Gleason Grading System, Modifications and Additions to the Original Scheme

Gleason Derecelendirme Sistemi, Modifikasyonlar ve Orijinal Şemaya Katkılar

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ABSTRACT

Histologic grade remains one of the most useful predictors of prognosis of prostate cancer. The Gleason scoring is now the only grading method recommended by the World Health Organization for prostatic carcinoma. While the basic principles of the Gleason grading remain relatively unchanged since it was established, several important modifications have been recently proposed to solve the controversial issues, to achieve higher concordance between the pathologists and to increase the prognostic utility of the system. This review provides a simplified approach to the application of the Gleason grading system in contemporary pathology practice and gives an update of the recent modifications taking into account several latest position papers.

Key Words: Prostate cancer, Gleason grading, Modification

ÖZ

Histolojik farklılaşma prostat kanserinde prognozu belirleyen en önemli unsurlardan biridir. Prostat karsinomu için Dünya Sağlık Teşkilatı'nca önerilen tek derecelendirme metodu Gleason Skorlama Sistemidir. Temel prensipleri ilk kullanımından bu yana genel olarak aynı kalmakla birlikte, tartışmalı konulara çözüm getirmek, patologlar arasındaki uyumu artırmak ve sistemin prognostik değerini yükseltmek maksadıyla Gleason sisteminde son zamanlarda önemli modifikasyonlar ortaya konmuştur. Bu makalede, günlük cerrahi patoloji uygulamasında yenilenmiş Gleason şemasının kullanımına özet yaklaşım sunulmakta, en son önemli makalelere dayanarak güncel değişiklikler vurgulanmaktadır.

Anahtar Sözcükler: Prostat kanseri, Gleason derecelendirme, Modifikasyon

INTRODUCTION

Donald F. Gleason in 1966 created a unique grading system for prostatic carcinoma (1) (Figure 1). In 1974 and 1977, he provided additional comments concerning the application of the Gleason system (2-3). Since its first proposal, the Gleason grading system has been accepted as one of the most powerful prognostic indicators in prostate cancer throughout the world.

Gleason grading depends solely on architectural patterns of the tumor. The grade is defined as the sum of the two most common grade patterns and reported as the Gleason score. Synonyms for "Gleason score" are "combined Gleason grade" and "Gleason sum". Both the primary (predominant) and the secondary (second most prevalent) architectural patterns are identified and assigned a number from 1 to 5, being 1 the most differentiated and 5 the least differentiated. When a tumor has only one histologic pattern, the primary and secondary patterns are given the same number. Thus Gleason scores range from 2 (1+1=2), which are the tumors uniformly composed of Gleason pattern 1, to 10 (5+5=10), which represents totally undifferentiated tumors. A tumor that shows predominant Gleason pattern 3 with a lesser quantity of Gleason pattern 5 has a Gleason score of 8 (3+5=8), as does a tumor that is predominantly Gleason pattern 5 with a lesser amount of Gleason pattern 3 (5+3=8).

Both primary and secondary Gleason patterns have to be assigned even for the cancer focus that is minute on a needle biopsy. When the pathologist signs out a case as "Gleason grade 4" to mean that the tumor is high grade (i.e. Gleason pattern 4), the urologist may interpret it as Gleason score of 4 (i.e. Gleason grade 2+2=4). By assigning both a primary and secondary pattern even in cases with a limited amount of cancer, the urologists will be prevented from confusion.

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Value of Gleason Scoring

While the decision for the definitive therapy of prostatic carcinoma is based on multiple factors including the clinical stage, patient age, preoperative PSA, patients general health, life expectancy, etc., the Gleason grade in needle biopsy is another variable that can potentially help stratify patients into different therapeutic modalities. Gleason score on biopsy correlates with all of the important pathologic parameters at radical prostatectomy (pathologic stage, tumor volume, inked margin status, lymph node metastasis), with prognosis after radical prostatectomy (recurrence and survival), and with outcome following radiotherapy as well as serum pre-op PSA levels and many molecular markers. (4-8). Gleason score 7 tumors behave significantly worse than Gleason score 5-6 tumors and do better than Gleason score 8-10 tumors. If one wants to combine Gleason scores on biopsies into groups the following categorization is reasonable: Gleason score 2-4 (well-differentiated); Gleason score 5-6 (moderately differentiated); Gleason score 7 (moderately-poorly differentiated); and Gleason 8-10 (poorly differentiated). However, one loses some discrimination by combining Gleason scores. For example, Gleason score 4+4=8 has a better prognosis than Gleason score 5+5=10. Grade is one of the most influential factors used to determine treatment for prostate cancer. Whereas some younger men with limited amounts of Gleason score 5-6 on needle biopsy and low PSA values may be followed expectantly ("watchful waiting"), almost all men with Gleason score 7 tumor will be treated more definitively (9-10). The presence of a Gleason pattern 4 (score ≥7) dictates, in most cases, prompt intervention by at least one of the many therapeutic modalities available for prostate cancer.

