**Title**
Limited value of perineural invasion in radical prostatectomy specimens as a predictor of biochemical recurrence in Japanese men with clinically localized prostate cancer

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LIMITED VALUE OF PERINEURAL INVASION IN RADICAL PROSTATECTOMY SPECIMENS AS A PREDICTOR OF BIOCHEMICAL RECURRENCE IN JAPANESE MEN WITH CLINICALLY LOCALIZED PROSTATE CANCER

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The objective of this study was to determine whether the presence of perineural invasion (PNI) in radical prostatectomy specimens could be a useful prognostic parameter in Japanese men with prostate cancer. Between January 1995 and September 2003, 202 Japanese men underwent radical retropubic prostatectomy for prostate cancer without any neoadjuvant therapies prior to surgery. We retrospectively analyzed the relationship between PNI in radical prostatectomy specimens and other prognostic factors, and also assessed the significance of PNI in biochemical recurrence after radical prostatectomy. The presence of PNI was significantly related to clinical stage, pathological stage, Gleason score, seminal vesicle invasion, lymph node metastasis and tumor volume, but not pretreatment serum prostate specific antigen value. During the observation period, biochemical recurrence occurred in 20 patients (3 in patients without PNI and 17 in those with PNI), and the biochemical recurrence-free survival rate in patients with PNI was significantly lower than that in patients without PNI. In addition to PNI, pathological stage, seminal vesicle invasion, lymph node metastasis and tumor volume were significantly associated with the biochemical recurrence-free survival rate; however, among these five factors, only seminal vesicle invasion was an independent predictor of biochemical recurrence on multivariate analysis. Despite a significant association between several prognostic parameters, PNI was not an independent predictor of biochemical recurrence; therefore, it may not provide an additive effect to consider the presence of PNI in predicting the prognosis of Japanese men who underwent radical prostatectomy if there are other conventional parameters available.

Key words: Prostate cancer, Radical retropubic prostatectomy, Perineural invasion, Biochemical recurrence

INTRODUCTION

Perineural invasion (PNI) is a well-known feature of prostate cancer.¹ The presence of PNI in prostatic needle biopsy specimens ranges from 17% to 38%, but is more frequently observed in a radical prostatectomy specimen.²⁻⁵ Furthermore, McNeal et al. demonstrated that PNI was localized selectively to the area where the nerve penetrates the prostate capsule,⁶ and thereafter PNI has been regarded as representing one of the major routes of prostate cancer to spread extraprostatically. However, the significance of PNI in systematic biopsy specimens for predicting extraprostatic extension in patients with clinically localized prostate cancer is controversial. Some investigators reported that the presence of PNI in biopsy specimens could be used as an independent predictor of extraprostatic extension,¹⁰,¹¹ while others failed to confirm these findings.¹²⁻¹⁴ Hence, the assessment of PNI in prostate needle biopsy has not been recommended by the College of American Pathologists.¹⁵

To our knowledge, the significance of PNI in radical prostatectomy specimens has been analyzed in only a few studies, and the conclusions of these studies were controversial. For example, Ozcan found PNI in radical prostatectomy specimens to be an independent predictor of biochemical recurrence on multivariate analysis; however, Maru et al. were able to show the prognostic significance of PNI in radical prostatectomy specimen by univariate analysis, but not by multivariate analysis. In the present study, we, therefore, retrospectively investigated the association between PNI in a radical prostatectomy specimen and other prognostic factors to determine whether PNI could be a useful predictor of biochemical recurrence in Japanese men who underwent radical prostatectomy for clinically organ-confined disease.
**PATIENTS AND METHODS**

Between January 1995 and September 2003, 202 patients underwent radical retropubic prostatectomy and bilateral pelvic lymphadenectomy in our institution after histopathological diagnosis of prostate cancer by systematic transrectal ultrasound (TRUS)-guided needle biopsy. These 202 patients did not receive any neoadjuvant therapies prior to surgery. TRUS examinations were performed using a Bruel and Kajer 1846 console with a multiplane transducer (model 8551; Bruel & Kajer, Naerum, Denmark). Transrectal biopsies of the prostate were obtained with a spring-loaded biopsy gun (Biopry, CR Bard, Covington, GA) and an 18-gauge True-cut biopsy needle under TRUS guidance as described previously (7).

