Review Article

Literature Review on The Evolutional Steps in Updating Gleason Grading System of Prostatic Adenocarcinoma

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Abstract

The evolution of the famous original grading system for prostatic adenocarcinoma which initially described by Dr. Donald Gleason in the 1960s–1970s passed through two steps of modifications according to two major consensus meetings achieved by the International Society of Urologic Pathology (ISUP) in 2005 and 2014 respectively according to many researches and clinical trials to be finely incorporated into the recent World health organization (WHO) classification of prostate cancer and staging system as one of the powerful prognostic factor and treatment decision factor .This articles briefly review historical aspects of the original Gleason grading system and the recent modifications , describing the major changes over the years that finely resulted in the contemporary Gleason grading system, which proposed a new "Grade Group" system established by the 2014 ISUP meeting , and then incorporated to the recent (2016) WHO classification of tumors of the prostate.

Key words: prostatic adenocarcinoma, gleason grade, International Society of Urologic Pathology

Introduction

Prostatic adenocarcinoma is the most common cancer worldwide and the second leading cause of cancer related death among men, generally it is of two types, acinar which represent 95% of all prostatic cancer and the remaining 5% were of ductal type [(1)]. peripheral zone (posterior and lateral)is the most common location, 70% grossly present as a Gritty and firm mass , gray-yellow, poorly circumscribed, accurate identification of prostate carcinoma by gross examination is possible in only 63% of cases, with a 19% false positive rate [(2)] the Most common histological pattern of acinar cancer is infiltrative, small to medium sized glands detect usually on low power as closely packed glands with irregular outline, smooth inner luminal surface growing in between stromal fibers. [(3)] perineural invasion, glomerulation, mucinous fibroplasia (collagenous micronodules, are regarded as the only definitive features of malignancy while some features favoring but not diagnostic of adenocarcinoma in needle biopsy : small glands among larger glands, crowded glands that stand out from adjacent benign glands, prominent nucleoli in at least 10% of cells, high nuclear to cytoplasmic ratio, hyperchromatic nuclei, luminal blue mucin, amphophilic cytoplasm, mitotic figures, crystalloids, adjacent high grade prostatic intraepithelial neoplasia PIN [(4)] .some histological Features are associated with false positive diagnoses including atrophic cytoplasm, atypical glands associated with inflammation, small crowded glands merging with larger benign glands (adenosis) [(5)]

Perineural invasion (PNI) is a Common characteristic feature (detected in 85% of all prostatic cancer) when present in needle core biopsy, suggests extraprostatic extension. [(6)]

Angiolymphatic invasion is infrequent finding, calcifications are more common in benign than malignant prostate, but present in with comedo-type necrosis (dystrophic calcification), within lumina of Gleason pattern cribriform and small acinar glands, and within collagenous micronodule. [(7)]

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There is a 50% rate of incidental prostatic adenocarcinoma in which 20% were clinically significant in cystoprostatectomy specimens for bladder cancer [8]

Prognosis of prostatic adenocarcinoma depend on Stage, Gleason score , surgical margins, preoperative PSA, perineural invasion Angiolymphatic invasion),Size of nodal metastases ,Poor prognostic factors are Gleason score > 6, prostatic specific antigen PSA > 40 ng/mL, stage 3 or higher, Caucasian [9] .Recurrence after radical prostatectomy occurred with a with Median interval 40 months and Mean tumor size 3.2 mm Often lacks overt histologic features of malignancy, but need lower threshold for diagnosis because atypical prostate glands should not be present at all .[10]

Radical prostatectomy is the main stay treatment, brachytherapy (radioactive seeds), targeted focal cryotherapy, external beam radiation therapy, watchful monitoring used (for low grade tumors, localized tumor or limited life expectancy), chemotherapy or hormonal therapy (LHRH analogs, antiandrogens, orchiectomy).Most tumors are androgen sensitive serum PSA monitoring is useful to detect tumor response [11]

