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Collaborative Review – Prostate Cancer

Contemporary Grading for Prostate Cancer: Implications for Patient Care

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Abstract

Context: The Gleason grading system is one of the most powerful predictors of outcome in prostate cancer and a cornerstone in counseling and treating patients. Since its inception, it has undergone several modifications triggered by a change in clinical practice and a better understanding of the cancer's histologic spectrum and variants and their prognostic significance.
Objective: To provide an overview of the implementation and the impact of the Gleason system as a predictive and prognostic tool in all available treatment modalities, and to compare the original and modified Gleason systems in major pathologic and clinical outcome data sets.
Evidence acquisition: A comprehensive nonsystematic Medline search was performed using multiple Medical Subject Headings such as *Gleason, modified, system, outcome, biopsy, prostatectomy, recurrence, prognosis, radiotherapy*, and *focal therapy*, with restriction to the English language and a preference for publications within the last 10 yr. All Gleason grade–related studies in the last 3 yr were reviewed. For studies before this date, we relied on prior culling of the literature for various recent books, chapters, and original articles on this topic.
Evidence synthesis: Using the modified grading system resulted in disease upgrading with more cancers assigned a Gleason score $\geq$7 than in the past. It also resulted in a more homogeneous Gleason score 6, which has an excellent prognosis when the disease is organ confined. The vast majority of studies using both systems showed that Gleason grading of adenocarcinomas on needle biopsies and radical prostatectomies was strongly associated with pathologic stage, status of surgical margins, metastatic disease, biochemical recurrence, and cancer-specific survival, with the modified system outperforming the original one in some large series. A description of the continuous incorporation of this parameter in the clinical decision making for treating prostate cancer using all currently used treatment modalities is presented, and the findings of studies before and after the inception of the modified grading system, if available, are compared. The proposed contemporary grading prognostic categories are 3 + 3, 3 + 4, 4 + 3, 8, and 9–10.
Conclusions: The Gleason score is one of the most critical predictive factors of prostate cancer regardless of the therapy used. Modernization of the Gleason grading system has resulted in a more accurate grading system for radical prostatectomy (RP) but has complicated the comparison of data before and after the updating. A better prognostication with the updated Gleason grading system for patients treated with modalities other than surgery can only be postulated at this time because there are limited conflicting data on radiation and no studies on other treatment modalities. Its greatest impact is the uniformly excellent prognosis associated with Gleason score 6 in RPs.

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1. Introduction

In 1966, Gleason created a unique grading system for prostatic adenocarcinoma based solely on architectural pattern using a five-tier scale in which the sum of the two most common grade patterns (grades) defined the final Gleason score (GS) of a given case. From its inception and up to the present, the Gleason system has proven to be the most dominant prognostic pathologic factor due to its correlation with disease stage, biochemical and clinical recurrence, and disease-specific survival, and it is therefore one of the cornerstones in counseling and treating patients with prostate cancer [1].

The nature of prostate cancer has changed dramatically since the original grading system was implemented. Many patients in the 1960s or 1970s did not undergo radical prostatectomy (RP) due to presentation with advanced disease and the greater morbidity of the procedure, so Gleason did not discuss grading RPs with multiple tumor foci and tertiary patterns. With the advent of prostate-specific antigen (PSA) screening and multiple 18-gauge needle biopsies, new grading issues arose, such as how to grade multiple cores with carcinoma of different grades and how to grade small foci of cancer. In addition, pathologists required guidance for grading newly described histologic patterns and variants of prostatic adenocarcinoma. Therefore, modification of the original Gleason grading system was needed to reflect the challenges of modern practice, which led to the implementation of the modified (updated) system at the 2005 International Society of Urological Pathology Consensus Conference [2].

In this review we provide an overview of the implementation and the impact of the Gleason system as a predictive and prognostic tool in all available treatment modalities. We also compare the original and modified Gleason systems in major pathologic and clinical outcome data sets.

2. Evidence acquisition

A comprehensive nonsystematic Medline search was performed using multiple Medical Subject Headings such as *Gleason, modified, system, outcome, biopsy, prostatectomy, recurrence, prognosis, radiotherapy*, and *focal therapy*, with restriction to the English language and a preference for publications within the last 10 yr. All studies related to Gleason grade in the last 3 yr were reviewed. For studies before this date, we relied on prior culling of the literature for various recent books, chapters, and original articles on this topic. Efforts were made to include major studies comparing the performance of the original and modified Gleason grading system, and a comparison of data before and after 2005 was undertaken whenever available.

