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PROGNOSTIC ROLE OF NEW CONTEMPORARY GRADING SYSTEM IN PROSTATE CANCER

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ABSTRACT

Gleason grade of prostatic carcinoma is an established prognostic indicator that has stood the test of time. The International Society of Urological Pathology first made revisions to the grading system in 2005, and subsequently in 2014. Additionally, a new grading system composed of Grade Groups 1 to 5 that was first developed in 2013 at the Johns Hopkins Hospital. This new grading system has been accepted by the World Health Organization (WHO). The aim of the present study was to categorize the cases of prostatic adenocarcinoma based on New contemporary grading system and to discuss it's prognostic significance. A total of 124 cases were studied at Osmania General Hospital, Hyderabad prospectively over a period of 1 year, from May 2015 to April 2016. In the present study, out of 124 cases, 108 cases(87%) were BPH and 16 cases(13%) were adenocarcinoma. The present study used New contemporary grading system for categorization, majority of the cases were in grade group IV (7 cases, 43.75%) followed by group I (3 cases, 18.75%) and group II, group III, group V each comprising of 2 cases. The new grading system provides more accurate grade stratification than current applications of the Gleason system. It is simple, with 5 grade groups as opposed to 25 scores depending on various Gleason pattern combinations, the lowest grade in the new system is 1 as opposed to 6 in the Gleason system avoiding unnecessary treatment of indolent cancers.

KEY WORDS: Adenocarcinoma, contemporary, Gleason, Grading, Prognostic, Prostate.

INTRODUCTION

Prostate cancer is globally the second frequently diagnosed cancer and the sixth leading cause of cancer death in males.[1] In India, it constitutes about 5% of all male cancers.[2]

Prostate tumor consists of malignant cells that form more or less differentiated glandular structures and a tumor stroma. Basal epithelial cells are absent in prostate tumors and the tumor vasculature partly lacks periendothelial cells.[3] The tumor stroma differs from the normal stroma in terms of composition and the expression of growth factors, cytokines, angiogenic factors and proteolytic enzymes. It consists of fibroblasts, myofibroblasts, endothelial cells, pericytes and inflammatory cells.

Hormonal factors play a role in the development of prostatic carcinoma. There have been a number of studies linking a high fat diet to the development of prostatic carcinoma.[4]There is no demonstrable correlation with venereal diseases, sexual habits, smoking or occupational hazards. 75% of the men diagnosed with prostatic cancer are of age 65 or older.

Gleasons scoring system- The Gleason scoring system is used to help evaluate the prognosis of men with prostate cancer using samples from a prostate biopsy. A Gleason score is given to prostate cancer based upon its microscopic appearance. 5 basic microscopic tumor patterns are assessed by a pathologist while interpreting the biopsy specimen. These five basic tissue patterns are referred to as tumor "grades". The original Gleason grading system was developed in 1966 by Donald Gleason, and was refined in 1974 en 1977.[5,6] Since then the Gleason system remained the state of the art classification system for prostate cancer. However, it became more and more apparent that changes were needed to adapt this scoring system to the scientific evolutions. The introduction of immunohistochemistry

for basal cells had indeed shown that several Gleason grade 1-2 tumours were in fact foci of adenosis and that Gleason grade 3 cribriform tumours were often in situ lesions.

A consensus conference was organized in 2005 by the International Society of Urological Pathology (ISUP) for standardizing both the perception of histologic patterns and how the grade information is compiled and reported. That conference led to the 2005 ISUP Modified Gleason System.[7]

Table 1 – Histological description of the Original Gleason System and the 2005 International Society of Urological Pathology (ISUP) Modified Gleason System[8]

Pattern	Original Gleason System	ISUP Modified Gleason System
1	Very well-differentiated, small, closely packed, uniform glands in essentially circumscribed masses.	Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3).
2	Similar to pattern 1 but with moderate variation in size and shape of glands and more atypia in the individual cells; cribriform pattern may be present, still essentially circumscribed, but more loosely arranged.	Like pattern 1, fairly circumscribed, yet at the edge of the tumour nodule there may be minimal infiltration. Glands are more loosely arranged and not quite as uniform as Gleason pattern 1.
3	Similar to pattern 2 but marked irregularity in size and shape of glands, with tiny glands or individual cells invading stroma away from circumscribed masses or solid cords and masses with easily identifiable glandular differentiation within most of them.	Discrete glandular units. Typically smaller glands than seen in Gleason pattern 1 or 2. Infiltrates in and among non-neoplastic prostate acini. Marked variation in size and shape. Smoothly circumscribed small cribriform nodules of tumour.
4	Large clear cells growing in a diffuse pattern resembling hypernephroma; may show gland formation.	Fused microacinar glands. Ill-defined glands with poorly formed glandular lumina. Large cribriform glands. Cribriform glands with an irregular border. Hypernephromatoid.
5	Very poorly differentiated tumours; usually solid masses or diffuse growth with little or no differentiation into glands.	Essentially no glandular differentiation composed of solid sheets, cords, or single cells. Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses.

