Original Article

Validation of the WHO 2016 new Gleason score of prostatic carcinoma

Vishal Rao, Gowri Garudadri, Arya Sahithi Shilpa, Daphne Fonseca, S. Murthy Sudha, Rakesh Sharma[1], T. Rao Subramanyeshwar[1], Sundaram Challa

Departments of Pathology and Lab Medicine and [1]Surgical Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, Telangana, India

Abstract

Context: New Gleason Score of Prostate.

Aims: The aim of this study is to assign the patients with carcinoma prostate into new prognostic grade groups (PGGs) based on revised Gleason score (GS) and follow-up according to the WHO 2016.

Subjects and Methods: All the biopsies/resected specimens of carcinoma prostate from January 2014 to June 2016 were reviewed, and GS was done according to the WHO 2016. Accordingly, cribriform, fused, and glomeruloid glands were assigned GS 4. Thus, two groups were identified with GS 7 (3 + 4 and 4 + 3). The patients were grouped into PGGs 1–5. The number of patients with change in the prognostic group along with follow-up was calculated.

Results: There were 143 patients with carcinoma prostate, with a median age of 65 years. The initial GS was revised, and there was a decrease in GS 3 + 4 from 13.9% to 9% and increase in 4 + 3 from 19.6% to 23.8%. There was upgradation of PGG in 11 (7.69%) biopsies; with PGG from 1 to 2 in one; 2to 3 in eight; and 3to 4 in two. Follow-up at 2 years in 22 showed the poor prognoses in the patients who were upgraded to the higher prognostic group.

Conclusions: A change in PGG according to the WHO 2016 criteria was assigned in 7.69% biopsies of carcinoma prostate, and it correlated with prognosis.

Keywords: Carcinoma prostate, Gleason score, prognostic grade group, WHO 2016 criteria

Address for correspondence: Dr. Vishal Rao, Basavatarakam Indo American Cancer Hospital and Research Institute, Road No 14, Banjara Hills, Hyderabad - 500 034, Telangana, India.
E-mail: vishalrao1980@gmail.com
Received: 02.12.2017, **Accepted:** 28.05.2018

INTRODUCTION

The Gleason grading system is the most powerful prognostic indicator of prostatic carcinoma and has undergone significant changes since its adoption for grading of prostate cancer. The Gleason grading system originated from a well-controlled, prospective, randomized study from 1959 to 1964 by Veteran's Affairs Cooperative Research Group. This is based on clinicopathological correlation of over 2900 patients. The architectural patterns were given Gleason score (GS) 1–5, and the net result was obtained by adding the most common and the second most common patterns.[1] In 2005, the International Society of Urological Pathology (ISUP) conducted a consensus

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_185_17

How to cite this article: Rao V, Garudadri G, Shilpa AS, Fonseca D, Sudha SM, Sharma R, *et al*. Validation of the WHO 2016 new Gleason score of prostatic carcinoma. Urol Ann 2018;10:324-9.

conference and modified the original Gleason grading system and recommendations on grading variants of prostate cancer, reporting on small biopsies, and radical prostatectomies were proposed. However, several aspects of the grading system yet remained unresolved.[2,3] In 2014, another consensus conference was conducted by ISUP where specific areas of controversy were discussed.[4] The major conclusions were to include cribriform, fused, and poorly formed glands into Gleason pattern 4. The evolution of the grading systems for carcinoma prostate is shown in Figure 1.

After 2014 ISUP consensus, a new classification of prognostic grade grouping was proposed and adopted by the WHO 2016.[4,5] The new classification provided more accurate stratification of tumors and simplified the number of grading categories from prognostic grade groups (PGGs) 1–5 with more permutations based on different pattern combinations with the potential to reduce overtreatment of indolent cancer.

The present study is aimed at applying the revised Gleason grading and assigning PGGs according to 2016 WHO classification for carcinoma prostate.