3. Evidence synthesis

3.1. Updated Gleason grading system

Updating the Gleason grading system, which officially took place at the International Society of Urological Pathology (ISUP) consensus meeting in 2005, has had a significant impact on the reporting of prostatic adenocarcinoma, especially in the context of needle biopsies. It has refined the criteria of different Gleason patterns and is expected to increase the likelihood of improving interpretive interobserver reproducibility [3]. It also established clear recommendations on the reporting of limited secondary patterns of lower or higher grades, as well as the grading of variants of adenocarcinomas [2,4]. Dominant tumor nodules would be graded separately in the final prostatectomy specimens. Importantly, the guidelines for reporting tertiary patterns were clearly defined. It was decided that in needle biopsy cores containing three patterns in which the highest pattern was the least predominant, the highest pattern should be reported as the secondary grade regardless of its percentage.

The most clinically relevant change was to limit the definition of pattern 3 and widen the scope of pattern 4 carcinoma, which resulted in disease upgrading. This being said, although the newly defined category of *poorly formed gland* of Gleason pattern 4 is well accepted and increasingly used consistently among pathologists, the potential margin of interobserver variability may be in differentiating true poorly formed glands from tangentially cut glands of Gleason pattern 3 that some pathologists may interpret as pattern 4. This issue has not been addressed in major studies yet; however, in biopsy cases with borderline pattern 3 versus 4, a prudent tendency would be to keep the pattern as 3 because potential undergrading due to sampling error is more acceptable than overgrading due to grading error.

With regard to cribriform glands, the participants at the 2005 consensus conference agreed that rare rounded well-circumscribed glands that are the same size as benign glands and that show evenly spaced lumina and cellular bridges of uniform thickness are Gleason pattern 3. However, at the time of the meeting, virtually no cases satisfied these criteria when examples were shown to the participants. In a subsequent study involving 10 well-known uropathologists, it was substantiated that the diagnosis *Gleason cribriform pattern 3* virtually does not exist in practice [5]. In routine practice, cribriform glands—regardless of their size—are nearly always considered pattern 4 [6] (Fig. 1). These findings fit conceptually because one would expect the change in grade from pattern 3 to pattern 4 to be reflected in a distinct architectural paradigm shift wherein cribriform as opposed to individual glands are formed rather than reflected merely in a subjective continuum of differences in the size, shape, and contour of cribriform glands.

The only reason why cribriform pattern 3 even exists is because of the original Gleason schematic diagram. Gleason never specifically published the prognostic difference between what he called cribriform Gleason pattern 3 compared with Gleason pattern 4. Many of Gleason's cribriform Gleason pattern 3 cancers may not even have been infiltrating carcinomas due to the lack of availability of immunohistochemistry for basal cell markers. Today we might have diagnosed them either as cribriform high-grade prostatic intraepithelial neoplasia or intraductal carcinoma of the prostate (concepts unknown in Gleason's era).

