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Risk factors associated with perineural invasion in prostate cancer

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Abstract
Objectives: The prognostic importance of perineural invasion (PNI) in prostate cancer (PC) has been postulated by some authors. Few studies have investigated the risk factors associated with PNI. The aim of this study was to identify factors associated with PNI in PC.
Patients and methods: The study group of 113 patients diagnosed with PC during the period 2005–2010 consisted of 66 who underwent radical prostatectomy (RP) and 66 who did not. Each group was further divided into those with and without PNI. The association between clinicopathological parameters and PNI in prostate biopsy (Pbx) and RP specimens was investigated using *t*-test and logistic regression analysis. Discordance in PNI prevalence and PNI up-migration between Pbx and RP specimens were also studied.
Results: In patients who did not undergo RP, Pbx Gleason score (GS) ≥ 7 was a significant predictor for the presence of PNI. In patients who underwent RP, Pbx GS > 7 increased the risk of PNI in Pbx and RP samples, while a high RP GS predicted PNI in the RP specimen. The discordance rate for PNI in Pbx and RP specimens was 27.3%. Up-migration to a PNI positive cancer between Pbx and RP specimens was seen in 45.5% of cases and RP GS was the only factor associated with PNI up-migration.

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Conclusion: The association of PNI with a high GS and the high rate of discordance between Pbx and RP specimens indicate that in patients with a high GS on Pbx, the pathologist should look more carefully for PNI, and the surgeon should be aware of sampling errors and the unreliability of Pbx specimens in detecting PNI.

Introduction

Prostate cancer (PC) is common, with an estimated 218,890 new diagnoses and 27,050 deaths in the USA in 2007 [1]. PC is usually diagnosed by means of transrectal ultrasound-guided biopsy and the type of treatment chosen is based on prognostic parameters such as the patient's age, serum PSA levels, Gleason score (GS), tumor volume, the presence of perineural invasion (PNI) and tumor stage [2–5].

PNI is defined as infiltration of cancer cells in the epineurium and perineurium, or even the endoneurium. The involvement of peripheral nerves has been overlooked for a long time but is now receiving more attention as a potentially important component of the cancer microenvironment [6]. One reason for the prognostic importance of PNI is the possibility of metastatic spread of cancer cells along nerves. Although the effect of PNI on long-term outcome in patients with PC has been challenged by some authors [7,8], its importance in making treatment decisions cannot be overlooked [9].

PNI is associated with higher grade and stage in radical prostatectomy (RP) specimens [10] and it may have prognostic value after RP or external beam radiotherapy (RT) for localized and low risk PC [2,3]. D'Amico et al. considered PNI an independent prognostic factor for PC recurrence [2]. Resection of the neurovascular bundle on the side of biopsy detected PNI may decrease the positive surgical margin rate and improve outcome for low risk patients [2]. Therefore, until it is proven that PNI has no prognostic significance, the decision to perform nerve-sparing surgery should be made with care.

Because biopsy samples may not be representative of the real extent of PNI [2,9], pathologists should carefully examine Pbx and RP specimens, and urologists should not rely on the results of Pbx samples alone to determine the presence of PNI.

The objective of this study was to assess the association of patient age, smoking history, serum PSA and GS with the presence of PNI in the Pbx and RP samples of patients with PC, and to determine whether these factors could predict up-migration from a cancer with no PNI to a PNI positive cancer.

Subjects and methods

A total of 208 patients were diagnosed with PC by means of transrectal ultrasound guided sextant Pbx at two University Hospitals between 2005 and 2010. The exclusion criteria were [1] patients diagnosed with PC after a simple prostatectomy or transurethral resection of the prostate (TURP), [2] patients with transitional cell carcinoma (TCC) of the bladder invading the prostate, [3] if the pathology reports of both Pbx and retropubic RP were not available and [4] patients diagnosed at other centers whose Pbx was not reviewed by our hospital's pathologist.

The study population consisted of 113 patients who were not suitable candidates for RP and 66 who had undergone RP. The association between clinical and pathological data and PNI in Pbx and RP samples was analyzed in each group. Clinical data included the patient's age, smoking history and serum PSA level, while pathological data included histological grade (Gleason score).

The discordance rate with regard to PNI prevalence between Pbx and RP samples was studied, and the PNI up-migration rate between Pbx and RP specimens was calculated.

