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International Society of Urologic Pathology (ISUP) Grade Grouping in Prostatic Adenocarcinoma and Its Prognostic Implications

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Research note

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Abstract

Objectives: International Society of Urologic Pathology (ISUP) grade grouping of prostatic adenocarcinoma was introduced to simplify gleason score-related categories of prostatic adenocarcinoma. Prognostic reproducibility of ISUP/WHO grade grouping was not well studied in our population, therefore in this study, our aim was to evaluate the association of ISUP/WHO grade groups with various pathological prognostic parameters.

Results: This retrospective cross-sectional study was done in Liaquat National Hospital, Department of Histopathology from February 2011 to January 2018, over a period of seven years. A total of 172 patients were included in this study. The mean age of patients was 66.97±10.51 years. In this study we noted, 27 (15.7%) cases of grade group 1, 22 (12.8%) of grade group 2, 30 (17.4%) of grade group 3, 40 (23.3%) of grade group 4 and 53 (30.8%) of grade group 5. A significant association of tumor grade with perineural invasion (p=0.005) and tumor volume (tumor quantification was noted. In this study, we found a high frequency of grade group 4 and 5 in prostatic adenocarcinoma. Moreover, a significant association of grade groups was noted with perineural invasion and tumor volume, signifying prognostic significance of grade grouping in prostatic adenocarcinoma.

Introduction

Prostate cancer leads to an estimated 366,000 deaths annually, worldwide [1]. In this era of oncologic practice, there is a continued search for clinical and pathologic prognostic parameters. Apart from clinical and radiologically determined staging, preoperative prostate-specific antigen (PSA) levels are a well known prognostic parameter [2]. Histologic parameters that predict prognosis include gleason score, tumor volume (tumor quantification), extra-prostatic soft tissue/fat involvement, seminal vesicle invasion, perineural and lympho-vascular invasion [3]. Besides these well-defined histologic parameters, biomarkers such as, ERG, PTEN, FSN and androgen receptor (AR), also possess some prognostic value, but their routine use is not considered justified in all patients, up till now [4–7]. Among above-mentioned pathologic prognostic parameters, gleason score is given much importance in pathological reporting. Gleason score is a sum of major and minor architectural patterns in prostatic biopsy specimen, and the total score ranges from two to ten. Due to this wide range, International Society of Urologic Pathology (ISUP) and World Health Organization (WHO) classification of tumors of male genital tract introduced the concept of grading in prostatic biopsies. ISUP/WHO grades range from one to five, and have good reproducibility in pathologic reporting [8]. The need for this grouping was to stratify patients into prognostic groups in order to evaluate the treatment response in different prognostic groups. Prognostic reproducibility of ISUP/WHO grade grouping was not well studied in our population, therefore in this study, our aim was to evaluate the association of ISUP/WHO grade groups with various pathological prognostic parameters, such as tumor volume and perineural invasion.

Materials And Methods

This retrospective cross-sectional study was conducted in Liaquat National Hospital's Histopathology Department from February 2011 to January 2018, over a period of seven years. Specimens were received in Histopathology laboratory, Liaquat National Hospital and included prostatic chips (transurethral resection of the prostate) and radical prostatectomies. After gross examination, representative sections were submitted according to standard guidelines. For prostatic chips specimens weighing less than 12 grams, whole specimens were submitted. For those weighing more than 12 grams, one cassette per additional 5 grams over 12 grams was submitted. For radical prostatectomies, after submission of urethral and bladder neck margins, seminal vesicles and vas deferens, systemic sampling was employed. If tumor was not identified on initial sections then complete/ total sampling was done. Clinical parameters were recorded by evaluating records of histopathology archives. Immunohistochemical studies including PSA, CK7 and CK7 were done where there was a need to confirm primary prostatic origin or to rule out metastatic carcinoma. Immnuohistochemical stains p63 and 34 beta E12 were performed in cases of low grade prostatic carcinoma to differentiate from benign mimickers of malignancy. Slides of all specimens were retrieved, and additional sections were performed from tissue blocks, where necessary. ISUP/WHO grade grouping was done by senior histopathologists as shown in Figures S1–S3, and compared with other prognostic pathologic parameters.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) sofware, version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics were computed for quantitative and qualitative variables. Chi square and Fisher exact tests were used to check the association. P-values ≤ 0.05 were considered significant.