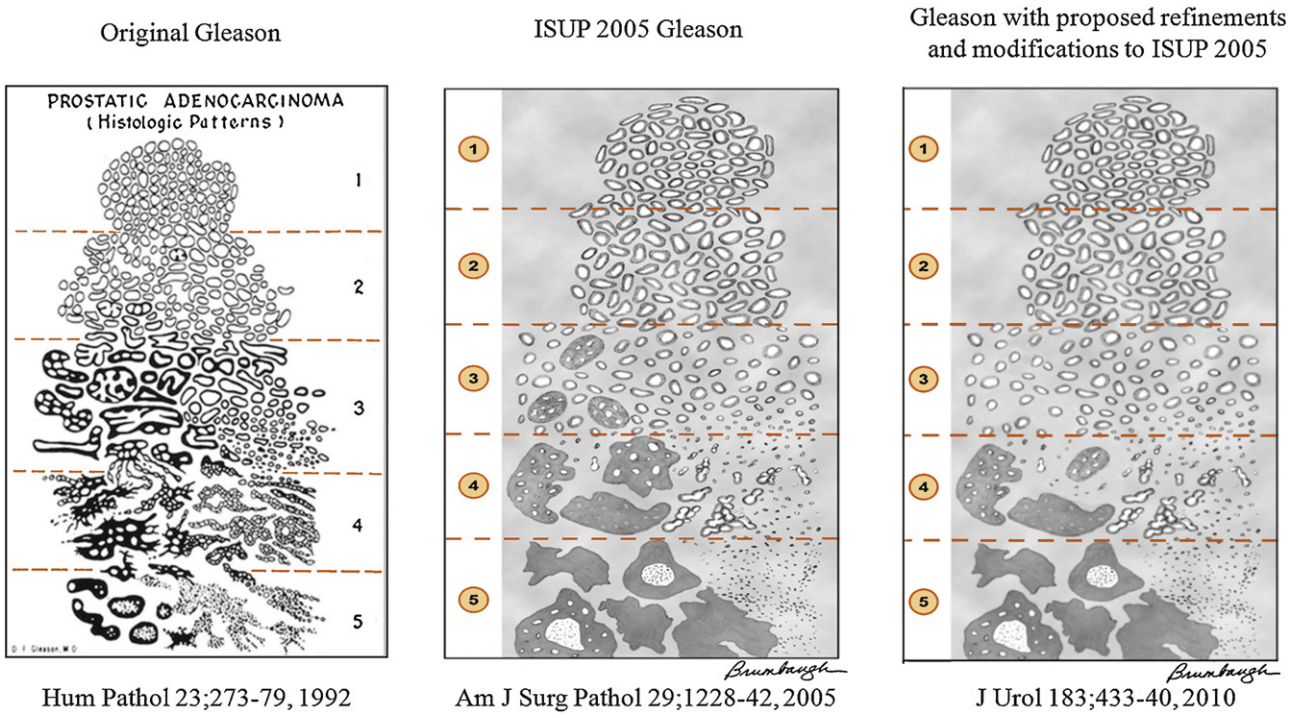

Fig. 1 – Schematic representations of Gleason grading systems. The most important changes between them are in patterns 3 and 4. In the modified system, most cribriform patterns and also poorly defined glands are included in pattern 4. In the currently used system, all cribriform glands are included as pattern 4.

Testing the validity of the modified system requires large cumulative data about its correlation with patients' outcome, and very few studies have addressed this issue mainly due to short follow-up periods since the inception of the modified system in 2005. However, in a recent large study including 806 RPs performed between1993 and 1999, cases assigned a GS of 3 + 3 or 3 + 4 using the original grading system were retrospectively reassigned a grade according to the modified system [7]. In that study, 34% of cases (210 of 622) originally diagnosed as GS 6 were regraded as GS $\geq$7 with the vast majority of those reassigned a grade 3 + 4. In comparison, 26% of patients (48 of 184) originally assigned a GS 3 + 4 were considered to be either 4 + 3 or 4 + 4 on review. Compared with the classic scoring system, the modified system results in a better correlation with pathologic stage, rate of positive margins, and biochemical recurrence with GS the only independent predictor of the development of metastatic disease [7]. The contemporary group of cancers with GS 6 is therefore a homogeneous group associated with a better prognosis than GS 6 tumors under the original system, which included mixed cases of what today would be diagnosed as GS 7. In addition, cases in the past graded as Gleason 2–5 are currently considered Gleason 6, further contributing to a better prognosis. The false impression that survival rates have improved, when in fact much of the changes are due to changes in classifications, is referred to as the *Will Rogers phenomenon* [8]. Other factors may have also contributed to the observed change in survival rates and include overtreatment of men with minimal cancers coming to clinical attention and the lack of sufficient follow-up time in most large studies using the contemporary Gleason grading system.

Another implication of the change in the grading system is in relation to patients with high-grade tumors (GS 8–10). Those patients traditionally were discouraged from undergoing surgery due to the high likelihood of locally advanced or even systemic disease at presentation. However, a number of more recent studies have suggested that men with high-grade tumors may do better than previously thought with surgery [9]. Therefore the tendency toward upgrading may be balanced by an increasing trend to perform surgery in the context of high-grade disease [10]. The change in the Gleason grading system makes it difficult to compare data sets of prostate cancer patients that span the time when grade modifications were implemented.

3.2. Relation of Gleason grade in needle biopsy to pathologic features in radical prostatectomy

Biopsy Gleason grade has been incorporated in several models predicting findings in RPs. The two most commonly used are the Partin tables and the Kattan nomogram. It has become common practice to integrate the highest GS in a core rather than the most common GS in such predictive models. Such practice was initiated by two studies. The first study showed that when a core had GS 4 + 4 while the rest of positive cores were GS $\leq$7, the pathologic stage at RP was comparable with cases in which all cores have a GS of 4 + 4 [11]. In a similar fashion, the second study showed that the highest GS of a biopsy correlated best with the final GS on RP