Statistical analysis was performed using the *t*-test and logistic regression analysis (univariate and multivariate). A p-value <0.05 was accepted as statistically significant.

Results

There were 113 patients who had undergone Pbx but not RP, 66 showed evidence of PNI (group 1) while 47 had no PNI in the Pbx (group 2) (Table 1). The mean patient age was not statistically different between the two groups. There were statistically significant differences in mean serum PSA ($p=0.04$) and mean biopsy GS ($p=0.01$) between the groups (Table 1). On uni- and multivariate

Table 1 Clinical and pathological characteristics in groups 1 and 2.

Patient characteristics	Group 1 *N* (%) 66 (58.4%)	Group 2 *N* (%) 47 (41.6%)
Age (years)		
50–59	5 (7.6%)	3 (6.4%)
60–69	22 (33.3%)	22 (46.8%)
70–79	27 (40.9%)	16 (34%)
80 and above	12 (18.2%)	6 (12.8%)
Mean age	70.9 ± 8.6	69.5 ± 8.3
Smoking		
Smoker	35 (53%)	21 (44.7%)
Non-smoker	31 (47%)	26 (55.3%)
PSA (ng/ml)		
<10	5 (7.6%)	3 (6.4%)
10–20	5 (7.6%)	4 (8.5%)
>20	56 (84.8%)	4 (85.1%)
Mean PSA	233.3 ± 454.8	97.1 ± 107.6
Biopsy GS		
<7	12 (18.2%)	19 (40.4%)
7	25 (37.9%)	14 (29.8%)
>7	29 (43.9%)	13 (27.7%)
Mean biopsy GS	7.4 ± 1.2	6.7 ± 1.7
Missing data		1 (2.1%)

Table 2 Univariate analysis of association between GS and PNI.

GS	Groups 1 and 2			Groups 3 and 4			Groups 5 and 6		
	p-Value	Crude OR	CI	*p*-Value	Crude OR	CI	*p*-Value	Crude OR	CI
Pbx GS									
All	0.018	1.393	1.06–1.83	0.002	2.38	1.36–4.14	0.003	2.3	1.33–3.96
<7	ref.	ref.	ref.	ref.	ref.	ref.	–	–	–
7	0.04	2.83	1.02–7.49	0.20	2.27	0.65–7.92	–	–	–
>7	0.01	3.53	1.33–9.36	0.01	20.40	2.19–190	–	–	–
RP GS									
All	–	–	–	–	–	–	0.021	1.46	1.06–2.00
<7	–	–	–	–	–	–	ref.	ref.	ref.
7	–	–	–	–	–	–	0.355	1.73	0.54–5.54
>7	–	–	–	–	–	–	0.017	5.769	1.36–24.5

analysis there were no significant associations between patient age, smoking history or serum PSA and PNI. Univariate analysis showed a significant association between high Pbx GS and PNI (Table 2). Multivariate analysis confirmed this association ($p = 0.034$ for all GS, $p = 0.03$ for Pbx GS = 7, and $p = 0.01$ for Pbx GS > 7).

Comparison of the 66 patients who had undergone RP and the 113 who had undergone Pbx but not RP showed that the former group had significantly lower mean age (64.8 years vs 70.3 years, $p = 0.000$), serum PSA (16.7 ng/ml vs 176.7 ng/ml, $p = 0.001$) and Pbx GS (6.6 vs 7.1, $p = 0.000$). In the group of 66 patients who had undergone RP, 22 had PNI in the Pbx (group 3) and 44 did not (group 4) (Table 3). The mean age and PSA were not significantly different between these two groups, but Pbx GS was significantly different ($p = 0.00$). Univariate analysis showed no association of patient age, smoking history or PSA with PNI. Univariate analysis showed a significant association between Pbx GS and PNI (Table 2). Multivariate analysis did not show a significant association, possibly because of the small sample size.

In the group that had undergone RP, 40 patients had PNI in the RP specimen (group 5) while 26 patients did not (group 6). Univariate analysis showed no significant association of patient age, smoking history and PSA with PNI, but Pbx GS and RP GS were significantly associated with the presence of PNI in the RP specimen (Table 2).

Table 3 Clinical and pathological characteristics in patients who had undergone RP.

