

Exploring the association of WHO grade groups and perineural invasion in prostatic carcinoma-A study from Karachi Pakistan

Yousra Zahid¹, Armaghana Qamar Khan², Sabeen Afshan³, Sara Babar¹, Shahzadi Noor¹, Atif Ali Hashmi⁴

¹Liaquat National Hospital and Medical College, Karachi Pakistan

²Pakistan Institute of Medical Sciences, Islamabad Pakistan

³Sheikh Khalifa Bin Zayed Hospital Quetta/ Liaquat National Hospital and Medical College, Karachi Pakistan

⁴Fellow at Memorial Sloan Kettering Center, New York, USA/ Liaquat National Hospital and Medical College, Karachi Pakistan

ABSTRACT

Objective: To evaluate the prevalence of perineural invasion with the WHO grade group in patients with prostatic carcinoma.

Material and Methods: This Cross Sectional Study was conducted at Department of Histopathology, Liaquat National Hospital Karachi, Pakistan from 1st January 2019 to 31st December 2020, This study included 221 male patients diagnosed with prostate carcinoma. A specimen labeled as prostatic tissue was received, and after labeling and data entry, a gross examination of the tissue was done. Specimens diagnosed as prostatic carcinoma were assessed for grade groups. All data was systemically recorded in a pre-structured proforma.

Results: 61 years was the average age of the patients. Perineural invasion among patients with prostatic carcinoma was observed in 36.65% (81/221). According to WHO grade group in patients with prostatic carcinoma, positive perineural invasion patients, there were 49.4% had grade group 1, 32.1% had grade group 2, 11.1% had grade group 3, 4.9% had grade group 4, 2.5% had grade group 5 while in negative perineural invasion patients, there were 35.7% had Grade group 1, 41.4% had grade group 2, 14.3% had Grade group 3, 5.7% had Grade group 4 and 2.9% had Grade group 5. A comparison of perineural invasion was not statistically significant for the WHO grade group in patients with prostatic carcinoma.

Conclusion: The analysis demonstrated no substantial variations in PSA levels, clinical stage, Gleason scores, or under- and over-staging between the PNI-positive and PNI-negative groups.

Keywords: Prostate cancer, Perineural invasion, Grade-groups

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INTRODUCTION

Cancer of the prostate is the second most frequent malignancy in men [1,2]. It predominantly occurs in older individuals, with a steadily increasing prevalence and mortality rate in the Asian population [1]. In cases of localized prostate cancer, the 5-year survival rate in developed countries is nearly 100%, whereas it drops to 2.8% in cases with metastasis [3-4]. The male prostate gland is below the bladder,

and the urethra extends through it before continuing as the penile urethra. Prostate cancer, benign prostatic hyperplasia (BPH), and prostatitis are the most common prostate-related disorders [5].

With increasing age, the frequency of both benign and malignant prostate disorders tends to rise [6]. The lowest incidence rates have been observed in Asia and Northern Africa [7-8]. A key factor contributing to the variation in prostate cancer incidence across different regions is the extensive utilization of the PSA test, which aids in detecting dormant, low-risk cancers [9-10]. Historically, clinical staging and histological grading have been critical in determining the prognosis of prostate cancer [11]. Dr. Donald Gleason developed a grading framework categorizing prostate cancer by

Correspondence: Dr. Yousra Zahid, Senior Registrar, Department of Pathology, Liaquat National Hospital and Medical College, Karachi Pakistan

Email: yzahid07@yahoo.com

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specific histological characteristics. Given that most tumors exhibit two predominant patterns, the Gleason score was established by summing the two most common grades within the cancer, resulting in a score from 2 to 10 [12].