Based on 703 patients with clinically localized prostate cancer, Partin et al. showed that combinations of 3 variables (serum PSA, Gleason score and clinical stage) allowed for construction of probability plots and nomograms, which assist in the preoperative prediction of final pathologic stage for patients with clinically localized prostate cancer (11). Clinicians use the grade as part of the nomograms to predict tumor extent, post-radical prostatectomy progression, and post-radiotherapy failure (12-16). These nomograms factoring preoperative variables such as Gleason score, clinical stage, serum PSA and more recently the extent of cancer on biopsy calculate the risk of extraprostatic disease, seminal vesicle invasion, and lymph node metastases. A man with a Gleason score 6 tumor may be a candidate for interstitial radiotherapy (brachytherapy) as a monotherapy. However, if this man had a Gleason score 7 tumor, due to a greater probability of extra-prostatic extension by the neoplasm, he would most likely be given external beam radiotherapy with or without brachytherapy, as radioactive seeds may not effectively treat extra-prostatic disease. Gleason score 7 tumor can also be offered radical prostatectomy as a treatment option. An accurate diagnosis of Gleason scores 8 and above is also critical for patient management. For a man with a Gleason score ≥ 8 cancer on biopsy, surgery may not be preferable treatment choice, depending on the extent of tumor and other clinical factors, due to the higher probability of extraprostatic extension, seminal vesicle or lymph node involvement. The patients with Gleason score 8-10 may benefit more from radiation to the prostate rather than radical prostatectomy.

Another use of the nomograms, which factor in the needle biopsy grade, is to predict the likelihood of lymph node metastases. In a man with a biopsy Gleason score of 6, a normal digital rectal examination, and a serum PSA value of less than 10 ng/ml, the risk of having lymph node metastases is so low that some urologists might leave out lymphadenectomy at the time of radical prostatectomy. On the other hand, the presence of Gleason score 8-10 may prompt intraoperative evaluation of pelvic lymph nodes by frozen sectioning so that positive node(s) may abort a prostatectomy while negative result at frozen section may allow for the procedure to be completed. Thus, accurate Gleason scoring is critical for correct patient management.

Gleason Patterns in Prostatic Adenocarcinoma

As described by Gleason, the grading of prostate carcinoma has to be performed under low magnification (4x or 10x objective) (3). One should not initially use the 20x or 40x objectives to look for rare fused glands or a few individual cells seen only at higher power which would lead to an overdiagnosis of high Gleason patterns.