SUBJECTS AND METHODS

All the patients who underwent core biopsies, transurethral resection of prostate (TURP), and radical prostatectomy (RP) with a clinical suspicion of carcinoma prostate from January 2014 to June 2016 were included in the study. The patients diagnosed on core biopsy and subsequently underwent RP were included in radical specimen only. The patients who underwent core biopsy or TURP biopsy were numbered separately. The demographic and clinical data were noted from the medical records. The hematoxylin- and eosin-stained slides were reviewed, and biopsies with no evidence of carcinoma were excluded from the study. All the slides were seen separately by two pathologists trained in oncopathology and uropathology. GS was done on all samples diagnosed as carcinoma, and

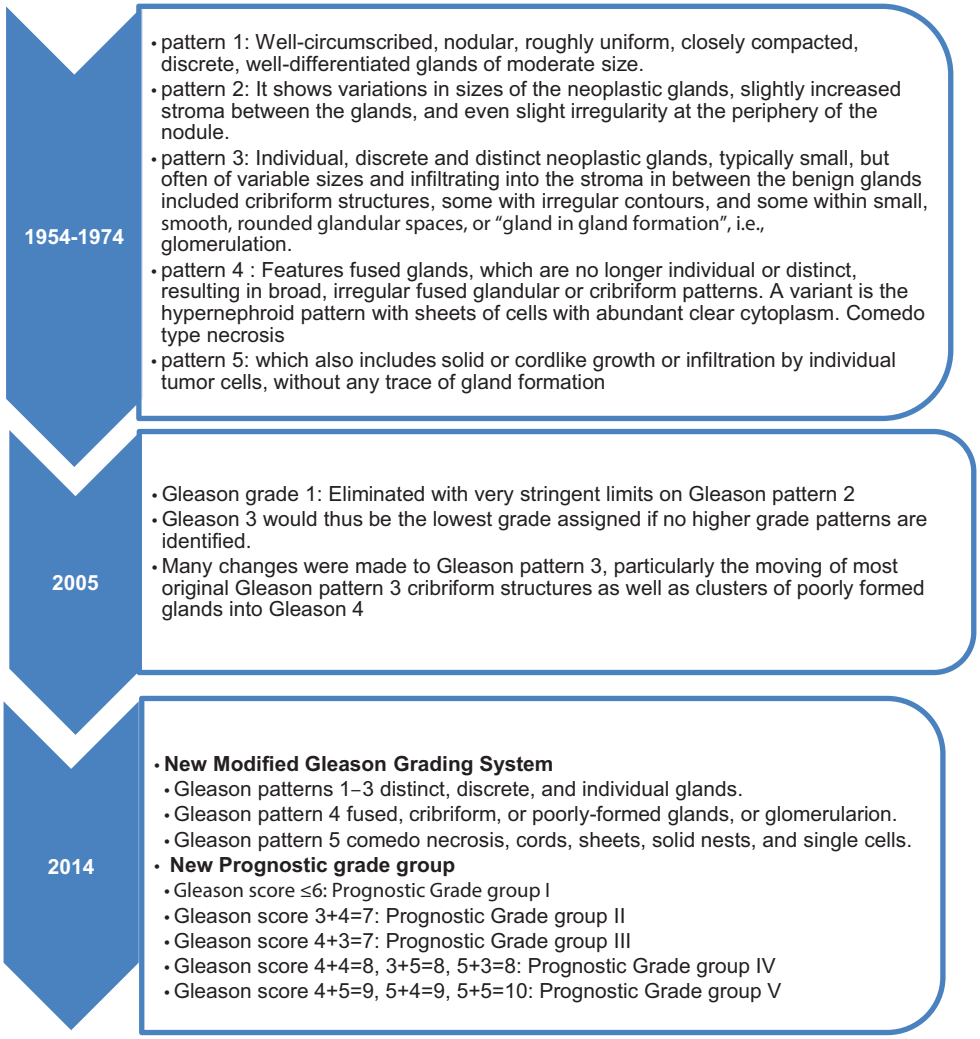

Figure 1: Evolution of Gleason grading system

prognostic group was assigned as per the recommendations of the consensus meeting of ISUP in 2014 which was later adopted by 2016 WHO classification of tumors of the urinary system and male genital organs.[4,5] Accordingly, cribriform, fused, and glomeruloid glands were assigned pattern 4, forming two groups of GS 7 (3 + 4 and 4 + 3). The patients were grouped into prognostic groups based on GS into Group 1 (3 + 3); Group 2 (GS 3 + 4); Group 3 (GS 4 + 3); Group 4 (GS 3 + 5; 4 + 4; 5 + 3); and Group 5 (GS 5 + 4; 4 + 5; 5 + 5). The number of patients with change in GS and PGG was calculated. The prognostic group was correlated with the follow-up data wherever available and correlated with the prostate-specific antigen (PSA) at the time of diagnosis, at 12th and 24th month.