The original gleson grading system

Dr. Donald Gleason, the Chief of Pathology at the Veteran's Hospital in Minnesota depending on a study from 1959 through 1964, created a grading system for prostate cancer based on its different histologic patterns. As most of the tumors typically had two histologic patterns, a score was created that added the two most common grade patterns in a tumor, with scores ranging from 2 to 10. The study demonstrated a progressive increase in cancer specific mortality with an increase in score, for ease of grading, the five prognostic patterns were demonstrated by a simple diagram drawn by Dr. Gleason (figure 1) [12,13]

Gleason grading of prostatic adenocarcinoma often typically performed using the 4x objective light microscope although in certain instances (ie. back-to-back glands vs. fused glands) that require higher magnification at 10x objective. Gleason scores should be reported as a mathematical equation, for example, Gleason score $4 + 3 = 7$.[14]

The classical Gleason system defines five histological growth patterns (grades) on architectural patterns of prostate adenocarcinoma seen on hematoxyllin and eosin (H&E sections), rather than cellular features (figure1). Gleason 1 represents the best differentiated and is correlated with the most favorable prognosis, whereas Gleason 5 is the least differentiated and correlated with poor prognosis. As many prostate adenocarcinomas harbored two or more Gleason patterns, the Gleason score was developed, which was later found to have a strong correlation with the biological behavior of prostate adenocarcinoma.[15,16,17]

Grade	Description
1	Single, separate uniform glands in closely packed masses with a definite usually rounded edge, limiting the area of tumour.
2	Single, separate slightly less uniform glands loosely packed and separated by small amount of stroma. Edges are less sharp.
3a	Single, separate much more variable glands may be closely packed or irregularly ragged and separated. edges are poorly defined.
3b	Same as 3a with tiny cell clusters
3c	Sharp, smoothly circumscribed rounded mass of papillary or loose cribriform tumour (Papillary intraductal tumour)
4a	Ragged outline infiltrating fused glandular tumour
4b	Like 4a, large pale cells (hypernephroid)
5a	Sharply circumscribed, rounded masses of solid cribriform tumour, usually with central necrosis. (comedonecrosis)
5b	Ragged masses of anaplastic carcinoma with just enough gland formation to identify it as adenocarcinoma.

Figure 1. The basic five growth patterns originally described by Dr. Gleason

The first 2005 modification of the original grading system:

Many changes since the 1960s–1970s have occurred for updating of the original Gleason system. For example, new growth patterns or variants of prostate adenocarcinoma have been established, which need to be incorporated into this system. Modified needle biopsy protocols and modern surgical approaches in combination with increased screening by serum prostatic specific antigen PSA and other modalities provides samples which required pathologists to assess many new subjects such as grading multiple core biopsies from different sites or multiple nodules in radical prostatectomies (RP). There are also some rising questions as how to interpret and score biopsies with tertiary (in addition to the primary and secondary) patterns, and how to differentiate between cribriform patterns in well-demarcated spaces from high grade prostatic intraepithelial neoplasia (PIN) , which have been better appreciated with the availability of basal cell immunohistochemical markers. The most important advance in this regard is the ISUP consensus published in 2005 .[18-23]

One of the most prominent changes in the meeting is that Gleason score 1+1=2 should not be diagnosed since a "Gleason 1" nodule cannot be assessed by a core biopsy. Even with transurethral resection of prostate (TURP) or open prostectomy samples thus, the original Gleason score 1+1=2 nodules mostly are adenosis .[24]

Gleason score 3 or 4 on needle biopsies (comprised of grades 1+2, 2+1 and 2+2) has also been controversial, given its poor reproducibility and poor correspondence with the grading on later radical prostatectomy samples .The ISUP consensus recommended that diagnosis of Gleason score 3 or 4 be made only "rarely, if ever. [25]

