

Prostatic Carcinoma: Frequency, Pattern and Evaluation of Gleason Grading in Prostate Biopsies

Uzma Bukhari¹, Anita George¹, Yusra Shafique¹, Asma Bukhari²

Dow University of Health Sciences¹, Karachi, Riphah International University², Islamabad.

Abstract

Background: Prostate carcinoma is the second most common cancer and fifth preeminent cause of cancer associated deaths globally in men. In spite of significant changes in the clinical and histologic diagnosis of prostate carcinoma, the Gleason grading system still remains one of the most powerful prognostic predictors in prostate cancer. The correct diagnosis and grading of prostate carcinoma is critical for a patient's prognostic and treatment options.

Objective: To determine the frequency and pattern of Prostate cancers in histopathology specimens diagnosed at Dow Diagnostic Research and Reference Laboratory and also to correlate the association of Gleason grade group with histopathological prognostic indicators in Dow University Hospital.

Study type, settings and duration: A retrospective study was conducted in Histopathology section of Dow Diagnostic Research and Reference Laboratory, Karachi from year 2016 to 2018.

Methodology: Retrospective analysis of all consecutive cases of prostatic adenocarcinoma diagnosed at Histopathology section of Dow Diagnostic Research and Reference Laboratory (DDRRL) for three years between January 1st, 2016 and December 31st, 2018 was done. Statistical analysis was done by using Chi square and Fishers exact test on SPSS version 21 to see the association between Gleason grade group and histopathological prognostic indicators.

Results: A total of 1065 prostate biopsies were analyzed for three years from 2016-2018. Out of them 128 (13%) cases were of prostate adenocarcinoma and 937 (87%) cases were of benign prostatic hyperplasia. The mean age of the patients was 68.9 years and majority (34%) of the cases were in 8th decade of their age. Majority of the tumors (40%) were reported as Gleason grade group 5 on biopsy. In 11% cases carcinoma was an incidental finding as there was no suspicion of carcinoma. There was significant association between Gleason grade group and histopathological prognostic indicators that is perineural invasion and lympho vascular invasion.

Conclusion: Majority of the tumors were in grade group 5 which has increased mortality rate and it indicates that prostate adenocarcinoma is an aggressive disease.

Key words: Prostate adenocarcinoma, gleason score, benign prostate hyperplasia.

Introduction

Prostate carcinoma is the 2nd most common malignancy and fifth preeminent cause of malignancy associated mortality worldwide in men.¹ According to Globocon 2018 statistics the reported incidence of prostate carcinoma in 2018 was 1.3 million and total number of reported deaths due to caners were 3.5 million (3.8%) in 2018.¹

Most cases are reported were over 50 years of age. There are many diagnostic tools that help in pre-diagnosis of cancer before prostatectomies such as Prostate specific antigen (PSA) levels, Digital Rectal Examination (DRE), transrectal ultrasonography along with biopsy that is considered as gold standard.²

Gleason grading system is the up to date classification system for reporting prostate carcinoma modifications. The Gleason grading

Corresponding Author:

Yusra Shafique
Dow University of Health Sciences
Karachi.
Email: memon.yusra@hotmail.com

Received: 29 October 2019, Accepted: 17 Aug 2020,
Published: 04 September 2020

Authors Contribution

UB, AG & YS conceptualized the project and did the drafting, revision & writing of manuscript. AG did the data collection. YS & AB performed the statistical analysis. Literature search was also done by UB, AG, YS & AB.

system helps in predicting biologic behavior along with evaluating prognosis of prostate carcinoma and helps in determining patients treatment along with easier counseling of patients. The greater the Gleason score, more aggressive the tumor and worst the prognosis.²

The World Health Organization (WHO) approved five well defined grade groups for reporting of prostate adenocarcinomas.^{3,4} (Table-1). Patients with Gleason grade of 2-4 does not develop aggressive disease whereas patients with Gleason grade of 8-10 have high mortality rates.⁵

Table 1: Modified Gleason grading system for prostate cancer.³

<i>Gleason Pattern</i>	<i>Gleason Score</i>	<i>Gleason Grade Group</i>
<i>Gleason pattern 1</i> (discrete, distinct, individual well formed glands)	Gleason score ≤ 6	Grade group 1
<i>Gleason Pattern 2</i> (Predominantly well formed glands with lesser component of poorly formed fused glands)	Gleason score 3+4=7	Grade group 2
<i>Gleason Pattern 3</i> Predominantly fused, poorly formed, cribriform glands with lesser component of well formed glands)	Gleason score 4+3=7	Grade group 3
<i>Gleason Pattern 4</i> (only cribriform, fused or poorly formed glands, gomeruloid pattern or predominantly lacking glands)	Gleason score = 8	Grade group 4
<i>Gleason Pattern 5</i> (cords, solid nests, sheets, single cells, comedo necrosis or may lack gland formation)	Gleason score = 9,10	Grade group 5