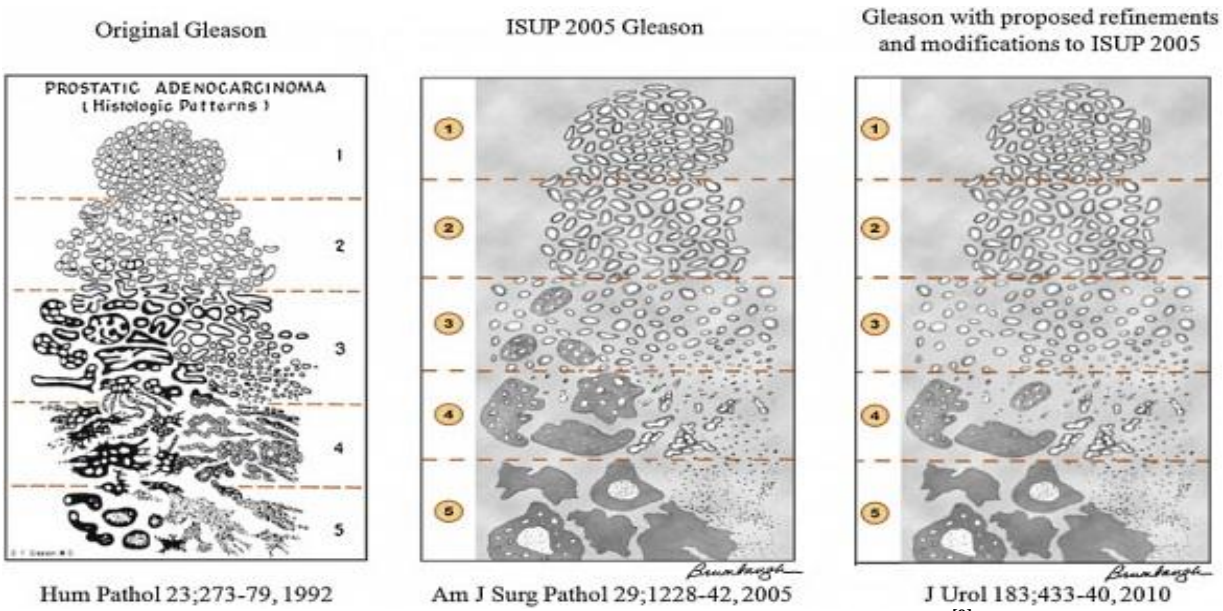

Fig 1 – Schematic representations of Gleason grading systems[9]

The biopsy Gleason score is a sum of the primary grade (representing the majority of tumor) and a secondary grade (assigned to the highest grade), and is a number ranging from 2 to 10. The higher the Gleason score, the more aggressive the tumor is likely to act and the worse patient`s prognosis.[7]

Gleason score	Type of tumor
2 – 4	Well differentiated tumor
5 – 7	Moderately differentiated tumor
8 – 10	Poorly differentiated tumor

Gleason scores of 2-4 should not be attributed to prostatic adenocarcinoma on needle biopsies. Recommended lowest Gleason growth pattern that can be assessed in needle biopsies is 3, implying that a Gleason score of 6 is the lowest possible score.[6]

A New Contemporary Prostate Cancer Grading System[10]

Problems with the Current Gleason System:

1) Scores 2-5 are currently no longer assigned and certain patterns that Gleason defined as a score of 6 are now graded as 7, thus leading to contemporary Gleason score 6 cancers having a better prognosis than historic score 6 cancers.
2) The combination of Gleason scores into a 3-tier grouping (6,7,8-10) is used most frequently for prognostic and therapeutic purposes, despite 3+4=7 vs. 4+3=7 and 8 vs. 9-10 having very different prognoses.
3) In practice the lowest score is now assigned a 6, although it is on a scale of 2-10. This leads to a logical yet incorrect assumption on the part of patients that their cancer is in the middle of the scale, compounding the fear of their cancer diagnosis with the belief that the cancer is serious, thus leading to an expectation that treatment is necessary.