In this series, all pathological examinations were performed by a single pathologist. The resected prostatectomy specimens were fixed and whole-mount step sections were cut transversely at 5 mm intervals from the apex of the prostate to the tips of the seminal vesicles. Each section was examined for cancer location, capsular penetration, and seminal vesicle invasion. In addition, the presence of PNI, which was defined as carcinoma within the perineural space adjacent to a nerve, was also examined. Both the clinical and pathological stages were determined according to the UICC (TNM) tumor stage classification (15). Total tumor volume was determined by planimetry using a digitizer tablet as described previously (16). All areas of tumor, including the index tumor and all satellite tumors, were used to determine the total tumor volume in each specimen.

We usually followed the patients by periodic measurement of serum prostate-specific antigen (PSA) values using an ultrasensitive assay system (Roche Diagnostics, Mannheim, Germany), and the measurement interval was determined in consideration of the potential risk of recurrence in each patient. Biochemical recurrence was defined as PSA persistently greater than 0.4 ng/ml.

In this series, adjuvant therapies were not performed, even in patients with pathological risk factors for recurrence, such as extracapsular penetration, seminal vesicle invasion and lymph node metastasis, and post-biochemical recurrence treatment included hormonal therapy alone or hormonal therapy plus pelvic radiotherapy, which initiated immediately after diagnosis of biochemical recurrence. All survival data were calculated by the Kaplan-Meier method, and the difference was determined by a log rank test. The prognostic significance of some factors was assessed by multivariate Cox proportional hazards regression model. Differences between the two groups were compared using Fisher's exact test, chi-square test or unpaired t test. Differences with p values <0.05 were considered significant, and all statistical calculations were done using the Statview 4.5 software (Abacus Concepts, Inc., Berkeley, CA).

**RESULTS**

The characteristics of the 202 patients included in the present study are summarized in Table 1. PNI was detected in 131 radical prostatectomy specimens (64.9%). We then analyzed the association of PNI in radical prostatectomy specimens with various clinicopathological factors. As shown in Table 2, the presence of PNI was significantly related to clinical stage, pathological stage, Gleason score, seminal vesicle invasion, lymph node metastasis and tumor volume, while there was no significant association between pretreatment serum PSA value and the presence of PNI in radical prostatectomy specimens.

Postoperative serum PSA values in all patients became less than 0.4 ng/ml; however, during the observation period of this study, biochemical recurrence occurred in 20 patients, and the distribution of these 20 patients was as follows: 3 in patients without PNI and 17 in those with PNI. As presented in Fig.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Median age at prostatectomy (year, range)</td>
</tr>
<tr>
<td>Median observation period (month, range)</td>
</tr>
<tr>
<td>Pretreatment median PSA (ng/ml, range)</td>
</tr>
<tr>
<td>Clinical T stage (%)</td>
</tr>
<tr>
<td>T1a</td>
</tr>
<tr>
<td>T1b</td>
</tr>
<tr>
<td>T1c</td>
</tr>
<tr>
<td>T2a</td>
</tr>
<tr>
<td>T2b</td>
</tr>
<tr>
<td>Pathological T stage (%)</td>
</tr>
<tr>
<td>pT2a</td>
</tr>
<tr>
<td>pT2b</td>
</tr>
<tr>
<td>pT3a</td>
</tr>
<tr>
<td>pT3b</td>
</tr>
<tr>
<td>pT4</td>
</tr>
<tr>
<td>Perineural invasion (%)</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Gleason score (%)</td>
</tr>
<tr>
<td>2-6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8-10</td>
</tr>
<tr>
<td>Seminal vesicle invasion (%)</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Lymph node metastasis (%)</td>
</tr>
<tr>
<td>pN0</td>
</tr>
<tr>
<td>pN1</td>
</tr>
<tr>
<td>Median tumor volume (cc, range)</td>
</tr>
</tbody>
</table>
Table 2. Clinicopathological findings according to perineural invasion