	Group 3*N* (%)22 (33.3%)	Group 4*N* (%)44 (66.7%)	Group 5*N* (%)40 (60.6%)	Group 6*N* (%)26 (39.4%)
Age (years)				
<50	1 (4.5%)	0 (0%)	1 (2.5%)	0 (0%)
50–59	4 (18.2%)	9 (20.5%)	10 (25%)	3 (11.5%)
60–69	8 (36.4%)	24 (54.5%)	16 (40%)	16 (61.5%)
70–79	9 (40.9%)	10 (22.7%)	13 (32.5%)	6 (23.1%)
≥80	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing data		1 (2.3%)	0 (0%)	1 (3.8%)
Mean	65.2 ± 8	64.6 ± 6.7	64.0 ± 8.1	66.1 ± 5.1
Smoking				
Smoker	10 (45.5%)	21 (47.7%)	21 (52.5%)	11 (42.3%)
Non-smoker	11 (50%)	21 (47.7%)	18 (45%)	13 (50%)
Missing data	1 (4.5%)	2 (4.5%)	1 (2.5%)	2 (7.7%)
PSA (ng/ml)				
<10	3 (13.6%)	18 (40.9%)	10 (25%)	11 (42.3%)
10–20	11 (50%)	15 (34.1%)	20 (50%)	6 (23.1%)
>20	5 (22.7%)	9 (20.5%)	7 (17.5%)	7 (26.9%)
Missing data	3 (13.6%)	2 (4.5%)	3 (7.5%)	2 (7.7%)
Mean	18.6 ± 12.4	15.9 ± 13.3	15.3 ± 9.7	18.9 ± 16.3
Pbx GS				
<7	10 (45.5%)	34 (77.3%)	23 (57.5%)	21 (80.8%)
7	6 (27.3%)	9 (20.5%)	10 (25%)	5 (19.2%)
>7	6 (27.3%)	1 (2.3%)	7 (17.5%)	0 (0%)
Missing data	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean	6.8 ± 1.1	5.6 ± 1.3	6.5 ± 1.2	5.4 ± 1.2
RP GS				
<7	–	–	13 (32.5%)	15 (57.7)
7	–	–	12 (30%)	8 (30.8)
>7	–	–	15 (37.5%)	3 (11.5)
Missing data	–	–	0 (0%)	0 (0%)
Mean	–	–	6.0 ± 1.7	7.0 ± 1.6

Table 4 Clinical and pathologic characteristics of groups 7 and 8.

Characteristics	Group 7 *N* (%) 20 (45.5%)	Group 8 *N* (%) 24 (54.5%)
Age (years)		
<50	0 (0%)	0 (0%)
50–59	4 (20%)	5 (20.8%)
60–69	11 (55%)	13 (54.2%)
70–79	5 (25%)	5 (20.8%)
80 and above	0 (0%)	0 (0%)
Missing data	0 (0%)	1 (4.2%)
Mean age	64.8 ± 6.7	64.5 ± 6.8
Smoking		
Smoker	11 (55%)	10 (41.7%)
Non-smoker	8 (40%)	13 (54.2%)
Missing data	1 (5%)	1 (4.2%)
PSA (ng/ml)		
<10	6 (30%)	12 (50%)
10–20	7 (35%)	8 (33.3%)
>20	6 (30%)	3 (12.5%)
Missing data	1 (5%)	1 (4.2%)
Mean PSA	18.5 ± 14.9	13.7 ± 11.7
Pbx GS		
<7	14 (70%)	20 (83.3%)
7	5 (25%)	4 (16.7%)
>7	1 (5%)	0 (0%)
Missing data	0 (0%)	0 (0%)
Mean	6.0 ± 1.4	5.3 ± 1.3
RP GS		
<7	11 (55%)	16 (66.7%)
7	4 (20%)	8 (33.3%)
>7	5 (25%)	0 (0%)
Missing data	0 (0%)	0 (0%)
Mean	6.5 ± 1.6	5.5 ± 1.5

Out of 66 patients who underwent RP, 40 (60.6%) had PNI in the RP specimen and 22 (33.3%) had PNI in the Pbx report, i.e. there was a discordance rate of 27.3% between Pbx and RP pathology reports. In order to study the factors increasing the risk of PNI up-migration, the 44 patients who had no PNI before RP (group 4) were further divided into 20 patients (45.5%) who showed PNI in the RP specimen (group 7) and 24 patients (54.5%) with no PNI in the RP specimen (group 8) (Table 4). The only significant difference between these groups was the mean RP GS ($p = 0.04$). Univariate analysis showed a significant association of PNI up-migration with RP GS ($p = 0.05$), but not with age, smoking, PSA and Pbx GS. Multivariate analysis did not show a significant association between PNI and RP GS, probably due to small patient numbers.