Table 2: Histological description of new grading system[10]

Grade group 1 (Gleason score 3+3=6) : Only individual discrete well-formed glands
Grade group 2 (Gleason score 3 + 4 = 7) : Predominantly well-formed glands with lesser component of poorly formed /fused/cribriform glands.
Grade group 3 (Gleason score 4 + 3 = 7) : Predominantly poorly formed /fused/cribriform glands with lesser component of well formed glands [a]
Grade group 4 (Gleason score 8) - Only poorly formed/fused/cribriform glands or - Predominantly well-formed glands and lesser component lacking glands or - Predominantly lacking glands and lesser component of well formed glands [b]
Grade group 5(Gleason scores 9 – 10) : Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands [a]
[a] For cases with > 95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy , the component of < 5% well-formed glands is not factored into the grade. [b] Poorly formed /fused/cribriform glands can be a more minor component

The new grading system for prostate cancer has obvious benefits[10]

1) More accurate grade stratification than the current Gleason system
2) Simplified grading system of 5 as opposed to multiple possible scores depending on various Gleason pattern combinations
3) Lowest grade is 1 as opposed to current practice of Gleason score 6, with the potential to reduce overtreatment of indolent prostate cancer.

The aim of the present study was to categorize the cases of prostatic adenocarcinoma based on New contemporary grading system and to discuss the advantages of New contemporary grading system over old Gleason grading system for prognostic purposes.

MATERIAL AND METHODS

A total of 124 cases of prostatic lesions undergoing multidisciplinary management in Osmania General Hospital, Hyderabad were studied prospectively over a period of 1 year, from May 2015 to April 2016. Samples included were 122 transurethral resection of prostate(TURP) chips, 1 needle core biopsy and 1 radical prostatectomy specimen. Available clinical data including patient age, sex, imaging, surgical findings and details of therapy were recorded. Haematoxylin and Eosin stain was done and slides were reviewed. Cases of benign prostatic hyperplasia and prostatic intraepithelial neoplasia were excluded.

Statistical analysis was done and cases with prostate adenocarcinoma were categorized using New contemporary grading system. Score was calculated as sum of most predominant pattern and next highest grade. Cases were segregated into grade groups based on Gleason scoring.

RESULTS

124 cases of prostatic lesions were received in the department during the study period, of which 16 cases were prostate adenocarcinoma(13%). Age group ranged from 58 years to 85 years with most cases in 70-80 years of age. 12 out of 16 cases(75%) were clinically suspected as benign prostatic hyperplasia and TURP chips were sent, histopathological diagnosis of adenocarcinoma was made in those cases.

Table 3: Categorization of cases into grade group

Grade group	Number of cases (Total-16)	percentage
Group I (3+3)	3	18.75%
Group II (3+4)	2	12.5%
Group III (4+3)	2	12.5%
Group IV	7	43.75%
Group V	2	12.5%

