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Relationship Between Perineural Invasion in Prostate Needle Biopsy Specimens and Pathologic Staging After Radical Prostatectomy

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Abstract

Background: Prostate cancer is the second most common malignancy among men worldwide and the sixth cause of cancer-related death. Some authors have reported a relationship between perineural invasion (PNI), Gleason score, and the invasion of peripheral organs during prostatectomy. However, it is not yet clear whether pathological evidence of PNI is necessary for risk stratification in selecting treatment type.

Objectives: The clinical and pathological stages of prostate cancer are compared in patients under radical prostatectomy and in patients without perineural invasion.

Patients and Methods: This cross-sectional study was conducted using a sample of 109 patients who attended a tertiary health care center from 2008 to 2013. The selection criteria were PNI in prostate biopsy with Gleason scores less than six, seven, and eight to ten. The participants were enrolled in a census manner, and they underwent clinical staging. After radical prostatectomy, the rates of pathological staging were compared. The under-staging and over-staging rates among those with and without perineural invasion in biopsy samples were compared.

Results: The concordance between Gleason scores according to biopsy and pathology was 36.7% (40 subjects). The concordance rate was 46.4% and 33.3% among those with and without PNI, respectively. The concordance rates were significantly varied in different subclasses of Gleason scores in patients without PNI ($P = 0.003$); the highest concordance rate was a Gleason score of 7 (63.6%) and the lowest was a Gleason score of eight to ten (25%). However, there were no significant differences in patients with PNI ($P > 0.05$).

Conclusions: Although the presence of PNI in prostate biopsy is accompanied by higher surgical stages, PNI is not an appropriate independent factor in risk stratification.

Keywords: Perineural Invasion, Prostate Needle Biopsy, Radical Prostatectomy

1. Background

Prostate cancer is the second most common malignancy among men worldwide and the sixth cause of cancer-related death. Approximately 914,000 new cases and 258,000 deaths due to this cancer were reported in 2008 (1). The incidence rate ranged from 3.9 (in India) to 178.8 (in Black Americans) per 100,000 persons. Higher incidence rates were found in north America, Oceania, northern, and western Europe. The lowest rates were in Asia and northern Africa (2). The main cause of these differences in the incidence rates of prostate cancer among various countries is the utilization of the PSA test, which may help in the diagnosis of latent low-risk cancer (3-5).

The outcomes of patients with localized prostate cancer depend on several variables, including PSA, Gleason score, tumor stage, etc. In patients with good prognostic factors, the probability of treatment failure after surgery or radiotherapy may be as high as 10%. Patients with bad prognostic factors could have worse prognoses although most intensive treatments and the probability of no recurrence within five years may be 40% - 50% (6). The importance of perineural invasion (PNI) for risk stratification in localized prostate cancer is a matter of debate. Although the results of previous studies have been controversial, authors have reported a relationship between PNI, Gleason score, and invasion to peripheral organs during prostatectomy (7, 8).

2. Objectives

It is not yet clear if the pathological evidence of PNI is necessary for risk stratification in selecting the type of treatment. Therefore, this study compared the clinical and pathological staging of prostate cancer between patients under radical prostatectomy and patients without PNI.

3. Patients and Methods

This cross-sectional study was conducted using a sample of 109 patients who attended a tertiary health care center from 2008 to 2013. The selection criteria were PNI in prostate biopsy with Gleason scores less than six, seven, and eight to ten. The participants were enrolled in a census manner, and they underwent clinical staging. Clinical and pathological staging were compared after radical prostatectomy. The under-staging and over-staging rates among those with and without PNI, respectively, were compared in the biopsy samples. The inclusion criteria were hospital admission, radical prostatectomy, preoperative biopsy, and records of biopsy and surgery pathology in medical documents. Patients with incomplete data were excluded. The required data included demographics, pathological results, and surgical results. The data were recorded in a checklist.

The data analysis was performed using SPSS (version 13.0) software (statistical procedures for social sciences; Chicago, Illinois, USA). Chi-square and Mann-Whitney-U tests were conducted, and the results were considered statistically significant at P values less than 0.05.