The study revealed a steady increase in cancer-specific mortality corresponding to higher Gleason scores [12-13]. Limitations of the Gleason System can lead patients to mistakenly believe that their cancer is intermediate on the scale, exacerbating the anxiety associated with their diagnosis due to the perception that their cancer is severe. To address these issues, a new 5-Grade Group system has been introduced. This system has demonstrated greater accuracy in predicting disease progression compared to the traditional Gleason risk stratification groups. Additionally, the Grade Groups exhibited comparable prognostic curves in biopsies of men undergoing radiation treatment, with or without hormonal therapy, as well as those who underwent radical prostatectomy [14].

The terms perineural, circumferential, or intraneural invasion refer to the occurrence of prostate cancer near, surrounding, or infiltrating a nerve. Additional descriptors, including extensive (multifocal) perineural invasion and increased nerve diameter, may improve the prognostic value of this factor [11-15]. Perineural invasion (PNI) is typically associated with higher Gleason scores and raised prostate-specific antigen levels. Even though perineural invasion (PNI) in needle biopsy samples is not a standalone prognostic factor when assessing the Gleason score, serum PSA levels, and cancer extent, most studies propose this condition is associated with extra prostatic extension [11,16]. Even though findings from previous research have varied, some investigators have established a connection between Perineural invasion (PNI), Gleason scores, and the extent of peripheral organ invasion during prostatectomy [17-18]. While other studies have found no significant association between PNI and prostate cancer outcomes [7,19-20].

One study examined perineural invasion, which was identified in 29.14% of cases. Among

patients with positive perineural invasion who were still alive, 7.51% were classified as Grade Group 1, 40.84% as Grade Group 2, 27.23% as Grade Group 3, 6.57% as Grade Group 4, and 17.8% as Grade Group 5. Conversely, in patients without perineural invasion who were still alive, the distribution was 45.5% in grade group 1, 29.20% in Grade group 2, 16.50% in Grade group 3, 4.45% in Grade group 4, and 4.29% in Grade group 5. Among patients with positive perineural invasion who succumbed to the disease, 15.95% were in Grade group 1, 24.46% in Grade group 2, 27.65% in Grade group 3, 5.31% in Grade group 4, and 26.59% in Grade group 5. In contrast, patients without perineural invasion who died from the disease showed no cases in Grade group 1, with 21.33% in Grade group 2, 34.66% in Grade group 3, 13.33% in Grade group 4, and 30.66% in Grade group 5 [21].

Several studies have been conducted in the past for the diagnosis of prostatic carcinoma after biopsies through Gleason scoring assessment but no work to date has been done for the WHO grading group in our local population. However, studies with WHO grading groups should continue to be performed so that they help guide clinicians in treating patients on time. Accurate diagnosis and grading of prostate cancer are essential for evaluating prognosis and selecting appropriate treatment plans. This study examines the association between grade groups and perineural invasion in patients with prostatic carcinoma.

MATERIAL AND METHODS

The study was conducted as a cross-sectional analysis in the Department of Histopathology at Liaquat National Hospital, Karachi, over two years, from January 1, 2019, to December 31, 2020 after approval vide reference number CPSP/REU/HSP-2017-192-655 dated 11th August 2018. The sample size was determined using the WHO sample size calculator, considering a perineural invasion frequency of 21.14% in prostatic carcinoma patients, with a 6% margin of error at a 95% confidence interval. Based on these parameters, the required sample size was 221. A

nonprobability consecutive sampling technique was employed for patient selection.

The inclusion criteria encompassed male patients aged between 50 and 80 years who were diagnosed with prostate carcinoma based on the operational definition. Exclusion criteria included patients diagnosed with urinary tract infections, hypertension, or those who had received hormone therapy before the diagnostic biopsy. Additionally, patients with benign prostatic hyperplasia, prostatitis, or PSA levels exceeding 100 ng/ml at diagnosis or within six months prior were excluded. The presence of metastatic disease also served as an exclusion factor.