The 2005 meeting extensively studied the issue of the controversial cribriform Gleason pattern 3, and remove individual cells, as well as large cribriform growths adding them to pattern 4, but still permit diagnosis of cribriform pattern 3 only in well-circumscribed, smooth and rounded glands having the size of normal glands .However, additional researches in larger centers, and discussions by urological pathologists (post-ISUP consensus conference) further led to the proposal that all cribriform glands should be considered Gleason pattern 4 . [24,26]

In summary, modified Gleason system (figure 2) based on the 2005 consensus and later developments basically eliminated Gleason grade 1, and put very stringent limits on Gleason pattern 2. Gleason 3 would thus be the lowest grade assigned if no higher-grade patterns are identified. Many changes were made to Gleason pattern 3, particularly the moving of most original Gleason pattern 3 cribriform structures as well as clusters of poorly formed glands into Gleason 4. [27]

Limited patterns of lower grade cancer should be ignored in the setting of high-grade cancer if they occupy less than 5% of the tumour area. The rationale here was that such tumours are expected to have a similar prognosis as 100% high-grade tumours.[28]

Tertiary patterns should be included in the Gleason score. Epstein et al defined a tertiary pattern as 'the presence of a third component of Gleason pattern higher than the primary and secondary grades, where the tertiary component is visually estimated to be less than 5% Needle biopsies should therefore be graded as the sum of the primary (most prevalent) and the highest grade only The reason is that the presence of Gleason patterns 4 and 5 on needle biopsy most likely indicates an overall high-grade tumor. In radical prostatectomy specimens the Gleason score should be described based on the primary and secondary patterns, with a comment on the tertiary pattern, since tertiary patterns have been found to have prognostic importance [27-28]