4. Results

According to the pathology report on the biopsied samples, 28 patients (25.7%) had PNI. The mean age of the patients was 66.2 $\pm$ 7.6 years (ranging from 51 to 85 years). The mean ages of patients with and without PNI were 65.1 $\pm$ 8.7 and 66.5 $\pm$ 7.2 years, respectively (P> 0.05). The mean serum PSA level was 11.4 $\pm$ 6.9 ng/mL (ranging from 1.1 to 36.6). The mean serum PSA levels in patients with and without PNI were 10.7 $\pm$ 6.6 and 11.7 $\pm$ 7.0 ng/mL, respectively (P > 0.05).

The pathology results of the biopsies showed a mean Gleason score of 6.2 $\pm$ 1.4 (ranging from 4 to 10). The mean scores in patients with and without PNI according to these results were 6.5 $\pm$ 1.3 and 6.1 $\pm$ 1.4, respectively (P > 0.05). The surgical pathology results showed a mean Gleason score of 6.7 $\pm$ 1.5 (ranging from 2 to 10). The mean scores in patients with and without PNI according to surgical pathology results were 7.1 $\pm$ 1.4 and 6.6 $\pm$ 1.5, respectively (P > 0.05).

The concordance between Gleason scores according to the biopsy and surgical pathology results was 36.7% (40 subjects). The concordance rates were 46.4% and 33.3% among those with and without PNI, respectively. The concordance rates were significantly varied in different subclasses of Gleason scores in patients without PNI (P = 0.003). The highest concordance rate was a Gleason score of 7 (63.6%) and the lowest rates were Gleason scores of eight to ten (25%). However, there were no significant differences in patients with PNI (P > 0.05).

The clinical stage was T1c and T2a in 93 patients (85.3%), and the remaining patients were in the T2b stage. There was no significant difference in the clinical stages of patients with and without PNI (P > 0.05). The pathological stage was T2 in 77 patients (70.6%). The pathological stage differed significantly between patients with and without PNI; the T1 and T2 stages were present in 21 patients with PNI (75%) but in 76 patients (93.8%) without PNI (P = 0.024). Furthermore, 7 patients with extra-prostate involvement (stages 3 and 4) had PNI (58.3%). Twenty-one patients (21.6%) without extra-prostate involvement had PNI (P = 0.012). The comparison of clinical and pathological staging showed concordance in only 12 patients (11%). Eighteen patients (16.5%) showed over-staging, and 79 patients (72.5%) showed under-staging. There were no differences in over-staging and under-staging in patients with and without PNI (P > 0.05).

5. Discussion

The results of this study demonstrated that PNI in prostate biopsy accompanied higher clinical stages and extra-prostate invasion. These findings support similar results in previous studies. A univariate analysis by Rubin et al. (9) demonstrated that PNI had a significant association with pT3. Egan and Bostwick (10) reported that the presence of PNI in needle biopsy was significantly associated with extra-prostate invasion and seminal vesicle involvement. A univariate analysis by Ukimura et al. (11) also showed that PNI was a good prognostic factor for extra-prostate invasion. However, PNI was not considered a prognostic factor in these previous studies. Although Vargas et al. (12) added PSA to their model, the results showed that PNI was not an independent prognostic factor in extra-prostate invasion.

D'Amico et al. (13) evaluated the utility of PNI in biopsy for the prediction of PSA levels after radical prostatectomy in 750 patients with localized prostate cancer or with cancer recognized by PSA assay. In their study, the presence of PNI was not a prognostic factor after radical procedure in medium-risk and high-risk patients. O'Malley et

al. (14) compared 78 biopsies with PNI and 78 cases without PNI, demonstrating that PNI was not related to long-term tumor-free survival. Freedland et al. (15) evaluated 190 patients under radical prostatectomy. They found that the percentage of malignant tissue in biopsy was the most powerful prognostic factor in chemical recurrence shown by multivariate analysis. Moreover, PNI was not found to be an independent predictor of recurrence.