RESULTS

There were 215 patients who underwent prostate biopsies in the study period. The samples included 153 core biopsies, 51 TURP, and 11 RP specimens. There were 143 (67%) malignant and 72 (33%) benign lesions. The patients with malignancy (143) were included for further analysis. The age ranged from 40 to 90 (median-65) years. The initial and revised GS along with initial and revised PGG were given in Tables 1 and 2. There was change in GS and prognostic group from 1 to 2 in 1 case; Group 2–3 in 8 cases; and Group 3–4 in 2 cases. There was no change in prognostic group in the other patients. There was an upgradation of prognostic groups in 11 (7.69%) patients [Figures 2 and 3]. All the upgraded patients had high persistent PSA levels, one was asymptomatic, seven were symptomatic, and three developed skeletal metastasis.

Follow-up

Follow-up at 2 years was available for 22 patients. About 11 were clinically asymptomatic, however, were not biochemically free of disease. Two were clinically symptomatic with persistent elevated PSA levels. Nine patients died of disease, and 8 (88.9%) patients had high-grade prostatic carcinoma (GS 8–10). The GS, PGG, and PSA levels of the 22 patients are given in Table 3.

The GS and PSA levels did not correlate well with the patients who were alive and clinically asymptomatic. However, the patients who were symptomatic and expired had persistent high levels of PSA with higher grade carcinoma. Kaplan–Meier graphs with survival data were not attempted as the data are limited.

Table 1: Prostate adenocarcinoma-Gleason grade: Group wise number of patients before and after following the new grading system (*n*=143)

GS	Number of patients with initial GS (%)	Number of patients with revised GS (%)	PGG - initial	PGG - revised
3+3	14 (9.7)	13 (9)	PGG-1=14	PGG-1=13
3+4	20 (13.9)	13 (9)	PGG-2=20	PGG-2=13
4+3	28 (19.6)	34 (23.8)	PGG-3=28	PGG-3=34
4+4	31	33	PGG-4=32	PGG-4=34
3+5	00	00		
5+3	01	01		
4+5	23	23	PGG-5=49	PGG-5=49
5+4	20	20		
5+5	06	06		
Total	143	143	143	143

GS: Gleason score, PGG: Prognostic grade group

DISCUSSION

Prostate cancer is globally the second frequently diagnosed cancer and the sixth leading cause of cancer death in males.[6] In India, its prevalence was considered to be lower, however, with changing lifestyle, better awareness, and access to medical facilities, more patients are diagnosed, and the incidence is estimated to be 8/100,000 persons.[7-9]

Previous Gleason grading systems

Studies before the 2005 ISUP classification reported 41%–46% patients with GS 5–7.[8,10] With the modified Gleason system in 2005, there was a shift toward higher GS being reported. An Indian study showed that 60% of carcinoma cases presented with GS 5–7.[11] In a series of thin core biopsies, regrading by the 2005 ISUP criteria resulted in increase of Score 7 tumors from 25.5% to 67.9%.[12] In a review of 97,168 patients newly diagnosed of prostate cancers on needle biopsy in Sweden from 1998 to 2011, it was found that, after the standardization for stage and PSA, there was an increase of GS 7–10 diagnoses from 59% to 72%.[13] Among low-risk cases (clinical stage T1 and serum PSA 4–10 ng/mL), the increase was from 16% to 40% whereas among high-risk cases (stage T3 and PSA 20–50 ng/mL), the increase was from 65% to 94%. At the same time, diagnoses of GS 2–5 decreased from 27% to 1% whereas GS 2–4 was almost discontinued.[13] Relocation of original Gleason pattern 3 cribriform growths into