<table>
<thead>
<tr>
<th>Variables</th>
<th>Perineural invasion</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (n=71)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive (n=131)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment PSA (ng/ml)</td>
<td>0-9.9</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>10 or greater</td>
<td></td>
</tr>
<tr>
<td>Clinical T stage</td>
<td>T1</td>
<td>0.00045</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td></td>
</tr>
<tr>
<td>Pathological T stage</td>
<td>pT2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>pT3 or pT4</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td>2-6</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>7-10</td>
<td></td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>Negative</td>
<td>0.0018</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis (%)</td>
<td>pN0</td>
<td>0.0094</td>
</tr>
<tr>
<td></td>
<td>pN1</td>
<td></td>
</tr>
<tr>
<td>Tumor volume (cc)</td>
<td>0-0.99</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>1 or greater</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Comparison of biochemical recurrence-free survival of patients with clinically localized prostate cancer according to the presence of PNI in radical prostatectomy specimens by the Kaplan-Meier method. The biochemical recurrence-free survival rate in patients with PNI was significantly lower than that in those without PNI (p=0.047 by the log rank test).

Table 3. Association of clinicopathological factors with biochemical recurrence

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
<th>5-year biochemical recurrence-free survival (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment PSA (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9.9</td>
<td>95</td>
<td>90.3</td>
<td>0.23</td>
</tr>
<tr>
<td>10 or greater</td>
<td>107</td>
<td>85.6</td>
<td></td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>78</td>
<td>92.2</td>
<td>0.33</td>
</tr>
<tr>
<td>T2</td>
<td>124</td>
<td>85.4</td>
<td></td>
</tr>
<tr>
<td>Pathological T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>109</td>
<td>92.9</td>
<td>0.026</td>
</tr>
<tr>
<td>pT3 or pT4</td>
<td>93</td>
<td>82.2</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>71</td>
<td>94.3</td>
<td>0.047</td>
</tr>
<tr>
<td>Positive</td>
<td>131</td>
<td>84.4</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-6</td>
<td>98</td>
<td>91.4</td>
<td>0.13</td>
</tr>
<tr>
<td>7-10</td>
<td>104</td>
<td>82.8</td>
<td></td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>157</td>
<td>93.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive</td>
<td>45</td>
<td>70.1</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>181</td>
<td>90.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>pN1</td>
<td>21</td>
<td>66.0</td>
<td></td>
</tr>
<tr>
<td>Tumor volume (cc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-0.99</td>
<td>103</td>
<td>92.8</td>
<td>0.031</td>
</tr>
<tr>
<td>1 or greater</td>
<td>99</td>
<td>82.5</td>
<td></td>
</tr>
</tbody>
</table>

discussion

In an early study on PNI it was assumed to...
represent perineural lymphatic invasion\(^ {15}\), but more recent studies have demonstrated that there are no lymphatics within the perineurium and that tumor spread within the perineural space reflects extension of cancer along tissue planes of least resistance\(^ {16}\). In fact, Villers et al. found that extraprostatic extension was detected selectively in the area where nerves penetrate the capsule of the prostate\(^ {1}\). Furthermore, an immunohistochemical study by Yang et al. showed a significant association between PNI of prostate cancer cells and reduced apoptotic index, suggesting that neural components may favor the growth of prostate cancer cells by inhibiting apoptotic cell death and thereby help facilitate the spread of cancer cells along nerves\(^ {17}\). Collectively, these findings suggest that the presence of PNI in radical prostatectomy specimens is a characteristic phenomenon of advanced disease; however, to our knowledge, the prognostic significance of PNI remains controversial\(^ {8,9,12}\). Hence, we retrospectively analyzed the relation of PNI in 202 radical prostatectomy specimens to other prognostic factors in order to clarify whether PNI could be a useful indicator for biochemical recurrence in Japanese men who underwent radical prostatectomy for clinically localized prostate cancer.

In this series, PNI was found in 64.9% of the examined cases, which is a relatively lower incidence of PNI than that previously reported in Western countries\(^ {8,9,12}\). We then demonstrated a significant association between PNI and several other prognostic factors, including clinical stage, pathological stage, Gleason score, seminal vesicle invasion, lymph node metastasis and tumor volume. Moreover, biochemical recurrence-free survival in patients with PNI was significantly lower than that in those without PNI; however, multivariate analysis using Cox proportional hazards regression model showed that PNI was not an independent predictor of biochemical recurrence. These findings were consistent with the policy of the Cancer Committee of the College of American Pathologists that the presence of PNI in radical prostatectomy specimens is not an important prognostic predictor in patients with prostate cancer\(^ {11}\). Considering these findings, despite the controversy on the prognostic significance of PNI in the literature\(^ {8,9,12}\), it may not always be necessary to determine whether PNI is present in radical prostatectomy specimens to predict prognosis of patients with clinically localized prostate cancer, when conventional prognostic factors, such as seminal vesicle invasion, lymph node metastasis and tumor volume, are available.