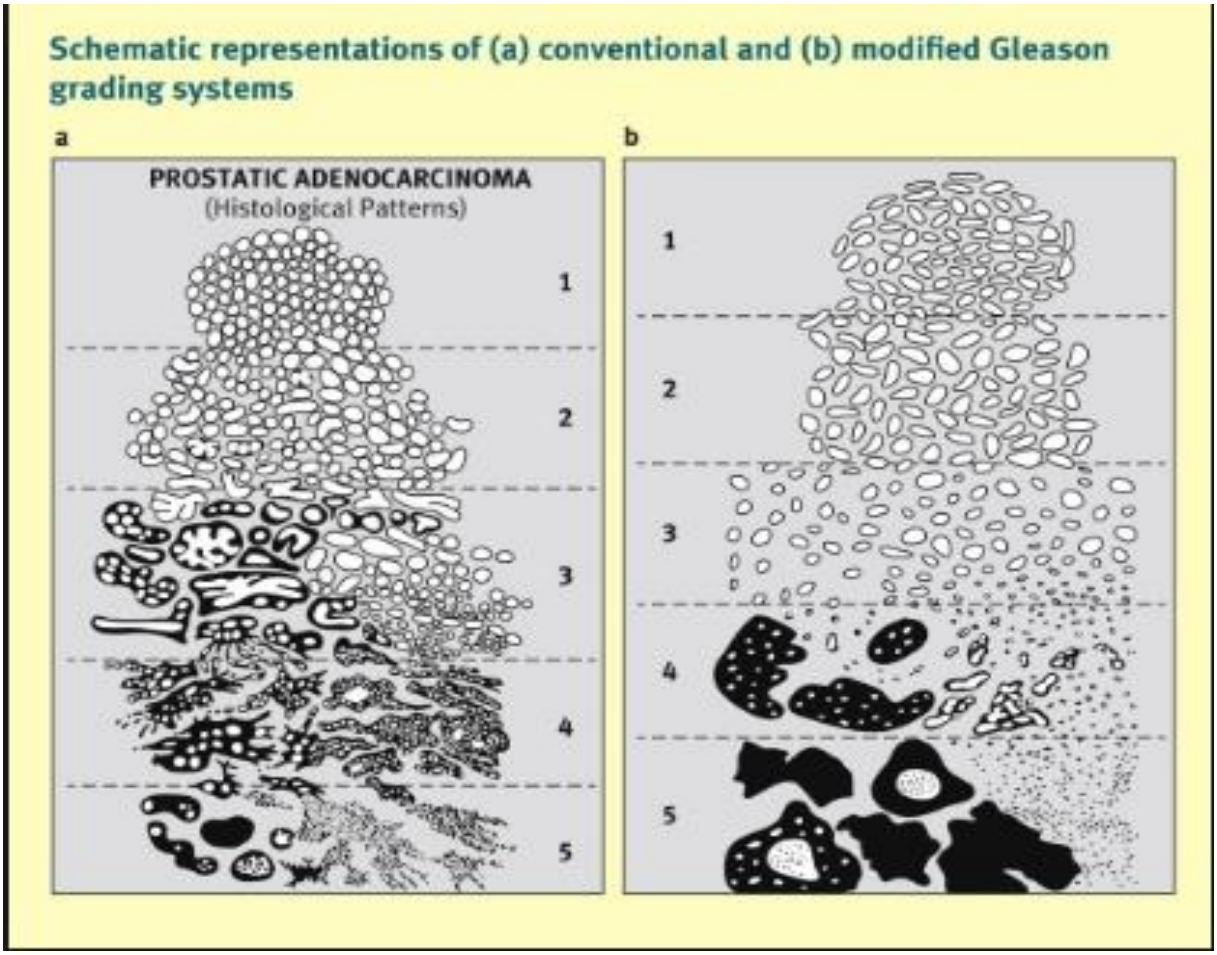

Figure 2. Schematic representation of conventional and modified gleason grading system[18]

In radical prostatectomy specimens a different Gleason score should be assigned to each dominant tumor nodule. In needle biopsies individual Gleason scores should be assigned to separate tumor cores as long as the cores are submitted in separate containers. If not, one should give an overall score for a container containing different cores.(29)

The grading of variants and subtypes of acinar adenocarcinoma of the prostate, including cancer with vacuoles, foamy gland carcinoma, ductal adenocarcinoma, pseudohyperplastic carcinoma and small cell carcinoma have also been modified (30)

The proposed that vacuoles should be ignored and that the grading should be based only on the underlying structural patterns. Similarly, focal mucinous extravasation as well as mucinous fibroplasia (collagenous micronodules) should be ignored and the grading done based on the underlying gland structures. For grading foamy gland carcinomas, the foamy cytoplasm should be ignored and the grading then based on the underlying structures. Consensus was also proposed to grade pseudohyperplastic adenocarcinoma as Gleason score 3+3=6, and ductal adenocarcinoma as Gleason score 4+4=8. However, the opinions in regard to the grading of colloid carcinomas were divided (grade as Gleason score 8, or ignore the extracellular mucin and grade according to underlying structures).(27.32)

There are many data showing that the overall agreement between grading of needle biopsy and radical prostatectomy specimens increased after the usage of the modified system in pathological recording of prostatic adenocarcinoma , particularly for biopsies with Gleason score of 3+4=7 .(30)

However, some studies showed no significant change in level of agreement between

needle core biopsy and subsequent radical prostatectomy specimens [31].

An important issue for any grading system to be clinically useful is its intra- and inter-observe reproducibility. Intraobserver agreement on Gleason scores has been reported to vary from 43% to 78% [32], whereas interobserver agreement have been reported to vary from 36% to 81% for exact agreement, and 69% to 86% when the agreement occurred within one Gleason score unit Similarly, the modified glison grading system, particularly the new definition of Gleason pattern 4 withthe decrease in the original number of patterns showed an improvement in overall interobserver reproducibility, rising to about 80% .[33]

The second 2014 modification of the Gleason grade:

