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Perineural invasion, Gleason score and prostate specific antigen; is there any association?

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ABSTRACT

Introduction: Prostatic cancer is one of the most common malignancies among males. Perineural invasion (PNI) is a common finding of prostate cancer associated with more aggressive malignancies.
Objectives: The current study was conducted to assess the association of PNI with serum prostate specific antigen (PSA) and Gleason score.
Patients and Methods: This analytical cross-sectional study conducted on 354 known cases of prostatic cancer (2015 until 2017). Patients' last PSA and Gleason score wit h presence/lack of PNI in their prostate biopsies were recorded. The association of PNI with PSA and Gleason score was assessed.
Results: Serum level of PSA and Gleason core were significantly higher in patients with PNI ($P<0.001$ for both). Gleason score was independently a predictor of PNI (odds ratio [OR]: 3.05, 95% CI:2.32-4.001; $P=0.001$). Serum PSA level of 17 ng/mL had specificity of 90.3% and sensitivity of 42.7% for prediction of PNI.
Conclusion: In this study we found, Gleason score is independently a prognostic factor of PNI among cases undergone prostate biopsy. In addition, serum PSA level of 17 ng/mL was 90.3% specific and 42.7% sensitive for PNI occurrence. However, our findings require further evaluations by larger studies.

Implication for health policy/practice/research/medical education:
In an analytical cross-sectional study conducted on 354 known cases of prostatic cancer, we found, Gleason score is independently a prognostic factor of perineural invasion among cases undergone prostate biopsy.

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Original Article

Introduction

Prostatic cancer is the second common malignancy in males and is the sixth underlying reason of mortality due to malignancies worldwide (1-3).

As prostatic adenocarcinoma can cause various complications including severe pain, urinary signs and symptom, genitourinary dysfunction, infertility and decreased quality of life, thus concise attention to signs and symptoms and early diagnosis of this malignancy is necessary (4).

Prostate cancer is known as an invasive tumor that invades easily to other structures nearby. Perineural invasion (PNI) is one of the prostate cancer features in which neurons lying around cancerous cells would be inflamed due to inflammatory environment around them (5,6). Given this fact, tumoral cells can develop to structures out of prostate by neural pathways and reach pelvic plexus (7).

Prevalence of PNI in prostatic needle biopsies has been estimated to be up to 40% while this rate was found to be even more in biopsies taken after prostatectomy (7). It seems that PNI in biopsy specimens is in association with extra-prostatic invasion. In addition, recent studies have presented that maximum diameter of PNI is associated with prostate cancer prognosis (8).

Prostate specific antigen (PSA) is one of the most common markers checked for prostate cancer. Its level is among usual markers that lead to malignancy diagnosis and even prognosis. In addition, Gleason score acts as the main scoring system for severity of prostate cancer since

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the invasion has been found to be in relation with PSA levels (2,9,10).

Objectives

Previous studies showed the association of PSA with PNI for the prognosis of prostatic cancer. However, some studies have not found this relationship (11-13). We therefore, aimed to evaluate the association of PSA serum level and Gleason score with PNI.

Patients and Methods

Study design

This is an analytical cross-sectional study conducted on 354 known cases of prostatic cancer in Khorshid hospital (Urology Center affiliated to Isfahan University of Medical Sciences) from 2015 to 2017.

Patients with documented presentation of prostate cancer were included and those who were not willing for participation in the study were excluded.

Then patients' last prostatic specific antigen before prostatectomy was checked through patients' records. Based on the pathologic findings and presence/lack of PNI in their prostate biopsies, their Gleason scores were recorded.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consents were obtained from all patients. The study was approved by the ethical committee of Isfahan University of Medical Sciences (ethical code; IR.MUI.REC. 295145). This study was extracted from the M.D thesis of Ali Karami at this university.

Statistical analysis

Gathered data were analyzed using SPSS-22 (IBM-United States). Descriptive data were reported in mean ± SD. For analysis, Pearson's or Spearman's correlation coefficient, independent t-test, exploratory and confirmatory factor analysis were applied. Accordingly, *P* value<0.05 was considered significant.

Results

This study was conducted on 354 patients with positive prostate biopsies representing prostate cancer. Mean age of patients was 68.62±8.81 years. Around 282 patients (79.9%) had presentations of PNI in their biopsies.

Mean age of patients with PNI was 69±8.88 years while mean age of those without PNI was 67.14±8.42 years ($P = 0.06$).

Serum level of PSA in patients with and without PNI was 26.12±33.38 ng/mL and 12.17±12.02 ng/mL, respectively ($P < 0.001$). In addition, Gleason score had a significant difference between two groups with and without PNI (7.70±1.34 versus 5.24±1.50; $P < 0.001$).

Contrary to serum level of PSA, Gleason score was statistically significant factor of PNI. We found, each score increase in Gleason score is accompanied with three times increase in PNI. Table 1 presents the logistic regression analysis.