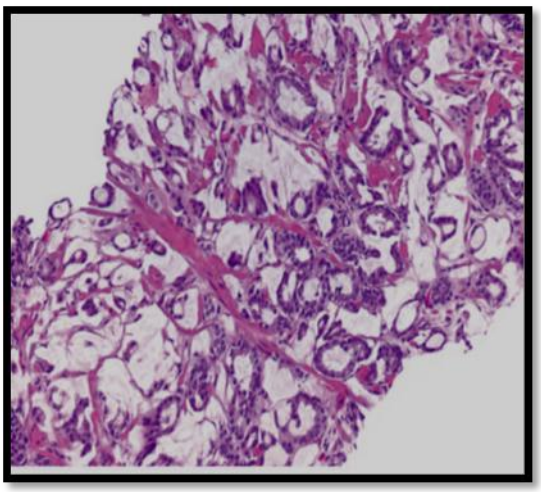

Fig 2: Grade group I – predominantly well formed Glands with Score 3 + 3 = 6

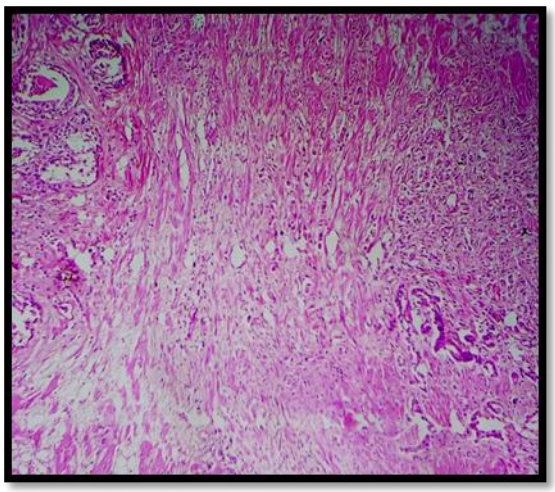

Fig 3: Grade group II – predominantly well formed glands on left side and ill defined glands on right side with score 3+4=7

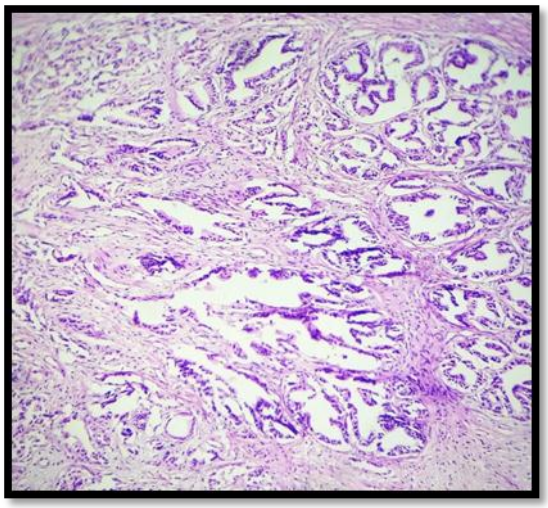

Fig 4: Grade group III- predominantly ill defined glands on left side and well defined glands with variation in size with score 4+3=7

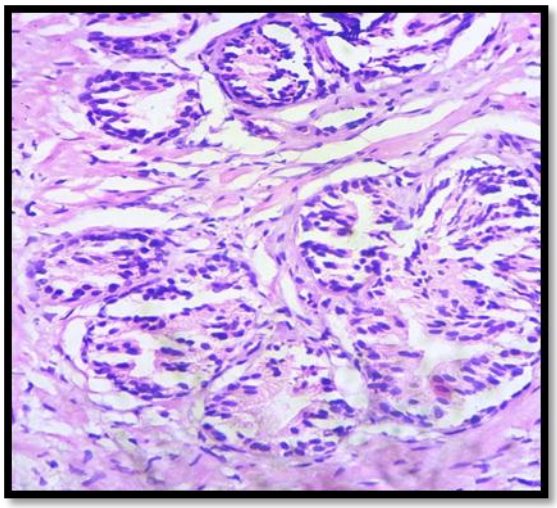

Fig 5: Grade group IV – predominantly fused microacinar and cribriform pattern with score 4+4=8