It had become clear over time, that the complexity of previous grading system impends survival analysis, [31] so an international consensus meeting done to update Gleason grading convened in Chicago (US) in 2014, which included not only experts in pathology, but also in urology , radiation and medical oncology [34]. The meeting was conducted by the ISUP to discuss issue not covered in the 2005 consensus basing on many new research data and challenges from clinicians to the current grading system. [14]

The most important development of this meeting is the establishment of a new prognostic grade Grouping system (figure 3) in order to accommodate the heterogeneity and the variety in architectural patterns characteristic of prostate cancer, which may bear a major impact on pathologists and clinicians. [12]

Gleason scores less than or equal to 6 were clumped into prognostic grade group I, Gleason score 3+4=7 to group II, Gleason score 4+3=7 to group III, Gleason score 4+4=8 to group IV, and Gleason score 9-10 to group V [36] .Thus it is regarded as a a new grading system although it is based on the original Gleason patterns.. Since the new "Grade Group" system has been incorporated into the recent edition of World Health Organization classification of prostate tumors (released in January 2016) and has been accepted by the 2016 World Health Organization (WHO), thus best understanding of the system by both pathologists and clinicians is mandatory. [34,14]

Advantages of the contemporary Gleason grade [37 ,38]

1) More accurate grade stratification than the previous modified Gleason system

2) Simplified way to record grading system of 5 groups as opposed to multiple possible scores depending on the combination of various histological patterns.

3) Lowest grade is 1 as opposed to previous lowest grade of the previous Gleason score 6, with the potential to avoid overtreatment of indolent prostate cancer

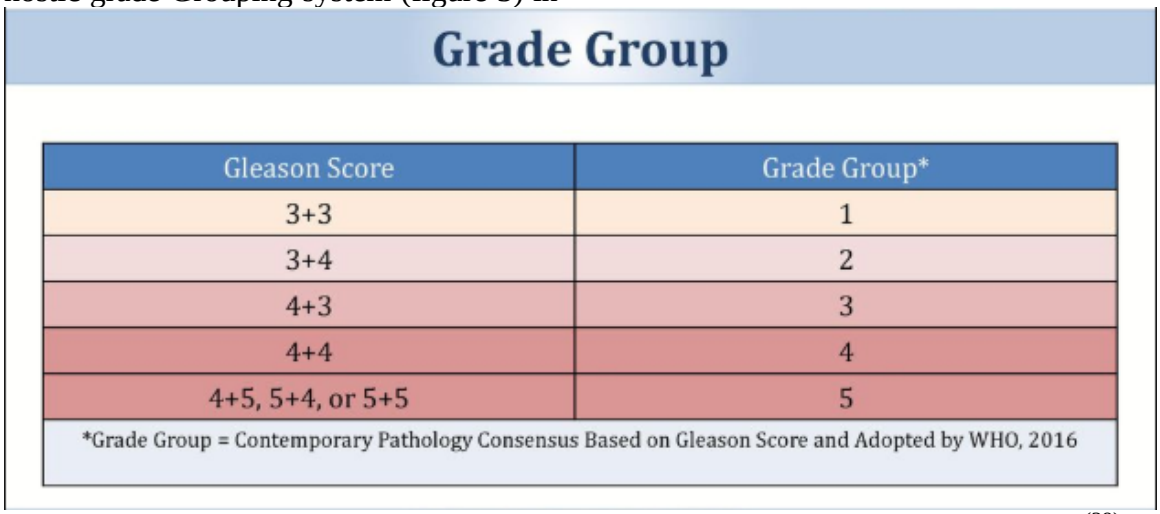

Figure 3. The new grade groups of the contemporary gleason grading system[38]