Results

A total of 172 patients were included in this study. The mean age of patients was 66.97 ± 10.51 years ranging from 33 years to 88 years. Among 172 patients, most cases were from the age group more than 60 years (72.7%). We found 62 (36%) patients with perineural invasion, 3 (1.7%) with lymphovascular invasion, 12 (7%) with extraprostatic extension and 8 (4.7%) with the seminal vesicle invasion. Total 97 (56.4%) cases had tumor volume (tumor quantification) more than 50% of the examined tissue (Table 1).

In the current study, we found 27 (15.7%) cases of grade group 1, 22 (12.8%) of grade group 2, 30 (17.4%) of grade group 3, 40 (23.3%) of grade group 4 and 53 (30.8%) of grade group 5 (Fig. 1).

We found that high grade tumors (grade 3–5) have higher frequency of perineural invasion compared to low grade tumors (grades 1–2) with significant association (p = 0.005). Similarly, high grade tumors were also found to have higher tumor volumes (> 50%) compared to low grade tumors with a significant p-value. Conversely, extra prostatic extension was noted more frequently in low grade tumors with a significant association (p = 0.0001). On the other hand, no significant association was found with age (p = 0.071), lymphovascular invasion (p = 0.582) and seminal vesicle invasion (p = 0.624) as presented in table 2.

Discussion

In this study, we evaluated grade groups in prostatic acinar adenocarcinoma and found a high frequency of grade group 5 (30.8%) in our population. Moreover, there was a significant association of the grade group with perineural invasion and tumor volume, which signifies the prognostic value of grade grouping in prostatic carcinoma.

WHO/ISUP grade grouping of prostatic adenocarcinoma is based on gleason score, which is assessed in prostatic cancers based on low power architectural patterns. Various studies have confirmed the prognostic implication of grade grouping in prostatic cancers [9].

Grade group 1 is gleason score less than or equal to six (3 + 3 or below). Gleason patterns 1 and 2 are rarely encountered. Gleason pattern 3 is defined as a discrete well-formed glandular proliferation. A large prospective cohort study with long term follow-ups revealed cancer-related deaths or metastasis in less than 1% of grade group 1 prostatic cancers [10]. We had 15.7% cases of grade 1 prostatic carcinoma, only 7.4% of which showed perineural invasion, and extraprostatic extension was noted in only 3.7% cases.

WHO/ISUP segregates gleason score 7 into grade groups 2 and 3 on the basis of predominant pattern. Gleason score 3 + 4 = 7 is known as grade group 2, while a score of 4 + 3 is categorized as grade group 3. Gleason pattern 4 includes raggedly infiltrating or cribriform glands. Studies have shown that the cribriform pattern is associated with recurrence and poor prognostic features, like extra-prostatic extension [11]. For similar reasons, gleason score 4 + 4 = 8 was identified as grade group 4. In our study 33.3% cases were of grade group 4, 37.7% of which revealed perineural invasion that is a marker of poor prognosis in prostatic adenocarcinoma.

Gleason score 5 is defined by sheets, cords or isolated tumor cells without any obvious gland formation. The presence of comedo type necrosis is also included in gleason pattern 5. Studies have shown that gleason pattern 5 is frequently under-reported and actual frequency is high in resection specimens [12]. We also noted a high percentage of grade group 5 in our study, concordant with these findings.

Conclusions

In this study, we found a high frequency of grade group 4 and 5 in prostatic adenocarcinoma. Additionally, a significant association of grade groups was noted with perineural invasion and tumor volume.