[12]. Two additional studies corroborated these findings [13,14]. Worth mentioning here is that the interpretation of the relationship between biopsy and RP GS in the contemporary era should take into account the presence of tertiary patterns either in the biopsy or RP that may result in a false impression of undergrading or overgrading of RP GS in relation to the biopsy, a factor that most related studies do not account for [15]. In a recent study including 7643 RPs and their corresponding biopsies in which the modified Gleason system was used for grading, 36.3% of cases were upgraded from a needle biopsy GS 5–6 to a higher grade at RP, and a biopsy GS 8 led to an almost equal distribution between RP GS 4 + 3 = 7, 8, and 9–10. Interestingly,12.4% and 3.6% of cases had biopsy GS 3 + 4 = 7 and GS 4 + 3 = 7, respectively, with GS 6 plus tertiary 4 (<5%) at RP. If the tertiary pattern 4 at RP was not recorded, the explanation would have been overgrading of the biopsy as opposed to the biopsy sampling of a small component of Gleason pattern 4. Similarly, 18.5% of cases with biopsy GS 9–10 had RP with GS 3 + 4 or 4 + 3 with tertiary pattern 5; these cases would have been explained as due to pathology overgrading the biopsy had the tertiary pattern 5 in the RP not been recorded [16].

In the original Partin tables that were constructed based on clinical stage, biopsy GS, and serum PSA levels, biopsy GSs were subdivided into the categories 2–4, 5–6, 7, and 8–10. The tables predicted organ-confined disease, seminal vesicle invasion, and lymph node metastases [17]. In the 2007 updated version, the biopsy GS categories were reclassified into 5–6, 3 + 4, 4 + 3, and 8–10 (GSs 2–4 were eliminated and should no longer be assigned in biopsies). In a contemporary cohort including 1781 men with biopsy GS 7, in comparison with cases with GS 3 + 4, those with GS 4 + 3 had an increased risk of cancer extension beyond the prostate (40.1% vs 34.8%) as well as seminal vesicle invasion/lymph node metastases (12.1% vs 8.2%), independent of serum PSA levels, number of positive cores, and highest percentage of involved cores [18]. Finally, in a reflection of recent data showing that patients with GS 9–10 have a significantly increased risk of advanced disease and lymph node metastases on RP in comparison with GS 8, the newest Partin tables are expected to further divide cases of GS 8–10 into two categories: 8 and 9–10 [19].

In contrast, the Kattan nomogram incorporates serum PSA, age, GS, clinical stage, and fraction of positive core and predicts pathologic stage as well as the side of extraprostatic extension with good accuracy [20]. Similar to the Partin tables, within the group of GS 7, a GS 4 + 3 is weighed differently than GS 3 + 4. Cancer of the Prostate Risk Assessment (CAPRA) is another less commonly used risk assessment tool that includes PSA, age, clinical stage, GS, and fraction of positive cores. In that system, GS is divided into three categories: 2–6, 3 + 4/3 + 5, and the primary pattern 4/5, with the latter category given an excessive weight equaling that given for PSA levels >20 ng/ml [21]. Of note is that the Kattan nomogram and CAPRA were published before the implementation of the modified Gleason grading system that precludes comparison of the performance of those two predictive models using the original and modified systems.

Finally, while the traditional D'Amico risk stratification categories use the traditional GS 6, 7, and >7 as one parameter along with clinical stage and PSA levels to define low-, intermediate- and high-risk cancer, similar models factoring in more accurate Gleason grades using the modified system do not yet exist. It is plausible that incorporating the modified Gleason grading system into a multiparametric easily usable predictive model including PSA and clinical stage would increase the accuracy of the modified Gleason system as a prognosticator.

In addition, and in an effort to minimize unnecessary resections of neurovascular bundles in individual cases, algorithms and nomograms that include biopsy GS and other presurgical parameters were developed to predict the side of extraprostatic extension. In that regard, the Ohori et al. nomogram is one of the highly accurate models that were validated in large contemporary cohorts of patients in which the highest GS of each side is incorporated separately in the model [20].

Finally, a large recent study looking at the correlation between pathologic stage and the conventional and modified Gleason grading systems showed significant changes in stage distribution among cases with GS 7, whereas pT2 was the most common (54%) using the modified system, pT3 (37%) predominated using the original system [22]. There was a dramatic difference in stage when comparing cases with GS 3 + 4 (pT2 in 95%) versus those with GS 4 + 3 (pT3/4 in 79%). This probably reflects the higher number of cases diagnosed as GS 3 + 4 on RP due to the inclusion of some cases previously considered GS 6 in the 3 + 4 category using the modified Gleason system [22]. If we assume that the disease has not changed over time but just how we grade has changed, GS 7 is more often associated with pT2 disease in current practice because it includes cases that would have been called GS 6 in the past. The practical aspect is that patients with GS of 3 + 4 = 7 on biopsy have more favorable disease at RP and can be counseled regarding their more favorable outcome.