The study was undertaken after receiving an endorsement from the institutional research and ethics committee along with the College of Physicians and Surgeons Pakistan. Patients who met the inclusion criteria were selected for the study. Informed consent was taken for patients' participation and the use of their data in research. A concise medical history of the disease was collected. The principal investigator took clinical histories from all the patients. Specimen coded as prostatic tissue was received, and after labeling and data entry, a gross examination of the tissue was done. The weight of the entire specimen, aggregate dimensions, and tissue consistency were recorded. Specimen weighing <12 grams was submitted entirely. After tissue processing, H&E slides were made and examined under the microscope. Specimens that are diagnosed as prostatic carcinoma were assessed for grade groups and patients were labeled for grade groups as per operational definition. The number of positive chips for the tumor should be counted and perineural invasion should be looking microscopically and taken positively when one-third of the nerve is encircled by a tumor. All data were recorded by the principal investigator using a pre-designed proforma. Bias and confounding factors were managed by adhering strictly to the inclusion criteria.

Patient information was collected and analyzed with SPSS 21. Frequencies and percentages were calculated for qualitative variables such as diabetes mellitus (DM),

perineural invasion, and grade groups. The mean $\pm$ SD (standard deviation) was computed for quantifiable variables, including age, duration of symptoms, and PSA levels. A comparison of the frequency of perineural invasion and the WHO grade group was performed. Stratification was conducted based on age, DM, and duration to assess the impact of such modifiers on outcomes and post stratification chi-square/fisher exact test was applied. A p-value of ≤ 0.05 was acknowledged as suggestive of statistical significance.

RESULTS

221 male patients diagnosed with prostate carcinoma were included for this study purpose. Most patients were between 50 and 70 years. The patients' average age and PSA level were 61 years and 6.81ng respectively (Table-I). Out of 221, 115(52.04%) had diabetes as shown in table-III.

The frequency of perineural invasion among patients with prostatic carcinoma was observed in 36.65% (81/221) as presented in Table 2. In positive perineural invasion patients, there were 49.4% had grade group 1, 32.1% had grade group 2, 11.1% had grade group 3, 4.9% had grade group 4 and 2.5% had grade group 5 while in negative perineural invasion patients, there were 35.7% had grade group 1, 41.4% had grade group 2, 14.3% had grade group 3, 5.7% had grade group 4 and 2.9% had grade group 5. Comparison of frequency of perineural Invasion was not statistically significant with the WHO grade group in patients with prostatic carcinoma as shown in Table-II.

It was also found that the rate of positive perineural invasion was not statistically significant with age groups($p=0.139$) and duration of disease($p=0.065$), as shown in Table-III, while there was significant association of perineural invasion with WHO grade($p=0.013$) among diabetes patients whereas there was no significant association of perineural invasion with WHO grade($p=0.950$) among non-diabetic patients as reported in Table -III

Table-I: Descriptive statistics of the patients with prostatic carcinoma n=221.

Variables	Mean	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
Age (Years)	61.12	7.09	60.18	62.06
Duration of Symptom (months)	2.41	1.23	2.25	2.58
PSA level	6.81	1.43	6.615	6.996

Table-II: Frequency of perineural invasion among patients with prostatic carcinoma by age groups & duration of disease.

Age Groups (Years)	Perineural Invasion		Total	P-Value
	Yes	No		
≤ 60	42(36.2%)	74(63.8%)	116	0.139
61-70	36(41.4%)	51(58.6%)	87	
71-80	3(16.7%)	15(83.3%)	18	
Duration of disease				
1-3	60(33.7%)	118(66.3%)	178	0.065
>3	21(48.8%)	22(51.2%)	43	
Total PNI	81(36.65%)	140(63.35%)	18	

n= 221

Table-III: comparing the frequency of perineural invasion with who grade group in patients with prostatic carcinoma for diabetic and non-diabetic patients

WHO GRADE group in diabetic patients = 115	Perineural Invasion		P-Value
	Yes n=52	No n=63	
Grade group 1	25(48.1%)	15(23.8%)	0.013
Grade group 2	17(32.7%)	35(55.6%)	
Grade group 3	7(13.5%)	13(20.6%)	
Grade group 4	2(3.8%)	0(0%)	
Grade group 5	1(1.9%)	0(0%)	