Limitations

We acknowledge a few limitations to this study, as long term follow up was not available to determine survival status and disease recurrence in different grade groups. Second, sample size was small especially cases with extraprostatic extension. Although we noted that low grade tumors had a higher

frequency of extraprostatic extension, but the number of cases with extraprostatic extension were small therefore definite conclusion regarding association with extraprostatic extension needs large scale studies.

Abbreviations

International Society of Urologic Pathology =ISUP

Prostate-specific antigen =PSA

Declarations

Ethics approval and consent to participate

Ethics committee of Jinnah Hospital, Lahore, Punjab, Pakistan approved the study. Written informed consent was obtained from the patients for participation.

Consent to publish

Not Applicable.

Availability of data and materials

The datasets used during this study are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

AAH and RH: main author of manuscript, have made substantial contributions to conception and

design of study. SM, RH, JA, MI, SKH, AK and MME have been involved in requisition, analysis of the data and provided final approval and revision of the manuscript. All authors read and

approved the final manuscript.

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Tables

Table-1: Descriptive statistics of population characteristics under study (n = 172)

Characteristics	N (%)
Age (years)	
Mean±SD	66.97±10.51
Groups	
≤45 years	4(2.3)
46-60 years	43(25)
>60 years	125(72.7)
Gleason score	
6	27(15.7)
7	52(30.2)
8	40(23.3)
9	53(30.8)
Perineural invasion	
Present	62(36)
Absent	110(64)
Lymphovascular invasion	
Present	3(1.7)
Absent	169(98.3)
Extra prostatic extension	
Present	12(7)
Absent	160(93)
Seminal vesicle invasion	
Present	8(4.7)
Absent	164(95.3)
Tumor quantification	
<10%	38(22.1)
10–50%	37(21.5)
>50%	97(56.4)

SD: Standard deviation

Table-2: Association of Tumor grade with clinicopathologic characteristics

Characteristic	Tumor Grade					p-value
	Grade-1 (n = 27)	Grade-2 (n = 22)	Grade-3 (n = 30)	Grade-4 (n = 40)	Grade-5 (n = 53)	
Age group						
≤45 years	0(0)	0(0)	0(0)	0(0)	4(7.5)	0.071
46-60 years	7(25.9)	7(31.8)	12(40)	10(25)	7(13.2)	
>60 years	20(74.1)	15(68.2)	18(60)	30(75)	42(79.2)	
Perineural invasion						
Present	2(7.4)	6(27.3)	13(43.3)	15(37.5)	26(49.1)	0.005*
Absent	25(92.6)	16(72.7)	17(56.7)	25(62.5)	27(50.9)	
Lymphovascular invasion						
Present	1(3.7)	0(0)	0(0)	0(0)	2(3.8)	0.582
Absent	26(96.3)	22(100)	30(100)	40(100)	51(96.2)	
Extra prostatic extension						
Present	1(3.7)	5(22.7)	6(20)	0(0)	0(0)	0.0001*
Absent	26(96.3)	17(77.3)	24(80)	40(100)	53(100)	
Seminal vesicle invasion						
Present	1(3.7)	2(9.1)	0(0)	2(5)	3(5.7)	0.624
Absent	26(96.3)	20(90.9)	30(100)	38(95)	50(94.3)	
Tumor quantification						
<10%	11(40.7)	9(40.9)	8(26.7)	8(20)	2(3.8)	0.0001*
10–50%	12(44.4)	6(27.3)	7(23.3)	1(2.5)	11(20.8)	
>50%	4(14.8)	7(31.8)	15(50)	31(77.5)	40(75.5)	
Chi square was applied						
Fisher exact test was applied.						
*P ≤ 0.05 was considered as significant.						