The association of lympho vascular invasion (LVI) having unfavourable consequences has been known for a long time. Lymphovascular invasion has a linear association with positive surgical margins, Gleason score, pathological stage, lymph node metastasis, extra prostatic extension and seminal vesicle invasion.⁶

Perineural invasion (PNI) also has positive relation with extra-prostatic invasion. Current researches have shown that in large number of cases perineural invasion is associated with prognosis of prostate carcinoma.⁷ According to studies conducted by Loeb et al and Quinn et al recurrence of prostate cancer following prostatectomy was associated with positive perineural invasion.^{8,9}

The purpose of our study was to evaluate the frequency and pattern of prostate cancer diagnosed at Histopathology section of Dow

diagnostic research and reference laboratory (DDRRL) and to evaluate Gleason scoring along with association of Gleason grade group to the prognostic histopathological parameters including lymphovascular and perineural invasion.

Methodology

A retrospective study was conducted in Histopathology section of Dow Diagnostic Research and Reference Laboratory (DDRRL). All cases of prostate adenocarcinoma from year 2016-2018 were included in the study. Specimen included in this retrospective study were Trans Urethral Resection (TUR) and core biopsies of prostate. The cases included were inpatients of Dow university hospital (DUH) and all specimens of TUR and prostatic biopsies received in various DDRRL collection points. Inclusion criteria was cases of prostate biopsies including TURP, enucleation and prostatectomies whereas cases of metastatic carcinoma of prostate were excluded.

Available clinical data including patient's age, Prostate Specific Antigen (PSA), surgical findings, clinical history and clinical diagnosis was recorded predesigned questionnaire. All Hematoxylin and Eosin (H&E) stained slides along with immunohistochemical stained slides of all cases were retrieved from pathology archives and reviewed. Prognostic pathologic parameters including Gleason score, lymphovascular invasion and perineural invasion were noted. Grading of prostate carcinoma was done according to Modified Gleason grading system of prostate carcinoma. 34BE12 was performed to confirm the diagnosis and CD34 was performed to confirm the presence of lymphovascular invasion. SPSS version 21 was used to perform statistical analyses. To evaluate the association of Gleason grade group to prognostic parameters that is perineural invasion and lymphovascular invasion chi square and Fishers exact test was used.

Results

Out of 1065 prostate biopsies received during three years of study period from 2016-2018 128 (13%) cases were diagnosed as prostate adenocarcinoma and 937 (87%) were diagnosed as benign prostatic hyperplasia. Amongst cases of prostate adenocarcinoma, age of patients ranged from 50-99 years. Mean age was of 68.9 years and median age of 70 years. The maximum number of patients 43 (34%) were in 8th decade (70-79 years) of their age i.e. 32cases (25%) were in 6th decade, while 35 (27%) cases were in 7th decade of age

while 15 (12%) were in their 9th decade and 3 cases (2%) were also above 90 years of age (Table-2).

Table 2: Age distribution of patients.

Age (years)	No. of cases (n=128)	Percentage
51-60	32	25
61-70	35	27
71-80	43	34
81-90	15	12
>90	3	2

As per new International society of urological pathology (ISUP) 2014 grading system of prostate adenocarcinoma, most number of cases i.e. fifty one (40%) were having Gleason grade of 9 and 10 were placed in Gleason Grade group 5 on biopsy. Twenty nine cases (23%) of Gleason grade (3+3=6) were kept in Gleason Grade group 1 on biopsy. Thirteen (10%) cases having Gleason grade of 3+4=7 was kept in Gleason Grade group 2 whereas seven (5%) cases of Gleason grade 4+3=7 were kept in Gleason Grade group 3. All twenty two (17%) cases of Gleason grade 8 were kept in Gleason Grade group 4. Six (5%) cases were not categorized in grade groups (Table-3).

Table 3: Distribution of prostate cancer among cases of prostatic carcinoma diagnosed at Dow Diagnostic Research and Reference Laboratory.