Bismar et al. (16) univariate and multivariate analyses showed that PNI and the number and percentage of involved nerves were not related to pathological stages. Tsuzuki et al. (17) demonstrated that PSA, Gleason score, DRE, and percentage of tumor involvement were prognostic factors in extra-prostate involvement in neurovascular bundles, but PNI was not a prognostic factor.

Cannon et al. (18) evaluated 452 patients under radical prostatectomy and found that despite the association of PNI in biopsy, it was related only to the higher probability of extra-prostate involvement and that PNI was not a prognostic factor in bilateral nerve-sparing technique or positive surgical burden.

Some studies reported that PNI was an independent factor in the prediction of pathological stage. De la Taille et al. (7) revealed that PNI, PSA, and Gleason score in biopsy were independent predictors of pathological stages of pT3. The authors concluded that PNI was an important preoperative factor. Sebo et al. (19) reported positive core percentage, PSA, PNI, and Gleason score between 7 and 9 as predictors of extra-prostate involvement.

Loeb et al. (20) showed that PNI was significantly associated with worse prognoses and disease progression. Their multivariate analysis showed that PNI was significantly accompanied by extra-prostate involvement and seminal vesicle invasion. Bastacky et al. (21) evaluated 302 patients with needle biopsy and reported that PNI had sensitivity and specificity of 27% and 96%, respectively, in the prediction of extra-prostate involvement. They concluded that PNI assessment in biopsy would help determine extra-prostate involvement and might help in programming for nerve-sparing radical prostatectomy and deciding whether one or all parts of the neurovascular bundle should be removed in the biopsy site. The multivariate analysis was not performed.

Some factors may be controversial. The number of obtained biopsies may affect the PNI diagnosis. In addition, different methods used to prepare the prostate tissue (partial or complete use of prostate) may result in different diagnoses of extra-prostate involvement. Different definitions of PNI in biopsy, extra-prostate involvement, and varied amounts of PSA in the assessment of disease progression after radical prostatectomy are some reasons for the controversial results of studies. In a systematic review from 1990 to 2005, Harnden et al. (22) assessed the association of PNI with the recurrence of prostate cancer. They found that differences in design, performance, and reporting of the results could lead to inconclusive results regarding meta-analysis and risk estimation.

The frequency rate of PNI in needle biopsy was reported to be from 11% to 38% in several studies (9-12, 15, 16, 19, 21). The present study found a frequency rate of 25.7%. The frequency rates were 21.6% and 58.3% in patients without extra-prostate involvement and in patients with extensive disease, respectively. Other studies also reported lower PNI rates in less extensive tumors. Thorson et al. (23) reported a rate of 2% in PNI tumors less than 1 mm in incidental autopsy samples, showing that PNI occurred in the first stages of disease. Byar and Mostofi (24) evaluated 208 prostates removed by the step-section technique for the early detection of prostate cancer and reported a high frequency of PNI (84.1%). They proposed that PNI occurs in the early stages of disease.

The present study has the following limitations. The PNI extension and quantity were not assessed, and only the presence of PNI in biopsy was considered. Moreover, because no follow-up patient data were obtained, the results of this study cannot be compared with therapeutic outcomes. Furthermore, because the only treatment considered in this study was radical prostatectomy, the results cannot be used to compare different therapeutic outcomes.

The presence of PNI in needle biopsy was associated with pathological stages higher than T2 in samples obtained by radical prostatectomy. The results showed no differences in PSA, clinical stage, clinical and pathological Gleason score, or rates of under-staging and over-staging between groups with and without PNI. Based on these findings, PNI is not an appropriate independent factor in risk stratification.

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Footnote

Authors' Contribution: Hassan Niroomand, Mohammadreza Nowroozi, Mohsen Ayati, Hassan Jamshidian carried out the operations. Amir Arbab and Seyed Ali Momeni collected the data, and Alireza Ghadian and Hamidreza Ghorbani contributed to the analysis and the writing of the manuscript.

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