Figures

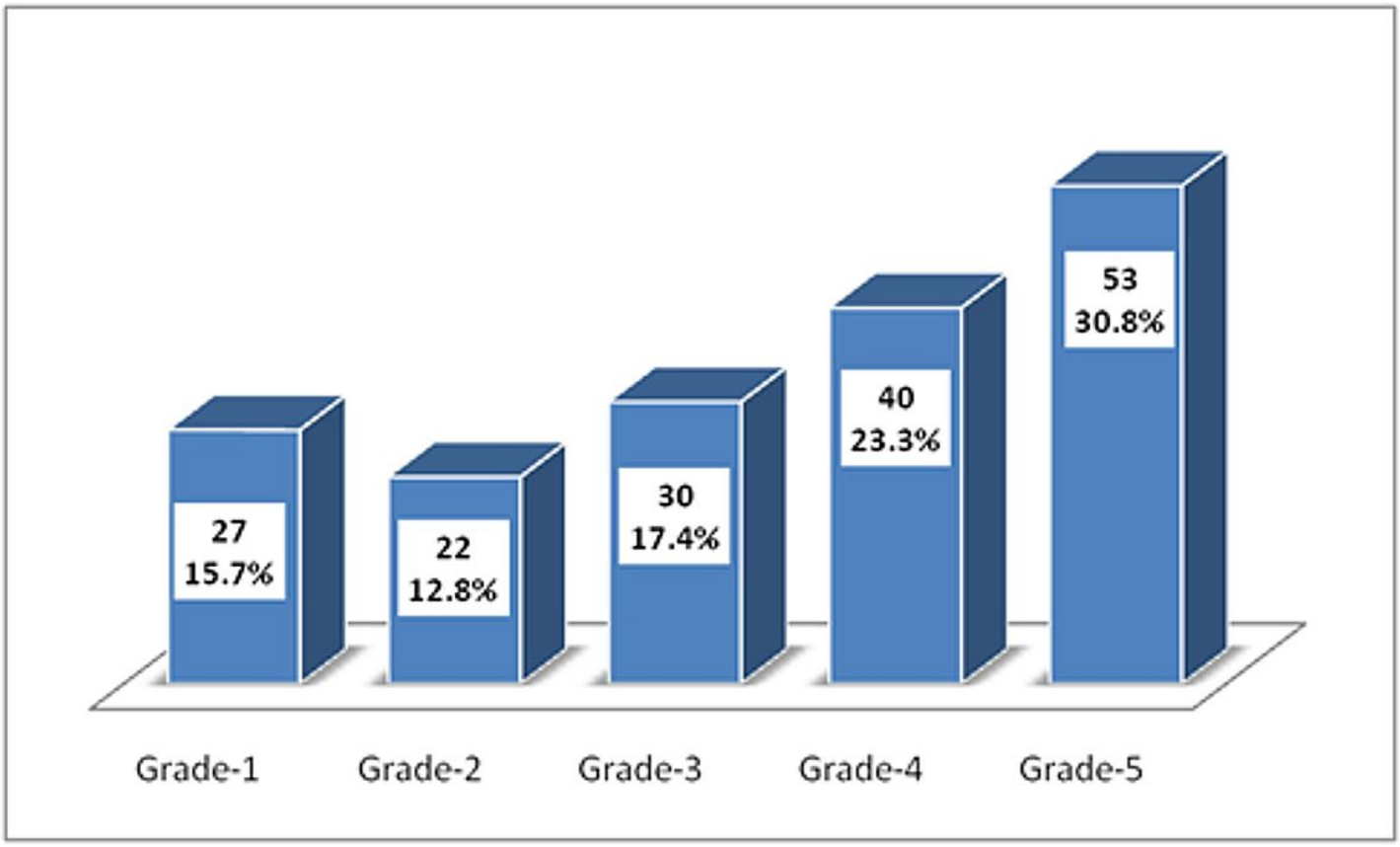

Figure 1

Distribution of the tumor grade among patients with prostatic adenocarcinoma

Supplementary Files

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- figureS1.png
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