Chi-Square= 12.59

WHO GRADE group in non-diabetic patients = 106	Perineural Invasion		P-Value
	Yes n=29	No n=77	
Grade group 1	15(51.7%)	35(45.5%)	0.950
Grade group 2	9(31%)	23(29.9%)	
Grade group 3	2(6.9%)	7(9.1%)	
Grade group 4	2(6.9%)	8(10.4%)	
Grade group 5	1(3.4%)	4(5.2%)	

DISCUSSION

As the second most commonly diagnosed cancer and the sixth leading cause of cancer deaths in men, prostate cancer constitutes 14% of all new cancer cases and 6% of overall cancer fatalities in this population (GLOBOCAN 2008) [22]. In China, the incidence of prostate cancer is lower than that in Western nations; however, the widespread implementation of serum prostate-specific antigen (PSA) testing and transrectal ultrasound (TRUS)-guided needle biopsy has caused an annual rise in the diagnosis of localized prostate cancer [22,23].

Patients with localized disease typically go through Radical prostatectomy (RP) as their standard treatment [24]. Traditionally, this procedure was performed via open retropubic

RP. Over the past decade, minimally invasive techniques, including laparoscopic and robot-assisted laparoscopic prostatectomies (LRP and RALP, respectively), have gained popularity globally. In China, laparoscopic radical prostatectomy (LRP) has emerged as the preferred method for treating localized prostate cancer. However, in Western countries, approximately 20% of patients undergoing RP exhibit positive surgical margins (PSM) in the final pathological evaluation [25]. which is linked to a higher likelihood of local recurrence and distant metastasis, potentially impacting survival and prognosis [26,27].

Perineural invasion (PNI) describes the spread of prostate cancer cells along nerve fibers, as noted in the pathology of the prostate [28]. PNI is identified in 20% of biopsy

specimens from patients with prostate adenocarcinoma [29]. PNI often correlates with high Gleason scores (GS) and elevated PSA levels [30]. Furthermore, several studies have indicated a relationship between PNI, extraprostatic extension, and surgical margin positivity [29-30]. Nevertheless, PNI has not been considered a factor in studies that predict local invasion. The current study's mean age and PSA levels were 61.12 ± 7.09 years and 6.81 ± 1.43 , respectively. In the study by Niroomand *et al* [7] 66 years was the average age of the patients. For those with PNI, the average age was 65 years, while for those without PNI, it was 66.5 years ($P > 0.05$). The average serum PSA level was 11.4 ng/mL, range was 1.1 to 36.6 ng/mL. Patients with PNI had an average PSA level of 10.7 ng/mL, while those without PNI had a mean of 11.7 ng/mL ($P > 0.05$).

In our study, the frequency of perineural invasion among patients with prostatic carcinoma was 36.65%. One investigation reported a perineural invasion prevalence of 29.14%. The occurrence of perineural invasion in needle biopsy specimens has been stated to range between 11% and 38% across different studies [28,29,30,31]. The current study observed a frequency rate of 25.7% and showed perineural invasion in this study. Around 21.6% did not have extraprostatic extension and 58.3% had advanced disease. Other studies have reported similar findings, indicating lower perineural invasion occurrence in less aggressive tumors. In a survey by Thorson *et al*. [32], a 2% incidence of perineural invasion was reported in tumors less than 1 mm identified in incidental autopsies, hinting that PNI might arise in the disease's initial stages. Byar and Mostofi [33] after examining 208 prostatectomy specimens reported a substantial perineural invasion rate of 84.1% implying that PNI emerges early in the progression of the disease. Patients with perineural invasion were distributed as 49.4% in Grade Group 1, 32.1% in Grade Group 2, 11.1% in Grade Group 3, 4.9% in Grade Group 4, and 2.5% in Grade Group 5. Meanwhile, those without perineural invasion distributed 35.7% in Grade Group 1, 41.4% in

Grade Group 2, 14.3% in Grade Group 3, 5.7% in Grade Group 4, and 2.9% in Grade Group 5. The frequency of PNI did not demonstrate a statistically significant correlation with WHO grade groups in cases of prostatic carcinoma.