It is of interest to address the mechanism involved in the close association between PNI and prostate cancer progression. Several investigators demonstrated that nerve growth factor (NGF) may participate in contributing to the malignant progression of prostate cancer\(^ {18,19}\). For example, immunohistochemical analysis of human prostate cancer by DeSchryver-Kecskemeti K et al. indicated that the area of PNI shows fairly uniform reactivity for NGF\(^ {18}\). Furthermore, Wheeler et al. demonstrated upregulation of neural cell adhesion molecule (N-CAM) in nerves with PNI compared with those without PNI\(^ {20}\). These findings suggest that the neural components may facilitate migration of prostate cancer cells toward nerves and promote the process of PNI, presumably through a paracrine mechanism.

Here, we must address the limitations of this study. Initially, we would like to emphasize that the present study was retrospective and included samples from patients with a comparatively short observation period. Then, we have to consider the definition of biochemical recurrence used in this study not to be strict. Furthermore, in the present study, the presence of PNI was examined by haematoyxlin-eosin staining; however, Zhou et al. reported that significantly more nerves were found in prostate needle biopsy specimens by the immunohistochemical technique using the S-100 staining than by routine haematoyxlin-eosin staining\(^ {21}\). We must also pay attention to the outcome of a recent study by Maru et al. demonstrating that despite the absence of independent significance of the presence of PNI, the maximal diameter of PNI in radical prostatectomy specimens could be an independent predictor of biochemical recurrence on multivariate analysis\(^ {9}\). Considering these findings, it would be necessary to perform a prospective study with a larger number of patients analyzing the quantitative features of PNI by immunohistochemical technique to draw a definitive conclusion concerning the prognostic significance of PNI in radical prostatectomy specimens. In addition, such an attempt may enable us to clarify in more detail the significance of PNI according to other prognostic parameters.

In conclusion, despite the significant relation to several prognostic indicators, PNI could not be an independent predictor for biochemical recurrence; therefore, considering the presence of PNI in radical prostatectomy specimens may not provide additional information for predicting the prognosis of Japanese men with clinically organ-confined prostate cancer, if there are other conventional prognostic parameters available.

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(Received on September 15, 2004
Accepted on November 15, 2004)
根治的前立腺全摘標本における神経線維周囲浸潤の
生化学的再発予知因子としての意義

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江藤 弘1, 原 熙2

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臨床的局限性前立腺癌に対して術前内分泌療法を施
行せずに根治的前立腺全摘除術を施行した202症例を
対象に、全摘標本における神経線維周囲浸潤の臨床病
理学的意義を検討した。神経線維周囲浸潤は131例
(64.9%) に陽性であった。また、神経線維周囲浸潤
の存在は、臨床病期、病理学的病期、Gleason スコ
ア、精巣浸潤、リンパ節転移および腫瘍体積と有意に
相関したが、術前 PSA 値との相関は認めなかった。

経過観察期間（中央値34ヶ月）中、20例に生化学的再
発を認めたが神経線維周囲浸潤はこの内17例に陽性で
あった。神経線維周囲浸潤陽性131例および陰性71例
の5年生化学的非再発率は、それぞれ84.4%および
94.3%であり統計学的有意差を認めた。神経線維周囲
浸潤の他、病理学的病期、精巣浸潤、リンパ節転移お
よび腫瘍体積が生化学的非再発率と有意な相関を示し
た。しかし、多変量解析の結果、これら5因子の内、
精巣浸潤のみが生化学的再発の独立した予知因子で
あった。以上より、根治的前立腺全摘標本における神
経線維周囲浸潤の存在は、種々の予後規定因子と有意
な相関を示すが、生化学的再発の独立した予知因子と
は成りえない可能性が示唆された。

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