3.3. *Relation of Gleason grade to the risk of progression following radical prostatectomy*

Knowing the likelihood of surgical cure using preoperative data is extremely important to guide clinicians about whether surgery should be considered as the primary treatment modality. Therefore, the biopsy GS has been incorporated into preoperative nomograms that predict the risk of biochemical recurrence. The Stephenson et al. model and the Johns Hopkins Han et al. table are such examples that include preoperative PSA, biopsy GS, and clinical stage [23,24].

Several studies have demonstrated that the correlation between GS on needle biopsies and the risk of biochemical recurrence was significantly higher using the modified grading system in comparison with the original one [25,26]. In the study by Uemura et al. [25] that included 103 patients with a clinical stage T1–2N0M0, using the modified grading system there was upgraded cancer between biopsy and RPs in 15.6% of cases compared with 20.4% using the original Gleason

system. In addition, stratifying cases to three groups based on the biopsy grade (≤6, 7, and ≥8) showed that grade was strongly associated with biochemical recurrence (defined by increased PSA to >0.2 ng/ml) only when the modified system was used [25]. There are more limited conflicting data with the updated system following radiation.

However, a study by Delahunt et al. [27] reported that the original system outperformed the modified one in predicting PSA nadir following external-beam radiation therapy (EBRT) and hormone therapy. That study is limited, however, by its inclusion of only locally advanced cancer cases and its consideration of the PSA nadir as a clinical end point for predicting recurrence following radiotherapy [27].

Although models based on needle biopsy findings carry useful outcome prognostic data, more accurate information about the risk of progression post-RP is usually obtained from pathologic data from the RP. An analysis of a cohort of 2404 RPs with a mean of 6.3-yr follow-up showed RP GS to be a significant predictor of recurrence independent from pathologic stage and surgical margins status. In that study, RP GS prognostic categories were 6, 3 + 4, 4 + 3, and 8–10 [24]. Similar observations were derived from the Kattan nomogram in which the risk of recurrence increases with higher RP GS (GS categories of 2–6, 3 + 4, 4 + 3, 8, 9, and 10) independently from other pathologic parameters [28]. One of the consequences of the modified Gleason system is homogenization of GS 6, where organ-confined adenocarcinoma with GS 6 (without tertiary pattern 4) virtually never progresses when the modified system is used in RPs, in contrast to rare progressions using the original grading system [29].

Using the modified Gleason system, a study from the Johns Hopkins Hospital correlated biopsy and RP GS with pathologic stage and biochemical recurrence in 6462 men [30] (Table 1). In this study, almost 95% and 97% of patients with GS 6 cancer at biopsy and RP (no tertiary pattern 4 at radical prostatectomy), respectively, did not show signs of biochemical recurrence at 5 yr following RP. Using the modified Gleason system, this study showed that a GS 3 + 4 = 7 tumor has a very favorable prognosis with an estimated 5-yr biochemical-free survival of 83% and 88% for biopsy and RP, respectively.

Table 1 – Biochemical recurrence at 5 yr stratified by biopsy and radical prostatectomy Gleason score

Biopsy Gleason score	Relative risk	Recurrence-free risk, %
2–6	1	94.6
3 + 4	2.2	82.7
4 + 3	4.7	65.1
4 + 4	7.6	63.1
9–10	12.6	34.5
RP Gleason score	**Relative risk**	**Recurrence-free risk, %**
2–6	1	96.6
3 + 4	2.6	88.1
4 + 3	4.4	69.7
4 + 4	8.5	63.7
9–10	12.7	34.5

RP = radical prostatectomy.
Overall model is $p < 0.0001$. Adapted from Pierorazio et al. [30].

Within the category of adenocarcinoma with GS 7, numerous studies have demonstrated that patients with cancer of GS 4 + 3 have a worse prognosis than those with a score of 3 + 4 both in needle biopsies and RPs [31–33]. Furthermore, a patient with a GS 9–10 tumor had almost twice the risk of progression compared with GS 8. An accurate grouping of GSs can be accomplished with five Prognostic Grade Groups, as opposed to the nine individual GSs. Oversimplification of the Gleason grade classification, such as combining GSs 8–10 or classifying patients into low-, intermediate-, and high-risk categories based on a GSs <7, 7, and >7, loses critical prognostic information. A problem with the current system is that GS 6 is typically the lowest grade assigned on biopsy material. However, the Gleason scale ranges from 2 to 10, so consequently patients are unduly concerned when told they have GS 6 cancer on biopsy, logically but incorrectly assuming their tumor is in the midrange of aggressiveness. In reporting grades on biopsy and RP, in addition to reporting the individual GS, Prognostic Grade Groups could be added using the grades 3 + 3, 3 + 4, 4 + 3, 8, and 9–10. For example, patients will be reassured that when diagnosed with a GS 6, their Prognostic Grade Group is I of V, not a GS score 6 of 10. The same would apply for a GS 3 + 4 = 7 tumor where the Prognostic Grade Group (II) is in line with its relatively less aggressive behavior. At the other end of the grade spectrum, men with either a GS 9 or 10 tumor will more accurately be considered to have more aggressive tumors than those with GS 8, which can be factored into their management.