As shown in Figure 1, cut-off of 17 ng/mL for PSA level has a sensitivity of 42.7% and specificity of 90.3% for incidence of PNI in cases with prostatic cancer. Area under curve (AUC) for this figure is 0.65.

Discussion

Although research regarding association of PNI with prognosis of prostate cancer requires further studies, previous experiences have strongly recommended that the evaluation of PNI after radical prostatectomy have predicted outcomes of this procedure (9,14).

In the current study we have assessed 354 known cases of prostate cancer. Findings of the current study showed no association between patients' age and PNI. This finding was stated in the study of Niroomand et al (2). Other studies conducted by Saadat et al and Antunes et al presented similar results as well (9,15). In fact, it seems that, the PNI in prostatic cancer is mostly in association with the duration of malignancy in comparison to age of

Table 1. Association of PSA level (ng/mL) and Gleason score with incidence of PNI in prostatic cancer (logistic regression analysis)

Variables	OR	95% CI		B	*P* value
		Minimum	Maximum		
PSA	1.005	0.98	1.02	0.15	0.69
Gleason score	3.05	2.32	4.001	65.17	<0.001

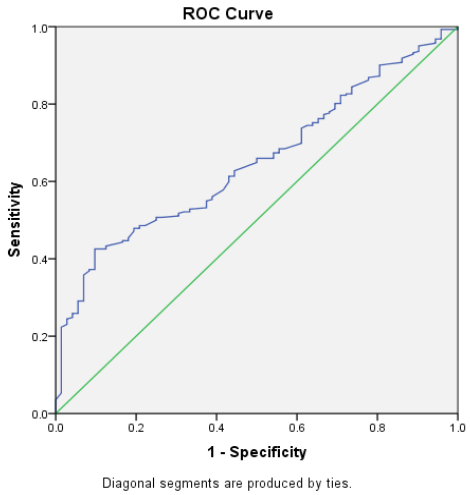

Figure 1. ROC curve of sensitivity and specificity of PSA level among patients with prostate cancer presenting PNI in their radical prostatectomy biopsies.

patients, though duration of this malignancy may have been longer among older patients.

Findings of our study showed that patients with presentation of PNI had statistically significant higher serum levels of PSA and higher Gleason score. This finding was confirmed by Saadat et al (9). In addition, Jeon et al presented that PSA level and Gleason score were significantly higher among patients who had PNI (16). On the other hand, Niroomand et al presented contrary results in their study which was conducted on over 500 patients with prostate cancer (2). This difference may be attributed to different studied samples among the studies.

Association of PSA with PNI shows the importance of such assessments prior to radical prostatectomy, since PSA is a marker checked after prostatectomy to assess recurrence of prostate cancer. Accordingly, Loeb et al (17) and also Quinn et al (18) presented that PNI assessment was in association with prostatic cancer recurrence following prostatectomy, however Freedland et al (19) and Ravery et al (20) stated no association between serum PSA and PNI.

The other assessment of this study showed that Gleason score is a predictive factor of PNI. In this condition, each unit increase in Gleason score was associated with three-times more probability of PNI. Beard et al, presented similar results, since they found, Gleason score of 7-10 was a better predictor of PNI than a Gleason score of 8-10 (21). Likewise, Lee et al detected a significant association between Gleason score and PNI too (22). Moreover, Kraus et al detected that PNI is an independent predictor of higher Gleason score (23). Furthermore, Stone et al presented that PNI is independently a predictor of lymph node metastasis which can affect Gleason score (24). The other study showed that the pathological progression of prostate cancer is in association with PNI independently (25). Since PNI is a predicting factor of prostatic cancer invasion, it is possible that a higher Gleason score is in relation to higher grades of prostate cancer, while this association would be bidirectional.

The last variable assessed in the current study was a cut-off for serum PSA level accompanied by PNI. Based on findings of our study, serum PSA cut-off levels of 17ng/mL had specificity of 90.3% and sensitivity of 42.7% for presence of PNI. In the study by Quinn et al, the serum cut-off level of PSA for presence of PNI is over 10 ng/mL. That is considerably less than what was applied in our study (18). This cut-off of 10 ng/mL was presented by Dell'Atti et al too (27). The notable difference between our findings and previous studies, may be attributed to racial difference or due to proportion of studied population, hence, further studies on this subject are recommended.

Conclusion

Based on findings of the current study, Gleason score is independently a prognostic factor of PNI among cases undergone prostate biopsy. In addition, serum PSA level of 17ng/mL was 90.3% specific and 42.7% sensitive for PNI occurrence. As this level was notably higher than previous studies, further evaluations are recommended.

Authors' contribution

MY, FT and AK designed the study, observed accuracy and validity of the study. AK collected the data and follow the study. MY, EYK and FT supervised the project. AK wrote the paper. All authors edited and revised the final manuscript and accepted its publication.

Conflicts of interest

The authors report no conflict of interest.

Ethical considerations

Ethical issues (including the fabrication of the data, plagiarism, and double publication) have been completely considered by the authors.

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