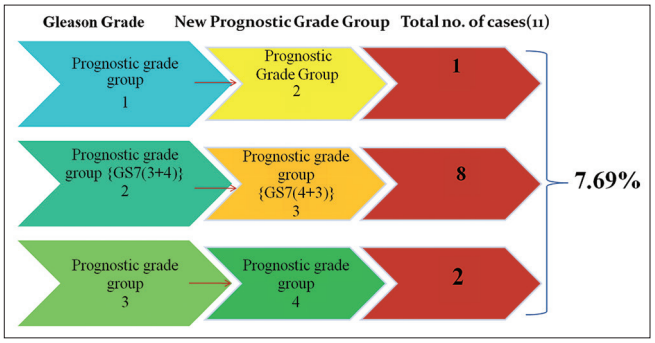

Figure 2: Change in prognostic grade group

Table 2: Change in prognostic grade group with following data of prostate-specific antigen levels at the time of diagnosis, 12th, and 24th month, respectively, with clinical course

Procedure	Age (years)	Initial GS	Modified GS	PSA levels (at the time of diagnosis)	PSA levels follow-up at 12th month	PSA levels follow-up at 24th month	Clinical course
Core biopsy	68	3+3	3+4	11.5	5.6	6.2	Asymptomatic
Core biopsy	59	3+4	4+3	26.2	14.4	4.0	Symptomatic
Core biopsy	74	3+4	4+3	6.2	12.6	5.5	Symptomatic
Core biopsy	78	3+4	4+3	38.1	2.2	14.8	Symptomatic
Core biopsy	52	3+4	4+3	355	52.3	12.5	Skeletal metastasis
Core biopsy	63	3+4	4+3	10.3	6.5	5.0	Symptomatic
Core biopsy	65	3+4	4+3	147	38	36	Skeletal metastasis
Core biopsy	65	3+4	4+3	15.5	NA	8.0	Symptomatic
Core biopsy	58	3+4	4+3	78	22.2	18.3	Symptomatic
Core biopsy	73	4+3	4+4	434	151	82.2	Skeletal metastasis
Core biopsy	69	4+3	4+4	1.5	NA	9.2	Symptomatic

PSA level units-ng/ml, NA: Not available, PSA: Prostate-specific antigen, GS: Gleason score

Table 3: Prostate adenocarcinoma: Follow-up at 2 years (*n*=22), patients' condition- I. Alive and asymptomatic, II. Alive and symptomatic, III. Patient expired

Patient condition	Serial number	Type of biopsy	Age (years)	Gleason score	PSA levels (at the time of diagnosis)	PSA levels at follow-up(12th month)	PSA levels at follow-up 24th month
I	1	Core biopsy	68	3+4	24.9	11.94	5.05
	2	Radical specimen	65	3+4	34.1	17.6	10.5
	3	Core biopsy	70	4+3	147.2	NA	0.22
	4	Core biopsy	59	4+3	38.5	5.2	1.0
	5	Core biopsy	73	4+4	12.8	4.9	0.19
	6	TURP biopsy	64	4+5	515	27.5	11.7
	7	Core biopsy	60	4+5	72.7	4.68	1.26
	8	Core biopsy	49	4+5	90.1	3.2	3.73
	9	Core biopsy	65	5+4	973	NA	2.5
	10	TURP Biopsy	64	5+4	17.8	3.5	2. 02
	11	Core biopsy	62	5+5	38.2	5.5	10.56
II	12	Core biopsy	72	3+4	11.3	22.4	15.2
	13	Core biopsy	68	4+4	400	153	110
III	14	Core biopsy	62	3+4	13.5	22.8	*
	15	Core biopsy	68	4+4	16.8	12.5	15.4
	16	Core biopsy	75	4+4	34.2	153.2	*
	17	Core biopsy	69	4+5	1.26	17.8	*
	18	TURP biopsy	60	4+5	10.2	44.3	29.3
	19	Core biopsy	63	4+5	90.1	*	*
	20	Core biopsy	72	5+4	19.8	NA	68.9
	21	Core biopsy	55	5+4	77.9	*	*
	22	Core biopsy	65	5+4	48.5	*	*

*Patient expired. NA: Not available. TURP: Transurethral resection of prostate

Gleason pattern 4 has shown to be valuable in predicting biochemical recurrence after RP.[14-17]