Discussion

It has been recommended to search for PNI in the Pbx sample, in order to use its prognostic value to select the most suitable therapy, and in the RP specimen to better determine the biological nature of the disease and to select adequate integrative therapies [9]. Although some authors showed that PNI does not predict biochemical recurrence [11,12], others have shown that the presence of PNI in the Pbx specimen represents an independent risk factor for biochemical recurrence in patients treated by RP or RT [2,3]. It has also been suggested that PNI has a predictive role in patients with a preoperative PSA > 10 ng/ml [13].

Although some authors have shown that nerve-sparing RP does not compromise the outcome in patients with PNI [8], others have shown that patients who had the corresponding neurovascular bundle resected had a significantly lower positive margin rate compared to those who had the neurovascular bundle spared (11% vs 100%) [2]. Patients with pathological stage T2 tumors and PNI were found to present a higher than pT2 stage and higher GS [10]. Stone et al. reported that PNI in RP specimens predicted pelvic lymph node metastases in men with PC [14]. A decrease in PSA progression-free survival after RT for low-risk patients with PNI-positive Pbx specimens was also found [3]. Although pathological features of PC are important outcome predictors, and some studies have investigated the association of clinical features with GS [15–18], very few studies have addressed PNI.

Our study showed that the patient's age had no association with PNI in Pbx or RP specimens. This differs from the findings of Antunes et al. [18] who showed that the <50 year and >81 year age groups showed higher percentages of PNI. This difference may be the result of the small number of patients >80 or <50 years old in our study.

There appear to be no studies that have investigated smoking as a variable associated with PNI in PC. Our study showed no association between a smoking history and PNI.

Although several studies have shown an association between serum PSA and GS [15,16], few have investigated its association with PNI. Two studies have shown a statistically significant association between the presence of PNI in RP specimens and higher preoperative serum PSA [19,20]. Our study showed that in patients who did not undergo RP there was a significant difference in mean PSA between patients with and without PNI in the Pbx specimen, and univariate analysis showed a trend toward association with PNI ($p = 0.09$). This trend was lost in patients who underwent RP, possibly due to the small sample size (PSA > 20 ng/ml was seen in only 5 patients in group 3 and in 9 patients in group 4). Considering the significantly lower PSA in RP patients, this supports a possible association between PSA and PNI.

Our study showed a significant association between GS and PNI in both Pbx and RP specimens. This is concordant with the findings of Beard et al. [3] who found a strong association between the presence of PNI in the Pbx specimen and a Pbx GS of 7–10. Although Loeb et al. showed that PNI is an independent risk factor for aggressive pathology [8], they did not investigate whether the reverse is also true (presence of PNI predicting aggressive pathology). Cambruzzi et al. showed that GS had a significant association with pathological criteria such as extra-capsular extension, PNI, lymphovascular invasion and staging [21].

An interesting finding in our study was that PNI in the RP sample was associated with high GS both in Pbx and RP samples, which is concordant with the findings of Lee et al. [6]. In patients who underwent RP, PNI was found in 33.3% of Pbx specimens and 60.6% of RP specimens. Other researchers have reported the prevalence of PNI in Pbx specimens as 7–43% and in RP specimens as 31.9–79.0% [2,6,8,22].

The 27.3% discordance rate in PNI between Pbx and RP specimens (60.6% vs 33.3%) confirms the unreliability of Pbx in determining the true features of PC. Discordance rates in other studies varied from 13% (15.8% vs 2.8%) reported by Nayyar et al. [22] to 45.4%

(52.8% vs 7.4%) reported by Lee et al. [6]. In our study, PNI upmigration was significantly seen in patients with higher RP GS, but this association was not seen with Pbx GS.

A limitation of our study was that detailed pathology reports (including percentage or laterality of cancer, primary and secondary GS and laterality of PNI) were not available for all patients. Another limitation was the relatively small number of patients, especially those who underwent RP.

Conclusion

The association of PNI with a high GS and the high rate of discordance between Pbx and RP specimens indicate that in patients with a high GS on Pbx the pathologist should look more carefully for PNI, and the urologist should be aware of sampling errors and the unreliability of Pbx specimens in detecting PNI.

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