References

1. Mygatt J, Sesterhenn I, Rosner I, Chen Y, Cullen J, Morris-Gore T et tal .Anterior tu-mors of the prostate: clinicopathological fea-tures and outcomes.Prostate Cancer Prostatic Dis. 2014; 17:75-80.
2. Sebo TJ, Cheville JC, Riehle DL, Lohse CM, Pankratz VS, Myers RP, et tal Perineural invasion and MIB-1 positivity in addition to Gleason score are significant preoperative predictors of progression after radical ret-ropubic prostatectomy for prostate cancer. Am J Surg Pathol. 2002; 26:431-9.
3. Iczkowski KA, Torkko KC, Wilson RS, Lucia MS, Bostwick DG. Prostatic atrophy: its spatial proximity to carcinoma and intraepithelial neoplasia based on annotation of digital slides. Hum Pathol. 2014 ;45:54-8.
4. Iczkowski KA, Bostwick DG Criteria for biopsy diagnosis of minimal volume prostatic adenocarcinoma: analytic comparison with nondiagnostic but suspicious atypical small acinar proliferation Arch Pathol Lab Med. 2000 ;124:98-107.
5. Srodon M, Epstein JI Hum Pathol. Central zone histology of the prostate: a mimicker of high-grade prostatic intraepithelial neo-plasia. 2002 May;33(5):518-23.
6. Bismar TA , Lewis JS Jr, Vollmer RT, Humphrey PA Am J Surg Pathol. Multiple measures of carcinoma extent versus perineu-ral invasion in prostate needle biopsy tissue in prediction of pathologic stage in a screening population. 2003;27:432-40.
7. Cohen RJ, McNeal JE, Redmond SL, Meehan K, Thomas R, Wilce M, Dawkins HJ Luminal contents of benign and malignant prostatic glands: correspondence to altered secretory mechanisms Hum Pathol. 2000 Jan;31:94-10
8. Mazzucchelli R, Barbisan F, Scarpelli M, Lopez-Beltran A, van der Kwast TH, Cheng L, Montironi R. Is incidentally de-tected prostate cancer in patients undergoing radical cystoprostatectomy clinically signifi-cant?Am J Clin Pathol. 2009 ;131:279-83.
9. Migowski A, Silva GA. Survival and prognostic factors of patients with clinically localized prostate cancer. Rev Saude Publi-ca. 2010;44:344-52.
10. Sebo TJ, Cheville JC, Riehle DL, Lohse CM, Pankratz VS, Myers RP, Blute ML, Zincke H Perineural invasion and MIB-1 positivity in addition to Gleason score are sig-nificant preoperative predictors of progression after radical retropubic prostatectomy for prostate cancer.Am J Surg Pathol. 2002 ;26:431-9.
11. Bangalore Ramalingiah Vani, Deepak Ku-mar, Burugina Nagaraj Sha-rath, Venkataramappa Srinivasa Murthy, Kempula Geethamala A comprehen-sive study of prostate pathology in correlation with prostate-specific antigen levels: An Indi-an study . clinical cancer investigation jour-na 2015 4: 617-620l .
12. Ennifer Gordetsky and Jona-than EpsteinGrading of prostatic adenocarci-noma: current state and prognostic implica-tionsDiagnostic pathology. 2016;11:25
13. Humphrey PA. Gleason grading and prognostic factors in carcinoma of the prostate. Mod Pathol 2004;17:292-306.
14. Ni Chen and Qiao ZhouThe evolving Gleason grading systemChin J Cancer Res. 2016 Feb; 28: 58–64.
15. Eble JN, Sauter G, Epstein JE, et al. World Health Organization Classification of Tumours. Pathology and genetics of the urinary system and male genital organs. Lyon: IARC Press, 2004:159-215.
16. Ackerman RJ. Male reproductive system- Prostate and seminal vesicles. In: Ackerman RJ, editor. Rosai and Ackerman′s Surgical Pathology. 10 th ed. Elsevier Inc.; 2011. p. 1295-8.
17. Amin MB, Grignon DJ, Humphrey PA,. Gleason grading of prostate cancer. A con-temporary approach. Philadelphia: Lippincott Williams & Wilkins, 2004:1-116.
18. Shah RB. Current perspectives on the Gleason grading of prostate cancer. Arch Pathol Lab Med 2009;133:1810-6.
19. Osunkoya AO. Update on prostate patholo-gy. Pathology 2012;44:391-406.
20. Lotan TL, Epstein JI. Clinical implications of changing definitions within the Gleason grading system. Nat Rev Urol 2010;7:136-42.
21. Helpap B, Egevad L. Modified Gleason grading. An updated review. Histol Histo-pathol 2009;24:661-6.
22. Epstein JI, Allsbrook WC, Jr, Amin MB, et al. Update on the Gleason grading system for prostate cancer: results of an international consensus conference of urologic pathologists. Adv Anat Pathol 2006;13:57-9.
23. Epstein JI, Allsbrook WC, Jr, Amin MB, et al. The 2005 International Society of Urologi-cal Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcino-ma. Am J Surg Pathol 2005;29:1228-42.
24. Epstein JI. An update of the Gleason grading system. J Urol 2010;183:433-40.
25. Egevad L, Mazzucchelli R, Montironi R. Implications of the International Society of Urological Pathology modified Gleason grad-ing system. Arch Pathol Lab Med 2012;136:426-34.
26. Latour M, Amin MB, Billis A, et al. Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology. Am J Surg Pathol 2008;32:1532-9.

