criteria, 106 patients were included in the final analysis.

The study was conducted in accordance with the ethical principles outlined by the TR Dizin standards. Although the study was retrospective in nature, written informed consent had been obtained from all participants for the use of their anonymized clinical data.

Results

The mean age of the 106 patients included in the study was 63.6 ± 6.2 years (range: 47-76 years). Pre-diagnostic clinical parameters—including total PSA, free PSA, free/total PSA ratio, prostate volume, and PSA density (PSAD)—are summarized in Table 1.

Tumor-related characteristics were also evaluated. The majority of patients (91.5%) underwent sextant biopsy, with a mean of 12.5 ± 2.5 cores obtained. The average preoperative Gleason scores were as follows: primary pattern 3.1 ± 0.3, secondary pattern 3.3 ± 0.5, and total score 6.3 ± 0.6. The distribution of Gleason scores was: 3+3 in 67% (n = 71), 3 +4 in 21.7% (n = 23), 4+3 in 5.7% (n = 6), 4+4 in 3.8% (n = 4), 4+5 in 0.9% (n = 1), and 5+5 in 0.9% (n = 1). Overall, 67% of patients had Gleason scores <7, while 33% had scores ≥7. The median tumor involvement in biopsy cores was 8.5% (Figure 1). Preoperative pathology revealed PNI in 25.5% of patients and high-grade prostatic intraepithelial neoplasia (PIN) in 8.5%. None of the cases exhibited bladder neck invasion, extraprostatic extension, seminal vesicle involvement, lymphovascular invasion, or intraductal carcinoma (Table 2).

Patient characteristics were compared based on the presence of PNI in radical prostatectomy specimens (PNIp). The PSA density was significantly higher among patients with PNIp (P = .031; Table 3), whereas no statistically significant differences were observed in the remaining clinical parameters. Multiparametric MRI findings were available for X patients. Among them, PIRADS ≥3 lesions were significantly more frequent in the PNIp-positive group (P = .048), suggesting a correlation between imaging findings and aggressive histopathological features.

Analysis of preoperative pathology demonstrated a significantly greater percentage of tumor involvement in biopsy cores in patients with PNIp (P = .001).

Postoperative histopathological findings and biochemical recurrence rates were also evaluated based on PNIp status. Patients with PNIp exhibited higher frequencies of Gleason scores ≥7 (P = .028), greater tumor burden (P < .001), and positive surgical margins (P = .009). Although biochemical recurrence occurred more frequently in PNIp-positive patients (21.1%) compared to PNIp-negative patients (6.7%), this difference did not reach statistical significance (P = .076). However, the approximately 9-month earlier recurrence observed in the PNIp-positive group may still hold clinical relevance, particularly in patients with otherwise borderline risk features.

Biochemical recurrence-free survival (bRFS) was assessed using Kaplan–Meier analysis. The mean bRFS time was 69.6 ± 2.5 months in the PNIp-positive group and 78.6 ± 2.3 months in the

Table 1. Pre-Diagnostic Clinical Characteristics

Feature (n = 106)	Mean ± SD or Median (Range)
Age (years)	63.6 ± 6.2
Total PSA (ng/mL)	7.6 (3.3-57.3)
Free PSA (ng/mL)	1.0 (0.3-6.4)
Free/total PSA (%)	12.1 (3.2-40.8)
Prostate volume (cc)	41 (10-173)
PSA density (ng/mL^2)	0.19 (0.04-1.13)

PSA, prostate-specific antigen; SD, standard deviation.

