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ORIGINAL ARTICLE

Prognostic significance of perineural invasion in patients who underwent radical prostatectomy for localized prostate cancer

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Summary

Purpose: *Perineural space invasion (PNI) is an important mechanism for progression of cancer through the prostatic capsule, the prognostic significance of PNI remains controversial. The purpose of the present study was to assess the prognostic significance of PNI between prostate biopsy and radical prostatectomy (RP) samples of patients affected by clinically localized prostate cancer (PCa).*

Methods: *75 patients undergoing RP who had PNI on prostate needle biopsy were retrospectively reviewed. To evaluate the correlation between PNI and adverse pathological characteristics of PCa we examined these demographic and clinicopathologic variables: patients age, family history, prostate specific antigen (PSA) level at the time of diagnosis, biopsy Gleason score (GS), clinical stage, extraprostatic extension (EPE), positive surgical margins (PSM), biochemical recurrence (BR), positive lymph nodes (PLN) involvement and seminal vesicle invasion (SVI).*

Results: *At RP 24% of patients had organ-confined disease, whereas EPE in neurovascular bundle (NVB) and SVI were present in 76% and 6.7%, respectively. PSM were shown in 32% and PLN in 17.3% of our cases. At a median follow-up of 44 months, 36% had BR, 9.3% developed metastatic disease, and 2.6% died of PCa. GS (>6) on needle biopsy and PSA level (≥10) were helpful in predicting which patients were likely to have tumor in the NVB ($p<0.002$).*

Conclusions: *PNI on biopsy is correlated with an increased risk of BR, while is not statistically associated with PSM. Nerve-sparing surgery does not compromise the oncological outcomes for patients with PNI on biopsy.*

Key words: *perineural invasion, prostate biopsy, prostate cancer, radical prostatectomy*

Introduction

Prostate core biopsy is an essential tool for the diagnosis and planning of treatment of PCa. Pathologic findings on prostate needle biopsy are essential to determine the optimal management of clinically localized PCa [1]. An average of 10-20% needle biopsy pathology reports will show a diagnosis of PNI [2]. It was first described by Ernst in 1905 and was defined as tumor cell infiltration in, around, and through the nerves [3]. Mortality in PCa patients is generally attributable to high Gleason score and extracapsular extension, which often result in treatment failure and are associated with poor prognosis [4]. Although perineural space invasion is an important mechanism for progression of cancer through the prostatic capsule, the prognostic significance of PNI remains controversial [5,6]. McNeal et al. [7] investigated PNI that was localized selectively to the area where nerves penetrate the prostate capsule, showing that PNI may promote extraprostatic spread. The underlying mechanistic bases for these relations are unclear but may relate to selective neural affinity in cells with apoptotic resistance or the ability to invade the prostate stroma or the neu-

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ral paracrine factors that inhibit apoptosis and/or stimulate disease progression.

The purpose of the present study was to assess the prognostic significance and association of serum PSA levels, GS, PSM and BR with the presence of PNI between prostate biopsy and RP samples of patients affected by PCa.

Methods

Clinical and pathological studies

Between March 2007 and May 2013, 75 patients undergoing RP (32 with laparoscopic technique and 43 with open technique) who had PNI on prostate needle biopsy were retrospectively reviewed. Pelvic lymph node dissection and a nerve-sparing technique were performed at the discretion of three experienced surgeons. Factors that influenced this decision were: the presence of PIN on needle biopsy; preoperative erectile function; evaluation of preoperative PSA level, GS, and clinical stage; induration or fixation of the neurovascular bundle intraoperatively. PNI was defined on pathologic analysis of the transrectal ultrasound-guided prostate biopsy (TPB) specimen. TPB was performed with the patient in the left lateral decubitus position using a General Electric Logiq 7 machine (GE Healthcare, Milwaukee, WI, USA) equipped with a 5-9 MHz multi-frequency convex probe "end-fire". After having imaged the prostate, sampling was carried out with a 18-Gauge Tru-Cut (Bard Biopsy Systems, Tempe, AZ, USA) needle powered by an automatic spring-loaded biopsy disposable gun. Patients who received neoadjuvant androgen ablation therapy and/or radiotherapy before RP were excluded. To evaluate the correlation between PNI and adverse pathological characteristics of PCa we examined the following demographic and clinicopathologic variables: patient age, family history, PSA level at the time of diagnosis, biopsy GS, clinical stage (T), EPE, percentage PSM, BR, percentage of PLN and SVI. Clinical and pathological stages were assigned based on the 2009 tumor node metastasis (TNM) system. The Gleason grading was based on the recommendations of the 2005 International Society of Urological Pathology consensus conference. All surgical specimens were analysed internally by our Pathology Department that specializes in genitourinary pathology. Follow-up was conducted according to the EAU Guidelines on PCa: 3, 6 and 12 months post-RP during the first year, and every 6 months in the second and third year. PSA level > 0.2 ng/ml by two subsequent measurements was defined as BR.