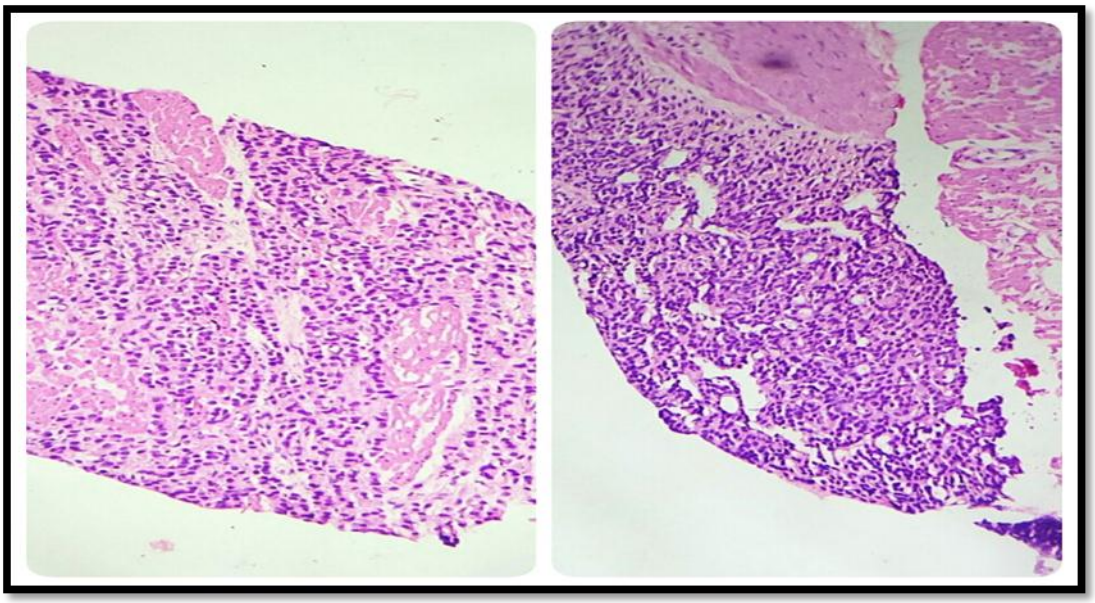

Fig 6: Grade group V – predominant sheet like pattern on left side and ill defined glands with poorly formed lumina with score 5+4=9

DISCUSSION

Prostatism is a common malady in the geriatric age group. Benign prostatic hyperplasia(BPH) and Carcinoma of the prostate are increasingly frequent with advancing age and are uncommon before the age of 40 yrs.[11] In patients with clinically detected nodules, raised PSA, needle biopsy/trucut needle biopsy is an established tool to confirm the diagnosis. It is currently estimated that in United States of America approximately 200,000 new cases are detected every year, of which approximately one fifth prove to be lethal.[12] In India the incidence of carcinoma of prostate is estimated at 8/100,000 persons.[11] The incidence of prostatic disorders increases with increasing age in male population. Mittal et al., in their study comprising of 185 biopsies, reported BPH in 172 (92.97%) cases and carcinoma prostate in 13(7.02%) cases.[13] In the present study, out of 124 cases, 108 cases(87%) were BPH and 16 cases(13%) were adenocarcinoma.

In the study done by Surveillance, Epidemiology, and End Results (SEER) Prostate cancer trends 1973-1995 (1998) 41% of patients had Gleason's score GS 5-7, 23% had GS 2-4 and 21% with GS 8-10.[12] In the study done by Bing – Yirshen et al, there were 46% of carcinoma prostate patients presenting with GS 5-7 and 33.3% with GS 2-4.[14] In the study by A.Josephine et al, 60% of carcinoma cases presented with GS 5-7, 25% with GS 8-10 and 15% with GS 2-4.[15] The present study used New contemporary grading system for categorization, majority of the cases were in grade group IV (7 cases, 43.75%) followed by group I (3 cases, 18.75%) and group II, group III, group V each comprising of 2 cases.

Development of a New Grading System

Many studies categorized cases using old system of Gleasons scoring method. As a result of problems with old Gleason grading system, it has been questioned whether Gleason score 3 + 3= 6 should retain the designation of cancer or be relabeled as indolent lesion of epithelial origin to avoid fear and consequential overtreatment of a proportion of potentially indolent prostate cancers.[16] This is also based on the observations from the two studies showing that using a contemporary grading approach, pure Gleason score 3 + 3= 6 at RP(radical prostatectomies) is incapable of regional lymph node metastasis.[17,18] At RP, pure Gleason score 3 + 3= 6, organ-confined, margin negative disease has an excellent prognosis, with only occasional men demonstrating detectable prostate-specific antigen that may be in part due to the presence of benign glands at the margin and the use of ultrasensitive methods.[19-21]

From a pathologist's viewpoint, Gleason score 6 is still cancer, with many of the same morphologic and even molecular features of higher-grade cancer, a lack of a basal cell layer, and the potential to locally invade.[22,23] Furthermore, whereas pure Gleason score 3 + 3= 6 cancer at RP may be associated with a favorable clinical course, when present on biopsy, upgrading at RP can be seen in 17% to 36% of cases.[24-27] Renaming Gleason score 3 + 3= 6 cancer as an indolent lesion of epithelial origin tumor on biopsy carries the risk that patients on active surveillance will not adhere to long-term follow-up because they have been told they do not have cancer. Rather than renaming Gleason score 3 + 3= 6 cancer as an indolent lesion of epithelial origin tumor, a new grading system for prostate cancer is needed to better align the grades with prognosis.