New Gleason grading system

The major revision in the WHO 2016 classification was to include cribriform, fused, and poorly formed glands into Gleason pattern 4 and also differentiate the GS 7 into two PGGs (3 + 4 and 4 + 3).[4,5] The identification of major pattern in the GS was correlated with the prognosis. In the present study, there was a decrease in GS 3 + 4 from 13.9% to 9% and an increase of GS 4 + 3 from 19.6% to 23.8% in the GS 7. There was mild increase in the other group; GS 8 increased from 22.4% to 23.8%. The 5-grade prognostic groups were shown to be more accurate in predicting progression than the 3 GS groups (<6, 7, 8–10).[4] The 5-year biochemical risk-free survival for the 5-grade groups based on RP grade was 96%, 88%, 63%, 48%, and 26%.[18] The overall grading of needle biopsy and RP specimens increased (e.g., from 58% to 72%) after the adoption of the modified system, particularly for biopsies with GS of 3 + 4 = 7 (88%).[19] Thus, increase of high-risk category tumors from 31.3% to 41.1% was noted.[20] Few studies appreciated no significant change in level of agreement between scores of needle biopsies and subsequent RP specimens, particularly with predominant pattern of GS7.[21,22] There was no change in both GS as well as prognostic group between core biopsies and RP specimens in the present study.

There was a strong correlation between the 5-grade groups and prostate cancer death. The new grade groups were simpler to apply and helpful for better stratification that correlated with the prognosis.[23,24] The biochemical

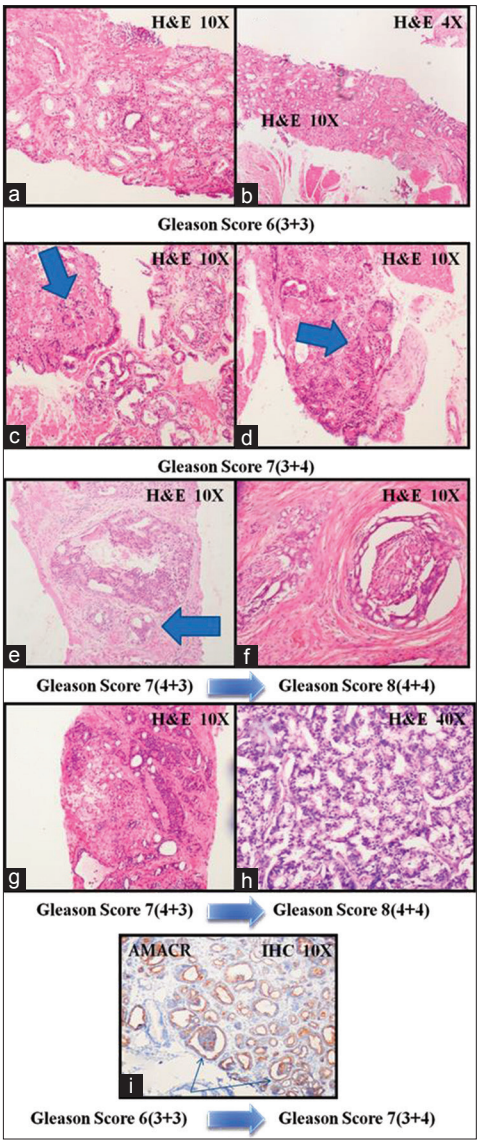

Figure 3: (a and b) Gleason Score 3 + 3; (c and d) Fused glands as Gleason score 4 with perineural invasion (thick arrow); (e-h) Glomeruloid and cribriform pattern as Gleason Score 4 (thick arrow); (i) Alpha methylacyl-CoA-racemase immunohistochemical highlighting the glomeruloid pattern (thin arrow)

risk-free survival and hazard ratio were reported to be in correlation with the new (2016) grading system.[4,17] With the 2016 criteria, the change in the prognostic group was into higher grade, and it was seen in 11 (7.69%) patients in the present study. Follow-up showed poor prognosis in the patients who were upgraded to the higher prognostic group. The patients who were symptomatic and expired had persistent high levels of PSA with higher grade carcinoma, highlighting the importance of prognostic grade grouping.