As a modification to the Gleason system, recording of the percentage of pattern 4/5 on transurethral resections, biopsies, and RPs has been proposed because this pattern has been shown to be a good predictor of cancer progression postsurgery [34–37]. However, the percentage of pattern 4/5 seems to be very predictive only for prognosis in RP specimens at the extremes of the percentages [35]. Further large studies are warranted before drawing definitive conclusions on the prognostic significance of recording the percentage of patterns 4/5. Notably, although tertiary grades in RPs have an impact on biochemical-free recurrence, it is unclear whether tertiary grades are independently predictive once all the other parameters available from the RP pathology are factored in.

RP GS has also been used to predict the risk of metastases following recurrence. In a study including 450 patients with a mean follow-up of 8 yr, the risk of metastases at 10 yr was 6%, 48%, and 81% for RP GSs of 6, 7, and 8–10, respectively [38]. In addition, in the setting of patients primarily treated with radiotherapy that subsequently develop local recurrence and are considered for salvage RP, presurgical GS can be used to assess the risk of progression postoperatively. In this context, the most favorable group is composed of patients with presalvage RP PSA <4 ng/ml and a postradiation biopsy GS ≤7 [39].

It has been recently demonstrated that the GS of cancer present at the positive margin carries in itself a prognostic

impact independent from the case final GS or the extent/length of positive margins. A large study noting this association is that of Brimo et al. [40] in which a homogeneous group of men with RP GS 7 and positive surgical margins had significantly different rates of biochemical recurrence when compared based on the grade of cancer present at the margin (3 + 3 vs 3 + 4 vs 4 + 3/4 + 4). These findings were substantiated in a study by Cao et al. where among patients with GS $\geq$7, those with a higher GS of the tumor at the margin had a higher likelihood of a biochemical recurrence than those with a lower GS [41]. Pathologists are currently encouraged to record this information in their RP reports.

3.4. Brachytherapy, external-beam radiation therapy, and supplemental androgen-deprivation therapy

Much of the radiation literature is based on the D'Amico risk group classification in which low-, intermediate-, and high-risk groups are defined based on biopsy GS (6 vs 7 vs 8–10), preoperative PSA, and clinical stage [42]. The modification of the Gleason system would ultimately lead to an improvement in the results of the low-risk group because some of the cases previously assigned GS 6 would be considered GS 7 in the contemporary era.

Brachytherapy is generally accepted as monotherapy in the low-risk group with GS 6, in which it was shown that long-term biochemical control averaged 90% at 12–15 yr posttreatment [43]. Brachytherapy in the intermediate-risk category with GS 7 can also be used in several ways: (1) low-dose brachytherapy plus EBRT, (2) high-dose brachytherapy plus EBRT, (3) high-dose brachytherapy as monotherapy, and (4) low-dose brachytherapy as monotherapy. The latter is recommended by some experts only in a subset of patients depending on clinical stage, serum PSA, biopsy GS, extent of cancer on biopsy, and the presence or absence of perineural invasion [44]. When brachytherapy is used to treat high-risk category patients, high doses are usually used, and a combination with hormonal therapy and EBRT is typically given [45].

Several studies have shown biopsy GS to be more influential than clinical stage and PSA in predicting biochemical recurrence, distant metastases, and cancer-specific survival following brachytherapy [46,47]. The biochemical-free risk of recurrence at 12 yr following brachytherapy was reported as 98.2%, 94.9%, and 89.6% for GS 6, 7, and 8–10, respectively [46]. In comparison, another large study showed the 10-yr disease-specific survival for patients receiving brachytherapy as a primary treatment to be in the range of 98% for biopsy GS 6, 91% for GS 7, and 92% for GS 8–10 [47].

Similar to brachytherapy results, the 10-yr recurrence-free survival rates and the 10-yr metastases-free rates following EBRT were lower with increasing risk groups (81% and 100% for the low-risk group, 78% and 94% for the intermediate-risk group, and 62% and 90% for the high-risk group, respectively) [48]. A study reporting the outcome of a high-risk group of patients treated with high-dose ERBT and supplemental androgen-deprivation therapy (ADT) demonstrated that of the three unfavorable parameters (GS 8–10, PSA >20 ng/ml, and clinical stage T3), GS was the only factor to correlate independently with cancer-specific survival [49].