Grade group	Total number of cases (n=128)	Percentage
Grade group 1 (GS=3+3=6)	29	23
Grade group 2 (GS=3+4=7)	13	10
Grade group 3 (GS=4+3=7)	7	5
Grade group 4 (GS=8)	22	17
Grade group 5 (GS=9,10)	51	40
Uncategorized cases	6	5

Perineural invasion was positive in 35% (45/128) of cases and lymphovascular invasion was noted in 12% (15/128) of cases.

Table 4: Association of Gleason grade group and perineural invasion among cases of prostatic carcinoma diagnosed at Dow Diagnostic Research and Reference Laboratory.

Grade group	Negative	Positive	Total	p-value
Grade group 1	27	2	29	0.01*
Grade group 2	5	7	12	
Grade group 3	2	5	7	
Grade group 4	15	7	22	
Grade group 5	28	24	52	
Total	77	45	122	

In 14 (11%) cases clinical impression was benign and carcinoma was an incidental finding.

Table 5: Association of Gleason grade group and Lymphovascular invasion among cases of prostatic carcinoma diagnosed at Dow Diagnostic Research and Reference Laboratory.

Grade group	Negative	Positive	Total	p-value
Grade group 1	29	0	29	0.002*
Grade group 2	12	0	12	
Grade group 3	7	0	7	
Grade group 4	21	1	22	
Grade group 5	39	13	52	
Total	108	14	122	

In order to evaluate the association between Gleason grade group and morphological prognostic indicators, chi square and Fishers exact test was performed which showed significant association/linear correlation between Gleason grade groups and perineural invasion (p-value =0.01) and lymphovascular invasion (p-value =0.002) (Table-4&5).

Discussion

Prostate carcinoma is more common in Western countries including USA than Asian countries as reported by studies conducted in western countries.^{5,10} According to year 2016 report of Karachi cancer registry age standardized rates (ASR) for prostate cancer are low in Karachi and it ranks at sixth among malignant tumors among male.^{11,12} The main reason could be that in western countries the screening of older aged males by using Prostate Specific Antigen is routine while in Pakistan there is no screening program at place for diagnosis of prostatic cancers.

In our study mean age of the patient was 68.9 years and most cases were reported in 8th decade of their age. This finding is in line with studies conducted in West.^{5,13}

In this study 14 cases (35%) were of adenocarcinoma, in which the tumor was an incidental finding which could be either due scattered areas of tumor, location of the tumor, infiltration of tumor without induration or palpable nodule.

It is suggested in a local study that in cases of prostate adenocarcinoma digital rectal examination should be followed by transrectal ultrasound and serum PSA levels.⁵

In our study 40% (51) of the cases had Gleason grade group 5 on biopsy. This is in contrast to a study conducted by Loeb et al¹³ in which only 1% of man had Gleason grade group 5 on biopsy whereas Gleason grade group 1 was the highest occurring grade group (67%). This is in contrast to our study in which 23 % cases had Gleason grade

group 1 on biopsy.¹³ Similarly in another study conducted by Pierorazo et al 66.3% cases had Gleason grade group 1 and 1.6% cases had Gleason grade group 5 on biopsy.¹⁴

In an Asian study conducted in Japan 55.1% cases were assigned Grade group 1 and 10.4% were assigned to Grade group 5.¹⁵

Our findings are in accordance with Manan B Shah who also reported 50% cases of adenocarcinoma as Gleason grade group 5.¹⁶

This shows that majority of cases of prostate adenocarcinomas behave aggressively in our setup as it shows correlation with mortality rates as similar findings are reported in another local study.⁵ This could be due to the reason that patients in our setup present with advanced disease and no PSA levels screening is done in older age groups.

Lymphovascular invasion LVI is an independently indicative of adverse prognosis in the prostate carcinoma.⁶ Occult metastasis should be suspected when lymphovascular invasion is identified, and diligent follow-up examinations for the evidence of metastasis should be done.¹⁷

In our study 14 cases are positive for lymphovascular invasion with high Gleason group grade. These findings are in accordance with multiple international studies which reported a high tumor grade with positive lymphovascular invasion.^{6,18,19}

Perineural invasion is positive in 45 cases in our study. Out of which, 24 cases showed grade group 5. These results are in agreement with Jeon et al and Lee et al who found a significant association between PNI level and Gleason score amongst patients. It is important that all prostate biopsies should be routinely evaluated for the presence of lymphovascular and perineural invasion.^{20,21}

Early diagnosis and grading of prostate cancer is crucial for a patient's prognosis and therapeutic options. Histopathology report should include the comment on lymphovascular and perineural invasion. There is a need for more vigilant prostate evaluation in vulnerable age group and more prospective and multicenter studies are necessary to confirm and validate these findings.