CONCLUSIONS

The application of the WHO 2016 modified Gleason scoring system and prognostic grade grouping criteria retrospectively to 143 carcinoma prostate biopsies resulted in the upgradation of prognostic groups in 11 (7.69%) patients. The identification of major pattern in the GS 7 correlated with the prognosis. There was no change in GS in core biopsies and RP specimens. The number of patients with the upgraded group is small but significant. Hence, awareness about the architectural pattern as per the revised Gleason Scoring system and assigning PGGs is essential for prognostication.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974;111:58-64.
2. Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, *et al*. Addressing overdiagnosis and overtreatment in cancer: A prescription for change. Lancet Oncol 2014;15:e234-42.
3. Epstein JI, Allsbrook WC Jr., Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228-42.
4. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, *et al*. The 2014 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: Definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244-52.
5. Epstein JI. An update of the Gleason grading system. J Urol 2010;183:433-40.
6. Dabir PD, Ottosen P, Høyer S, Hamilton-Dutoit S. Comparative analysis of three- and two-antibody cocktails to AMACR and basal cell markers for the immunohistochemical diagnosis of prostate carcinoma. Diagn Pathol 2012;7:81.
7. National Cancer Registry Program. Consolidated Report of Population Based Cancer Registries 2001-2004: Incidence and Distribution of Cancer. Bangalore (IND): Coordinating Unit, National Cancer Registry Program, Indian Council of Medical Research; 2006.
8. Stanford JL, Stephenson RA, Coyle LM, Cerhan J, Correa R, Eley JW, *et al*. Prostate Cancer Trends 1973-1995, SEER Program, National Cancer Institute. NIH Pub. No. 99-4543. Bethesda, MD, 1999.
9. Bid HK, Konwar R, Singh V. Benign prostatic hyperplasia: Is it a growing public health concern for India? Indian J Med Sci 2008;62:373-4.
10. Shen BY, Tsui KH, Chang PL, Chuang CK, Hsieh ML, Huang ST, *et al*. Correlation between the Gleason scores of needle biopsies and radical prostatectomy specimens. Chang Gung Med J 2003;26:919-24.
11. Josephine A. Clinicopathological study of prostatic biopsies. J Clin Diagn Res 2014;8:FC04-6.
12. Helpap B, Egevad L. The significance of modified Gleason grading of prostatic carcinoma in biopsy and radical prostatectomy specimens. Virchows Arch 2006;449:622-7.
13. Danneman D, Drevin L, Robinson D, Stattin P, Egevad L. Gleason inflation 1998-2011: A registry study of 97,168 men. BJU Int 2015;115:248-55.
14. Billis A, Guimaraes MS, Freitas LL, Meirelles L, Magna LA, Ferreira U, *et al*. The impact of the 2005 international society of urological

pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. J Urol 2008;180:548-52.
15. Uemura H, Hoshino K, Sasaki T, Miyoshi Y, Ishiguro H, Inayama Y, *et al.* Usefulness of the 2005 international society of urologic pathology Gleason grading system in prostate biopsy and radical prostatectomy specimens. BJU Int 2009;103:1190-4.
16. Billis A, Quintal MM, Meirelles L, Freitas LL, Costa LB, Bonfitto JF, *et al.* The value of the 2005 international society of urological pathology (ISUP) modified Gleason grading system as a predictor of biochemical recurrence after radical prostatectomy. Int Urol Nephrol 2014;46:935-40.
17. Kir G, Sarbay BC, Gümüş E, Topal CS. The association of the cribriform pattern with outcome for prostatic adenocarcinomas. Pathol Res Pract 2014;210:640-4.
18. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: Data based on the modified Gleason scoring system. BJU Int 2013;111:753-60.
19. Helpap B, Egevad L. Correlation of modified Gleason grading with pT stage of prostatic carcinoma after radical prostatectomy. Anal Quant Cytol Histol 2008;30:1-7.
20. Delahunt B, Lamb DS, Srigley JR, Murray JD, Wilcox C, Samaratunga H, *et al.* Gleason scoring: A comparison of classical and modified (international society of urological pathology) criteria using nadir PSA as a clinical end point. Pathology 2010;42:339-43.
21. Zareba P, Zhang J, Yilmaz A, Trpkov K. The impact of the 2005 international society of urological pathology (ISUP) consensus on Gleason grading in contemporary practice. Histopathology 2009;55:384-91.
22. Chen N, Zhou Q. The evolving Gleason grading system. Chin J Cancer Res 2016;28:58-64.
23. Egevad L, Algaba F, Berney DM, Boccon-Gibod L, Compérat E, Evans AJ, *et al.* Interactive digital slides with heat maps: A novel method to improve the reproducibility of Gleason grading. Virchows Arch 2011;459:175-82.
24. Matoso A, Epstein JI. Grading of prostate cancer: Past, present, and future. Curr Urol Rep 2016;17:25.