Several studies have demonstrated the adverse prognostic impact of Gleason pattern 5 in the high-risk group with cases with Gleason pattern 5 on the biopsy having higher rates of recurrence, metastasis, and cancer-specific deaths than those without Gleason pattern 5 [50]. Patel et al. demonstrated that biochemical recurrence post-EBRT with or without ADT is similar in biopsy with GS 8 and in those of GS 7 and tertiary pattern 5, highlighting the prognostic impact of pattern 5, even if present to a limited extent [51]. In that study the updated GS derived by adding the *most common and highest Gleason patterns* correlated better with biochemical failure as opposed to the original Gleason system that adds *the most common and second most common patterns* [51]. Consequently, pathologists are advised to include Gleason 5 as a secondary grade in biopsies in which it represents the least predominant pattern. These data indicate that GS 8–10 should not be regarded as a homogeneous group of cases with GS 9–10 carrying a worse outcome than GS 8 [50,52].

However, a conflicting study by Delahunt et al. [27] reported that the original system outperformed the modified one in predicting PSA nadir following EBRT and hormone therapy. That study is limited by inclusion of only locally advanced cancer cases and to consideration of PSA nadir as a clinical end point for predicting recurrence following radiotherapy [27].

ADT is mostly used in high-risk patients for whom the recommended treatment is a combination of radiation therapy and ADT [53]. In this group, some studies have shown that the benefit of ADT in terms of biochemical recurrence, metastases, and cancer-specific survival only applies to the subset of cases with GS 8–10 and Gleason pattern 5 but not with GS $\leq$7 [50]. In comparison, it is controversial whether ADT is beneficial in intermediate-risk disease [53]. The decision of its use as well as the application modality (neoadjuvant, concurrent, or short-term adjuvant) in this group of patients is usually individualized based on the estimated risk of having more adverse disease [53]. ADT is not the recommended treatment for patients falling in the low-risk category.

3.5. Active surveillance

Due to the earlier detection of cancer, active surveillance is increasingly used in managing older patients with comorbidities and a high likelihood of harboring insignificant cancer at RP (defined as organ-confined cancer with GS $\leq$6 and tumor volume <0.5 cm^3) [54]. Deciding when to include individual patients in an active surveillance program and subsequently determining the need for definitive therapy if more substantial disease is detected on repeat biopsies relies heavily on the GS of the biopsy cancer.

Most programs adhere to either the Epstein biopsy criteria, which define very-low-risk cancer (no Gleason pattern 4/5, one to two cores involved, and $\leq$50% core

involvement), or the D'Amico low-risk category definition as selection criteria and therefore exclude patients with GS ≥7 as candidates for active surveillance with rare exceptions [54–56]. In addition, most programs use an increase in GS to ≥7 on repeat biopsy as one of the parameters in recommending definitive therapy in men on active surveillance. Whether an increase in the GS of a biopsy in such situations represents disease progression or an originally unsampled high-grade component remains debatable, although the latter is favored based on the study by Sheridan et al. [57]. Among patients with GS 6 who were actively followed by yearly repeat biopsies, only 19% progressed in grade in the first 3 yr of follow-up with most of the grade changes occurring soon after the initial biopsy, suggesting that sampling issues rather than true dedifferentiation accounted for most of those so-called upgraded cases.

Tosoian et al. [58] recently reported the outcome of 769 men in the Johns Hopkins Active Surveillance Program. In that cohort, 30.6% of men demonstrated biopsy reclassification of which 45.1% (13.8% of the entire cohort) were reclassified based on GS upgrading (6 to ≥7). Although most were upgraded in the first 2 yr of follow-up, some were upgraded at longer follow-up periods, indicating that true grade progression or the emergence of a separate focus of high-grade cancer is possible. There was no difference in the rate of GS upgrading on repeat biopsies when comparing patients with very low-risk versus low-risk cancer categories [58]. Of note is that using the modified Gleason scoring system by homogenizing the GS 6 group intuitively makes active surveillance safer in the current era compared with the older system.