The Grade group distribution of living patients with positive perineural invasion was as follows: 7.51% in Grade Group 1, 40.84% in Grade group 2, 27.23% in Grade group 3, 6.57% in Grade group 4, and 17.8% in Grade group 5. In contrast, for patients without perineural invasion who survived, 45.5% were in Grade group 1, 29.20% in Grade Group 2, 16.50% in Grade group 3, 4.45% in Grade group 4, and 4.29% in Grade group 5. The distribution of patients with positive PNI who died from the disease was 15.95% in Grade group 1, 24.46% in Grade group 2, 27.65% in Grade group 3, 5.31% in Grade group 4, and 26.59% in Grade group 5. Among patients with positive PNI who passed away due to the disease, there were no individuals in Grade group 1, while the distribution was 21.33% in Grade group 2, 34.66% in Grade group 3, 13.33% in Grade group 4, and 30.66% in Grade group 5 [21].

Saeter *et al*. [34] illustrated that the prognostic implications of perineural invasion are connected to its relationship with high tumor grade and the presence of stromal reaction. Evaluating PNI is also time-intensive, and in many busy pathology practices, it might be deemed an inefficient allocation of resources to assess each case for perineural invasion when sufficient risk stratification has already occurred. From a practical standpoint, recognizing PNI could be most clinically valuable not just for its prognostic implications, but also in setting criteria for active surveillance, where pathology significantly influences eligibility [35].

Using univariate and multivariate analyses, Bismar *et al*. [36] determined that perineural invasion (PNI) and the count and proportion of nerves involved did not exhibit any significant association with pathological stages. Tsuzuki *et al*. [37] showed that levels of PSA, gleason score, digital rectal examination, and size of tumor were important prognostic features for extraprostatic involvement of neurovascular

bundles, while PNI itself was not a predictive factor.

In a study by Cannon *et al.* [37] involving 452 patients undergoing radical prostatectomy, findings revealed that while perineural invasion (PNI) identified in biopsies was associated with an increased risk of extraprostatic extension, it did not serve as a prognostic indicator in the bilateral nerve-sparing procedure or instances with significant surgical burden.

Certain analyses have indicated that PNI is an autonomous factor in forecasting pathological stages. De la Taille *et al.* [17] demonstrated that PNI, PSA levels, and Gleason scores from biopsy were independent predictors of pT3 stages, emphasizing PNI's role as a significant preoperative factor. Sebo *et al.* [38] highlighted that features such as the percentage of positive cores in biopsy, PSA levels, presence of perineural invasion (PNI), and Gleason scores between 7 and 9 served as significant indicators of extraprostatic extension.

CONCLUSION

In this study, the occurrence rate of perineural invasion (PNI) among patients diagnosed with prostate carcinoma was observed to be 36.65%. In needle biopsy specimens, perineural invasion (PNI) showed a strong correlation with pathological stages above T2 in radical prostatectomy samples. The analysis indicated that PSA levels, clinical and pathological Gleason scores, clinical stage, and rates of both understaging and overstaging remained comparable regardless of PNI presence. These results indicate that perineural invasion (PNI) may not serve as a reliable standalone factor for effective risk assessment.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Yousra Zahid: Main conception of study design and concept, questionnaire design, final approval, accountable for all aspects of the work

Armaghana Qamar Khan: data collection, data analysis, data interpretation, manuscript writing, final approval, accountable for all aspects of the work

Sabeen Afshan: Literature search, data interpretation, final approval, accountable for all aspects of the work

Sara Babar: Data analysis, data collection, final approval, accountable for all aspects of the work

Shahzadi Noor: Critical revisions for intellectual content, data collection, final approval, accountable for all aspects of the work

Atif Ali Hashmi: data interpretation, manuscript writing, final approval, accountable for all aspects of the work

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