Statistics

Continuous variables were evaluated using median and interquartile range, according to their distribution. The association between PI and primary outcomes of interest (BR, PSM, PLN, SVI) was evaluated using the Student's t-test or the Mann-Whitney U test, depending or their distribution. Statistical analyses were performed using Microsoft Excel 2010 platform 10.1. A p value<0.05 was considered to indicate statistical significance.

Results

The descriptive characteristics of the study cohort are shown in Table 1. The median age of the 75 patients was 61.3 years (range 56-76), the median preoperative PSA level was 5.8 ng/mL (range 2.03-15.13) and the median prostate volume was 42.9 mL (range 17-106). Clinical stage was T1 in 26 (34.6%), T2a/T2b in 31 (41.4%) and ≥ T2c in 18 (24%) patients. Biopsy GS (ranging from

Table 1. Clinical and pathological characteristics of patients undergoing radical prostatectomy

Baseline characteristics (N=75)	*N (%)*
Median age (years) at diagnosis, N (range)	61.3 (56-76)
Family history of PCa	31 (41.3)
Preoperative PSA ng/mL	
< 4	23 (30.7)
4-10	42 (56)
>10	10 (13.3)
Median prostate volume (mL; range)	42.9 (17-106)
Clinical stage	
T1	26 (34.6)
T2a/T2b	31 (41.4)
≥T2c	18 (24)
Type of surgery	
Open	43 (57.4)
Laparoscopic	32 (42.7)
Pathological Gleason score, N (%)	
≤6	39 (52)
7	30 (40)
≥8	6 (8)
Extraprostatic extension	57 (76)
Positive surgical margins	24 (32)
Positive lymph nodes	13 (17.3)
Seminal vesicle invasion	5 (6.7)
Biochemical recurrence	27 (36)
Median follow-up (months, range)	44 (12-84)
Metastatic disease	7 (9.3)
Overall mortality	2 (2.6)

PCa: prostate cancer, PSA: prostate-specific antigen

Table 2. Preoperative prediction of cancer extension in neurovascular bundle in patients with perineural invasion on needle biopsy

	Extraprostatic extension of tumor in NVB (N=57) N (%)	*No extraprostatic extension of tumor in NVB (N=18) N (%)*	*p value*
Preoperative PSA ng/mL			NS
<10	47 (82.5)	14 (77.8)	
≥10	10 (17.5)	4 (22.2)	
Biopsy GS			NS
≤6	33 (57.9)	14 (77.8)	
>6	24 (42.1)	4 (22.2)	
PSA and biopsy GS			< 0.002
PSA < 10 and GS ≤ 6	32 (56.1)	11 (61.1)	
PSA ≥ 10 and GS ≤ 6	1 (1.8)	3 (16.7)	
PSA < 10 and GS > 6	15 (26.3)	3 (16.7)	
PSA ≥ 10 and GS > 6	9 (15.8)	1 (5.5)	

NVB: neurovascular bundle, NS: not significant, PSA: prostate-specific antigen, GS: Gleason score

5 to 9) was: low (GS ≤ 6) in 47 (62.7%), moderate (GS =7) in 22 (29.3%), and high (GS ≥ 8) in 6 (8%) patients. At RP, 18 patients (24%) had organ-confined disease, whereas EPE in neurovascular bundle and SVI were present in 57 (76%) and 5 (6.7%) patients, respectively. PSM were shown in 24 (32%) and PLN in 13 (17.3%) of our cases.

At a median follow-up of 44 months (range 12-84), 27 (36%) patients had BR, 7 (9.3%) developed metastatic disease, and 2 (2.6%) died of PCa. GS (>6) on needle biopsy and the preoperative PSA level (≥10) were helpful in predicting which patients were likely to have tumor in the neurovascular bundle (Table 2) (p<0.002). Patients with presence of tumor in the neurovascular bundle had more aggressive disease, with 38.6% (22/57) of them having PSM compared with 11.1% (2/18) of cases without EPE of tumor in the neurovascular bundle. However, PLN and SVI occurred less frequently in patients who had tumor in the neurovascular bundle (15.8% [9/57] compared with 44.5% [8/18] of patients without tumor EPE (p<0.001).