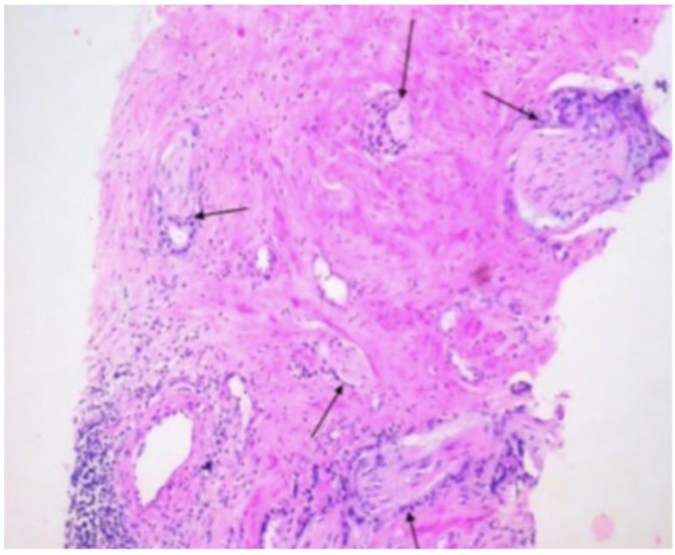

Figure 1. Perineural invasion in prostate adenocarcinoma: tumor cells invading the perineural space (H&E, ×200).

PNIp-negative group. While the difference was not statistically significant, recurrence occurred approximately 9 months earlier in patients with PNIp (Table 4).

Potential predictors of biochemical recurrence were analyzed using multivariate logistic regression. Variables included in the final model were selected based on clinical relevance and the results of univariate analysis. After addressing multicollinearity, the final model included age, PSAD, tumor percentage, Gleason scores, surgical margin status, and PNIp. Although the model was statistically significant (Nagelkerke $R^2 = 0.155$, $P < .001$), none of the included variables independently predicted biochemical recurrence.

Table 2. Pre-Operative Pathological and Biopsy Findings

Feature	Value
Biopsy type—sextant (%)	97 (91.5)
Biopsy type—cognitive (%)	4 (3.8)
Biopsy type—targeted (%)	5 (4.7)
Number of biopsy cores	12.5 ± 2.5
Gleason score—primary pattern	3.1 ± 0.3
Gleason score—secondary pattern	3.3 ± 0.5
Gleason score—total score	6.3 ± 0.6
Tumor percentage in biopsy cores (%)	8.5 (0.5-90)
Perineural invasion (PNIb) (%)	27 (25.5)
High-grade PIN (%)	9 (8.5)
Bladder neck invasion	0
Extraprostatic extension	0
Seminal vesicle invasion	0
Lymphovascular invasion	0
Intraductal carcinoma	0

PIN, prostatic intraepithelial neoplasia; PNIb, perineural invasion on biopsy; SD, standard deviation.

Table 3. Association Between PNIp and Preoperative Clinical Parameters

Variable	PNIp (+) (n = 76)	PNIp (–) (n = 30)	*P*
Age (years)	64.0 ± 6.6	62.8 ± 5.0	.357
Total PSA (ng/mL)	7.4 (3.3-57.3)	7.6 (4.0-20.9)	.623
Free PSA (ng/mL)	1.0 (0.32-6.4)	1.0 (0.4-5.9)	.855
Free/total PSA (%)	12.4 (3.2-40.8)	11.7 (7.2-35.3)	.861
Prostate volume (cc)	38 (10-173)	46.5 (22-156)	.071
PSA density (ng/mL^2)	0.20 (0.04-1.13)	0.14 (0.08-0.51)	.031
PIRADS ≥3 lesions, n (%)	52 (68.4)	14 (46.7)	.048

PNIp, perineural invasion in prostatectomy; PSA, prostate-specific antigen; SD, standard deviation.

Discussion

Perineural invasion is an established histopathological feature observed in various malignancies, including prostate cancer. It is generally associated with aggressive tumor behavior, local recurrence, and poor prognosis.[10] However, its prognostic utility, particularly in predicting biochemical recurrence following radical prostatectomy, remains a matter of debate.

In this study, PNI was detected in 25.5% of prostate needle biopsy specimens (PNIb) and in 71.7% of radical prostatectomy specimens (PNIp). This substantial discrepancy is likely attributable to the limited sampling area and smaller tissue volume inherent in needle biopsy procedures. Previous reports similarly indicate a wide range of detection rates for PNIb (4%-71%) and PNIp (31.9%-79%), supporting the variability observed.[11-15]

Consistent with earlier studies, it was found that PNIp was significantly associated with several adverse pathological features, including higher Gleason scores, greater tumor involvement, and increased rates of positive surgical margins, lymphovascular invasion, and seminal vesicle invasion.[16] These findings align with the literature suggesting a link between PNIp and aggressive disease characteristics.