27. RodolfoMonti-ro-ni,RobertaMazzucchell,iAntonioLopez,BeltranMarina,Scarpelli,Liang-ChengTh e Gleason grading system: where are we now? Diagnostic Histopathology.2011. 17: 419-427.
28. T. Gevaert, H. Van Poppel, S. Joniau, D. De Ridder, E. Lerut Current perspectives on the use of the Gleason grading system for prostate cancer (Belg J Med Oncol 2012;6:45-51).
29. Jang WS , Yoon CY, Kim MS, Kang DH, Kang YJ, Jeong WS, Abalajon MJ, Ham WS, Choi YD. The prognostic role of tertiary Gleason pattern 5 in a contemporary grading system for prostate cancer..Prostate Cancer Prostatic Dis. 2017 Mar;20(1):93-98.
30. Helpap B, Egevad L. The significance of modified Gleason grading of prostatic carcinoma in biopsy and radical prostatectomy speci-mens. Virchows Arch 2006;449:622-7.
31. Delahunt B, Lamb DS, Srigley JR, et al. Gleason scoring: a comparison of classical and modified (international society of urologi-cal pathology) criteria using nadir PSA as a clinical end point. Pathology 2010;42:339-43.
32. Griffiths DF, Melia J, McWilliam LJ, et al. A study of Gleason score interpretation in different groups of UK pathologists; techniques for improving reproducibil-ity. Histopathology 2006;48:655-62.
33. Egevad L, Algaba F, Berney DM, et al. Interactive digital slides with heat maps: a novel method to improve the reproducibility of Gleason grading.Virchows Arch 2011; 459: 175-82.
34. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pa-thology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Def-inition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244-52.
35. Pierorazio PM, Walsh PC, Partin AW, et al. Prognostic Gleason grade grouping: data based on the modified Gleason scoring sys-tem. BJU Int2013;111:753-60.
36. Kryvenko ON, Epstein JI. Changes in prostate cancer grading: Including a new patient-centric grading system. Prostate 2016;76:427-33.
37. Jonathan I. Epstein, Michael J. Ze-lefsky,Daniel D. Sjoberg,Joel B. Nelson,Lars Egevad , Cristina Magi-Galluzzi et tal. A Con-temporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score 2016 europian urology 69: 428–435.
38. Zumsteg ZS , Spratt DE, Pei I, Zhang Z, Yamada Y, Kollmeier M, Zelefsky MJ A new risk classification system for therapeutic decision making with intermediate-risk pros-tate cancer patients undergoing dose-escalated external-beam radiation therapy Eur Urol. 2013 Dec;64:895-902.