Furthermore, an analysis was performed between patients who underwent (unilateral or bilateral) nerve-sparing (N=44) and patients who did not undergo bilateral nerve-sparing surgery (N=31). There was no difference in the percentage of PSM between the two groups [31.9% (14/44) vs 32.2% (10/31) respectively, p>0.05]. BR and metastatic disease occurred less frequently in cases who had undergone a nerve-sparing surgery compared with those without bilateral nerve-sparing surgery: BR [22.7% (10/44) vs 54.9% (17/31) respectively, p<0.001]; metastatic disease [6.9% (3/44) vs 12.9% (4/31) respectively, p<0.001].

Discussion

PNI is a route of metastasis for many different types of tumors (particularly bladder, pancreatic, biliary and colorectal tumors) and a distinct pathological entity highly prevalent in PCa [2]. In the literature PNI has been observed in 31-74% of RP specimens [2,8], similar to the 32% rate in our data. The spread of tumor cells along nerves and vessels is an important mechanism of PCa progression. Some studies demonstrated that perineural invasion by PCa was associated with a reduced apoptotic index and increased tumor volume [9,10]. Although PNI is an important mechanism for progression of PCa through the capsule, the prognostic significance of PNI remains controversial [5,6,11-13]. De la Taille et al. [14] reviewed 319 patients undergoing RP and stated that PNI is not predictive of clinical stage, PSM, or seminal vesicle involvement. However, numerous authors have observed a correlation between the presence of PNI in the prostate biopsy and pathological features at RP. Lee et al. [15] showed that PNI at biopsy was associated with a significantly higher risk of PSM and pathological T3 disease. Sebo et al. [16] followed 454 patients who underwent RP and observed that not only was biopsy PNI significantly associated with disease progression, but patients with PNI were twice as likely to progress compared with those without PNI, although D'Amico et al. [17] performed resection of the ip-

silateral neurovascular bundles in patients when the prostate biopsy showed PNI and reported a significantly lower PSM rate (11 vs 100%). However, in our study there were 14 cases with PSM out of 44 cases with PNI who had both bilateral neurovascular bundles spared vs 10 cases with PSM out of 31 cases who did not undergo bilateral nerve-sparing surgery (31.9 vs 32.2%, p>0.05). Therefore, our study demonstrated that PNI is not statistically associated with PSM. Another controversy concerning PNI is whether it is predictive for BR. Although some studies showed that PNI does not predict BR [18,19], others have shown that PNI in the prostate biopsy specimens represents an independent risk factor of BR in patients treated by RP [20,21]. Our data have shown that BR occurred in 36% of the patients and was statistically associated with PNI (p<0.001). There was one report that PNI was an independent predictor of biochemical failure on multivariate analysis. Ozcan et al. [22] reviewed 191 RP specimens and found that PNI, PSM, and PLN involvement were independent predictors of recurrence in multivariate analysis. In the same study, PSA failure was defined as elevation of PSA >0.4 ng/mL on at least two consecutive measurements. However, in the present study, BR was defined when there were two consecutive detectable serum PSA levels >0.2 ng/mL. In our data, PLN involvement was shown in 17.3% of all patients with PNI who underwent RP. Previous authors have shown that the incidence of PLN in RP specimens was 12–53% [23-25]. In the current study, it was found that PLN involvement was associated with biologically aggressive PCa (p<0.001) and with the pathological stage, GS, PSM, SVI and preoperative serum PSA levels (p<0.002).

Several limitations need to be acknowledged in the present study. First, the pathological diagnosis was performed by different pathologists of our institute, which could potentially introduce significant interobserver variability, although the incidence rates of PLN involvement and PNI did not differ from previous studies. Second, our report had a relatively small number of patients and short follow-up. The median follow-up time of 3.6 years is rather insufficient, so that further studies with a longer follow-up are necessary. Additional studies with more detailed data are warranted to evaluate and answer questions about the percentage of diagnostic biopsies involved with PNI and if this should be considered in the selection of patients for additional treatment, and in planning the follow-up regimen of patients after RP for localized PCa. In conclusion, PNI on prostate biopsy is associated with more aggressive pathology findings at RP, such as EPE, SVI and PLN involvement. PNI is also a non-independent risk factor for BR. However, PNI biopsy did not statistically correlate with PSM. Therefore, nerve-sparing surgery is applicable with safety in a large number of patients with clinically localized PCa irrespective of PNI at biopsy, without compromising the oncological outcomes.

Conflict of interests

The authors declare no confict of interests.

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