Despite this association with adverse pathology, the data did not support a statistically significant relationship between PNIp and biochemical recurrence. Recurrence was observed in 21.1% of PNIp-positive patients vs. 6.7% in PNIp-negative patients; however, this difference was not statistically significant ($P = .076$). Mean biochemical recurrence-free survival was approximately 9 months shorter in the PNIp-positive group (69.6 ± 2.5 months vs. 78.6 ± 2.3 months, $P = .069$), suggesting a possible trend

Table 4. Biochemical Recurrence-Free Survival by PNIp Status

Group	Mean bRFS ± SD (Months)	95% CI (Months)	*P*
PNIp (+)	69.6 ± 2.5	64.6-76.8	
PNIp (–)	78.6 ± 2.3	74.1-83.1	.069

bRFS, biochemical recurrence-free survival; PNIp, perineural invasion in prostatectomy specimens; SD, standard deviation.

that did not reach statistical significance. Similar findings have been reported by Miyake et al and Ng et al, who concluded that PNIp was not an independent prognostic factor for biochemical recurrence when adjusted for established clinical and pathological parameters.[17,18] The lack of statistical significance should be interpreted with caution, as the nearly 9-month difference in recurrence-free survival may be clinically meaningful in patient management and risk stratification, especially when considered alongside other high-risk features.

In contrast, some studies have reported that PNIb is associated with poorer oncologic outcomes, including earlier recurrence and progression.[19,20] However, other investigations found no significant predictive value of PNIb for biochemical recurrence.[21,22] The study was limited in this regard by the relatively small number of PNIb-positive cases, which precluded robust statistical analysis of its prognostic role.

Interestingly, while Jeon et al[20] reported that most recurrences occurred within the first 2 years after surgery, the study observed peak recurrence in the third and fourth years, indicating a potentially more delayed pattern in this cohort.

There remains a lack of prospective, surgery-focused studies specifically examining the impact of PNIp on long-term oncologic outcomes in prostate cancer.[2] Many prior investigations have included patients who received radiotherapy and therefore emphasized PNIb findings, limiting generalizability to surgical populations.

In summary, although PNIp was significantly associated with adverse pathological characteristics, it did not independently predict biochemical recurrence. The findings suggest that while PNIp may reflect tumor aggressiveness, its role as a standalone prognostic biomarker remains uncertain. Limitations of the study include the small number of PNIb-positive patients and the inclusion of some patients with externally performed biopsies, where PNI status may not have been consistently assessed. It is also acknowledged that the number of biopsy cores may not substantially influence the detection rate of PNI.

In addition to the limited number of PNIb-positive patients, the inclusion of patients who underwent biopsy at external institutions posed challenges in the consistent evaluation of PNI, as pathological reporting standards may vary across centers. This heterogeneity may have influenced the reliability of PNIb-based comparisons. Furthermore, the lack of access to centralized pathology slides prevented a uniform histological re-review of PNI status.

The findings indicate that the presence of PNI in prostate needle biopsy specimens (PNIb) is a statistically significant predictor of its presence in radical prostatectomy specimens (PNIp). Although PNIp was significantly associated with several features indicative of biologically aggressive disease—such as higher Gleason scores and positive surgical margins—it was not identified as an independent prognostic factor for biochemical PSA recurrence or long-term oncological outcomes. Nevertheless, the earlier occurrence of biochemical recurrence in patients with PNIp (approximately 9 months earlier) may suggest potential clinical relevance, despite the absence of statistical significance.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences, Gülhane Scientific Research Ethics Board (Date: 14.03.2023, Number: 2023-86).

Informed Consent: Written informed consent was obtained from all participants included in this study.

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