Conflict of interest: None declared.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68(6): 394-424.

2. Sajjan GID, Agarwal V, Agarwal S. New perspectives in modified Gleason's grading for prostatic cancer and its comparison with original Gleason's. *Int J Res Med Sci* 2018; 7(2): 400-4.
3. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2016; 40(2): 244-52.
4. Holger MPAH, Ulbright TM, Reuter VE. WHO classification of Tumors of urinary system and male genital organs. 4th Edition ed. France: International Agency For Research On Cancer (IARC); 2016.
5. Ahmed Z, Muzaffar S. Prostatic carcinoma with emphasis on gleason's grading: an institution based experience. *J Pak Med Assoc* 2002; 52(2): 54-6.
6. Baydar DE, Baseskioglu B, Ozen H, Geyik PO. Prognostic significance of lymphovascular invasion in clinically localized prostate cancer after radical prostatectomy. *Scientific World J* 2008; 8: 303-12.
7. Ahmad AS, Parameshwaran V, Beltran L, Fisher G, North BV, Greenberg D, et al. Should reporting of peri-neural invasion and extra prostatic extension be mandatory in prostate cancer biopsies? correlation with outcome in biopsy cases treated conservatively. *Oncotarget* 2018; 9(29): 20555-62.
8. Loeb S, Epstein JI, Humphreys EB, Walsh PC. Does perineural invasion on prostate biopsy predict adverse prostatectomy outcomes? *BJU Int.* 2010; 105(11): 1510-3.
9. Quinn DI, Henshall SM, Brenner PC, Kooner R, Golovsky D, O'Neill GF, et al. Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy: importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. *Cancer: Interdisciplinary. Int J Am Cancer Soc* 2003; 97(8): 1884-93.
10. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol* 2012; 61(6): 1079-92.
11. Qureshi MA, Mirza T, Khan S, Sikandar B, Zahid M, Aftab M, et al. Cancer patterns in Karachi (all districts), Pakistan: First results (2010–2015) from a Pathology based cancer registry of the largest government-run diagnostic and reference center of Karachi. *Cancer Epidemiol* 2016; 44: 114-22.
12. Bhurgri Y, Bhurgri A, Hassan SH, Zaidi S, Rahim A, Sankaranarayanan R, et al. Cancer incidence in Karachi, Pakistan: first results from Karachi cancer registry. *Int J Cancer* 2000; 85(3): 325-9.
13. Loeb S, Folkvaljon Y, Robinson D, Lissbrant IF, Egevad L, Stattin P. Evaluation of the 2015 Gleason grade groups in a nationwide population-based cohort. *Eur Urol.* 2016; 69(6): 1135-41.
14. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int* 2013; 111(5): 753-60.
15. Chen C, Chen Y, Hu LK, Jiang CC, Xu RF, He XZ. The performance of the new prognostic grade and

- stage groups in conservatively treated prostate cancer. *Asian J Androl* 2018; 20(4): 366-71.
16. Shah MB, Raju K, Kumar H. Revisiting Prostate Biopsy with 2014 ISUP Modified Gleason Score and Gleason Grade—A Cross Section Study. *Biomed Res Ther* 2018; 5(12): 2918-25.
 17. Kang YJ, Kim HS, Jang WS, Kwon JK, Yoon CY, Lee JY, et al. Impact of lymphovascular invasion on lymph node metastasis for patients undergoing radical prostatectomy with negative resection margin. *BMC Cancer* 2017; 17(1): 321.
 18. May M, Kaufmann O, Hammermann F, Loy V, Siegsmond M. Prognostic impact of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 2007; 99(3): 539-44.
 19. Santoni M, Scarpelli M, Mazzucchelli R, Lopez-Beltran A, Cheng L, Epstein JI, et al. Current histopathologic and molecular characterisations of prostate cancer: towards individualised prognosis and therapies. *Eur Urol* 69(2): 186-90.
 20. Jeon HG, Bae J, Yi JS, Hwang IS, Lee SE, Lee E. Perineural invasion is a prognostic factor for biochemical failure after radical prostatectomy. *Int J Urol* 2009; 16(8): 682-6.
 21. Lee JT, Lee S, Yun CJ, Jeon BJ, Kim JM, Ha HK, et al. Prediction of perineural invasion and its prognostic value in patients with prostate cancer. *Korean J Urol* 2010; 51(11): 745-51.
-