If one were starting de novo in developing a new prostate cancer grading system, the goal would be a simple system with the least number of grades, each with its own distinct prognosis. The Grade Groups (Table 2)

were originally developed by the senior author of this work in 2013 on the data from 7869 patients who underwent RP at The Johns Hopkins Hospital, Baltimore, Maryland and more recently validated on 20 845 patients from 5 academic institutions.[10] The 5-year biochemical risk-free survivals for the 5 Grade Groups based on RP grade were 96%, 88%, 63%, 48%, and 26%. The 5 Grade Groups were also predictive for biopsy grade followed by RP or radiation therapy.

Benefits of the New Grading System

First, the new grading system provides more accurate grade stratification than current applications of the Gleason system. In clinical practice, Gleason score 7 disease is often considered one grade regardless of pattern composition (3+4 versus 4+3). The most common prognostic classification system used for prostate cancer in clinical practice is the D'Amico/National Comprehensive Cancer Network system, which divides prostate cancer into low-, intermediate-, and high-risk disease. In the intermediate category, one of the criteria is Gleason score 7 cancer. Based on this risk stratification, treatment protocols have been developed without recognizing the extensive literature showing the significantly different prognosis between Gleason scores 3 + 4 versus 4 + 3 prostate cancers.[28-31] Similarly, Gleason scores 8 to 10 are combined together as high-risk disease, despite numerous studies demonstrating that Gleason scores 9 to 10 are associated with a significantly worse prognosis. Having a distinct Grade Group 2 for Gleason score 3 + 4 = 7 and Grade Group 3 for Gleason score 4 + 3 = 7 will prevent combining these two very different prognostic groups of cancer for both prognostic and treatment purposes. Similarly, Grade Groups 4 and 5, representing Gleason score 8 and Gleason scores 9 to 10, respectively, will allow better stratification and foster future studies to determine whether Grade Group 5 cancers need more intensive therapy.

Second, the new grading system is simple, with 5 grade groups as opposed to 25 scores depending on various Gleason pattern combinations. The current Gleason system, with its primary and secondary patterns, is a complicated and nonintuitive grading system, whereas grading systems used for other tumors usually range simply from 1 to 3 (well, moderately, and poorly differentiated), or low to high grade. For nonurologists and patients, the system is confusing and difficult to understand. As patients increasingly have access to their medical records and are becoming more involved in their medical care, men with prostate cancer read their pathology reports and need to understand the terminology better.

Third, the lowest grade in the new system is 1 as opposed to 6 in the Gleason system. There is wide recognition that many Gleason score 6 cancers can be followed with active surveillance. However, active surveillance is still not widely accepted in many parts of the world because of the fear of not being treated definitively for cancer. In addition, a sizable amount of men abandon active surveillance despite favorable clinical and pathologic findings because of this anxiety.[32,33] Compounding this fear is that the lowest grade assigned in the Gleason system is 6 out of a scale of 2 to 10, implying that a 6 is in the middle of the grading scale in terms of aggressiveness.[34] In talking to patients on a daily basis, we have had to reassure numerous men that their Gleason score 6 cancer is the lowest grade possible. In addition, some patients with Gleason score 3 + 4 = 7 had thought they were going to die in the near future because their score of 7 was closer to highest grade of 10 than the lowest grade of 2. With the new grading system, patients can be reassured that they have a Grade Group 1 out of 5, which is the lowest grade, or a Grade Group 2 out of 5, which is still a relatively low grade.

There has been some confusion and controversy in the recent literature regarding the name of the new system. As noted earlier, the new grading system was first described in 2013 by work done at The Johns Hopkins Hospital by the senior author and was verified by a large multi-institutional study led by the same author, both prior to the 2014 consensus conference. The new system was termed Grade Groups. This new grading system has been accepted by the World Health Organization (WHO) for the 2016 edition of Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs.[34]

CONCLUSION

Gleason score continues to be the single most powerful predictor of prostate cancer prognosis and plays a significant role in clinical management. As the clinical field of prostate cancer has changed dramatically during the last few decades, so too has the grading of prostate cancer. These changes will enable clinicians to better manage prostate cancer patients, which is the ultimate goal of any grading system. The correct diagnosis and grading of prostate cancer is crucial for a patient's prognosis and therapeutic options. The 2005 and 2014 ISUP grading consensus conferences have improved the overall Gleason grading system. The enormous progress in molecular diagnostic applications is expected to have significant impact on the existing diagnostic and prognostic algorithms for prostate cancer, but it is unlikely that these new techniques will be able to replace the Gleason grading system. Instead a symbiosis between the existing and new diagnostic techniques might lead to the greatest benefit for patients with prostate cancer.

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