3.6. Cryosurgery

Although cryoablation of the prostate was traditionally used as salvage therapy following recurrence postradiotherapy, it is now increasingly used as a primary treatment modality. In a large study by Jones et al. [59] of 1198 patients treated initially by cryotherapy, patients tended to have a high clinical stage (with T2a as a median) and higher biopsy GSs (median: 7). Biopsy GS correlated with the risk of postcryosurgery biochemical recurrence [59]. In a salvage setting in which cancer recurs post-radiotherapy, cryotherapy is increasingly used in the subset of patients who are thought to experience a local recurrence only (versus systemic/micrometastatic disease) and who might benefit most from a salvage local therapy. In that regard, a nomogram predicting the risk of biochemical recurrence postcryotherapy was developed based on a multi-institutional large group of patients. Serum PSA, GS on initial biopsy (≤7 vs >7), and clinical stage at diagnosis were the predictive factors for recurrence [60]. A conflicting study of 183 patients correlated presalvage cryotherapy findings with a clinical bifecta as an end point (ie, achieving nadir postcryotherapy PSA levels of <0.6 ng/ml and the absence of urinary incontinence); the two groups with favorable and unfavorable outcomes did not differ in terms of their precryotherapy biopsy findings (about 84% with GS ≤7 in both groups) [61]. Cryotherapy does not alter the morphology of cancer, such that residual/recurrent carcinoma in a postcryotherapy biopsy can be assigned a GS.

3.7. High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) is not yet considered standard therapy for localized prostate cancer. It has been increasingly used in some centers in Europe, however, for men who are not candidates for surgery due to their advanced age or the presence of comorbidities precluding surgery. In one of the largest studies by Crouzet et al. [62] including 803 patients, biopsy GS was not a strict factor in patient selection for HIFU therapy, although most patients had GS 6 (63.5%) or 7 (30.1%). In this study, only pre-HIFU PSA levels and biopsy GS were significantly linked to post-HIFU disease progression. A biopsy GS ≥8 was significantly associated with progression in comparison with a GS ≤7 [62]. An article published in 2008 reviewing the HIFU-related literature reported that about 60% of patients where HIFU was used had a biopsy GS <7, indicating that HIFU as a primary treatment modality is in general not used for high-grade cancer [63]. Based on comparative correlation between different clinicopathologic variables and the rate of progression/recurrence post-HIFU, the authors recommended that the ideal candidates for HIFU are those ≥70 yr of age, T1–2N0M0, a GS <7, a PSA <15 ng/ml, and a prostate volume <40 ml [63].

Studies comparing the biopsy findings pre- and post-HIFU are scarce. A large study clearly demonstrates that HIFU does not alter the morphology of cancer; therefore, when cancer is detected on a biopsy post-HIFU, a Gleason grade can always be accurately assigned to it [64]. This is in contrast to radiotherapy or hormonal therapy, in which treatment effect can result in significant morphologic changes on cancerous tissue making the tumor's grade artifactually look higher than the pretreated tumor, which precludes proper grade assignment in some cases.

3.8. Focal therapy

Focal therapy in which cryotherapy, HIFU, photodynamic therapy, or radiation therapy is used is a newly emerging strategy that aims to treat the affected area of the prostate (half of the prostate or less) in presumably unilateral disease. In the future, this therapeutic approach may occupy a role in between current standard surgery and irradiation that overtreat some men with low-risk disease and active surveillance that risks undertreatment of some men. However, there are no standard criteria for the enrollment of patients in focal therapy programs. The most restrictive inclusion criteria is from the International Task Force on Prostate Cancer and the Focal Lesion Paradigm in which the pathologic criteria include a minimum of 12-core sampling and the absence of any Gleason pattern 4/5 in addition to other histologic, clinical, and imaging criteria [65]. One of the opinions surfacing in a recent large clinicopathologic North American and European consensus meeting was that patients with Gleason pattern 4 are still eligible for focal therapy, as long as pattern 4 is not the dominant pattern [66]. Along

those lines, the El Fegoun et al. group used HIFU-based hemiablation therapy in treating patients with three or fewer positive cores of the same lobe with cancer of GS $\leq$3 + 4. They report 5- and 10-yr recurrence-free survival of 90% and 38%, and cancer-specific survival of 100% (12 of 12) [67].

4. Conclusions

GS is one of the most critical predictive components for men with adenocarcinoma of the prostate regardless of the therapy used. Updating the Gleason system has provided previously lacking formal criteria for grading biopsy and RP specimens in various more contemporary clinical and pathologic scenarios. Modernization of the Gleason grading system has resulted in a more accurate grading system for RP but has complicated the comparison of data before and after updating. A better prognostication with the updated Gleason grading system for patients treated with modalities other than surgery can only be postulated at this time because there are limited conflicting data on radiation and no studies on other treatment modalities. The greatest impact of using the modified system is the uniformly excellent prognosis associated with a more strictly defined GS 6 in RPs.

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