<u>Gleason Pattern 1</u>

Gleason pattern 1 tumor is a circumscribed nodule composed of uniform, single, separate, closely packed glands (Figure 2). Gland spacing usually does not exceed one gland diameter. Gleason pattern 1 is so uncommon on any prostate specimen that its existence is now questioned. A Gleason score of 1+1=2 must be considered as an extremely rare exception regardless of the type of specimen. The Gleason system predated the use of immunohistochemistry. It is likely that with immunostaining for basal cells many of Gleason's original 1+1=2 adenocarcinomas of the prostate would today be regarded as adenosis (atypical adenomatous hyperplasia).
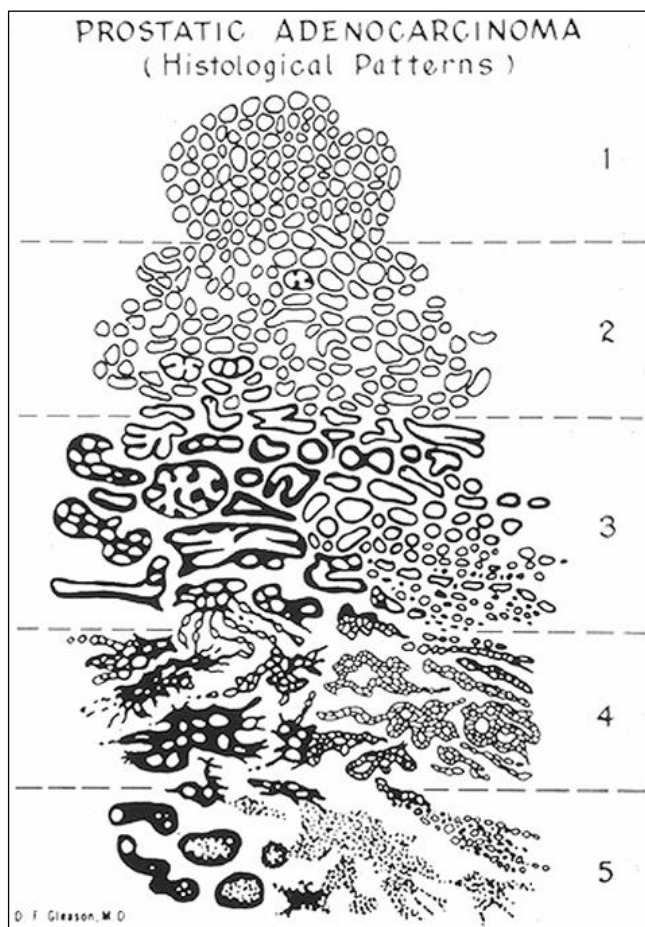
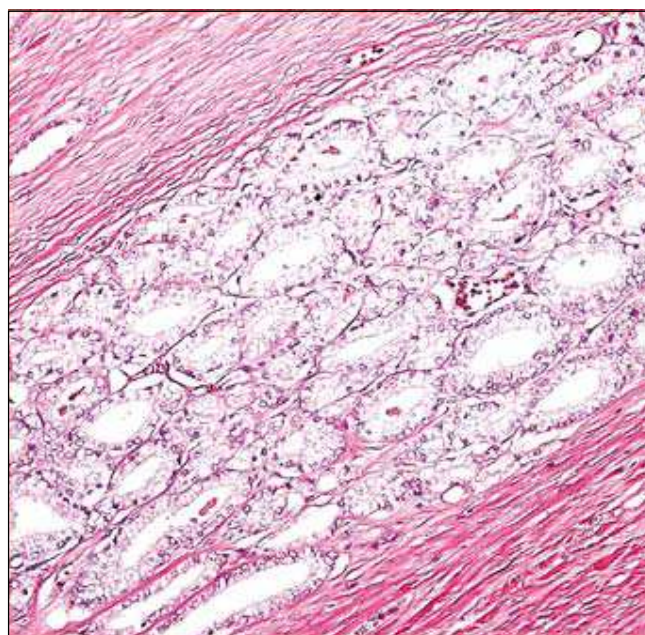**Figure 1:** Drawing that shows original Gleason grading.

Figure 2: Prostatic adenocarcinoma - Gleason pattern 1 (H&E, x200).

Gleason Pattern 2

In Gleason pattern 2, the tumor is still fairly circumscribed, however at the edge of the tumor nodule there can be minimal extension by neoplastic glands into the surrounding non-neoplastic prostate (Figure 3). The glands are more loosely arranged and not quite as uniform in comparison with Gleason pattern 1. The Gleason pattern 1 and Gleason pattern 2 glands tend to be larger than intermediate grade carcinomas. Contrary to the original Gleason system, cribriform glands are not allowed in pattern 2. Typically, both Gleason pattern 1 and pattern 2 carcinomas have abundant pale eosinophilic cytoplasm.
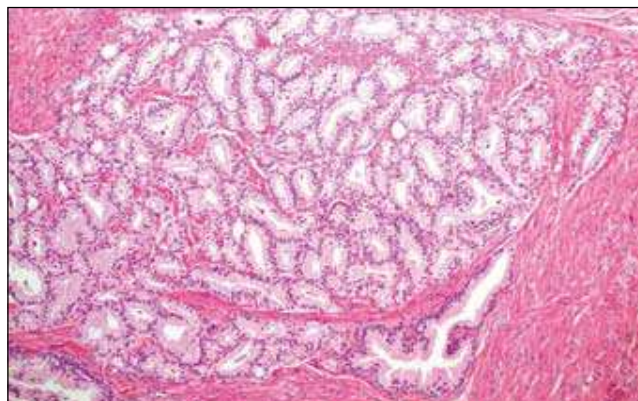

Figure 3: Prostatic adenocarcinoma - Gleason pattern 2 (H&E, x100).

Gleason Pattern 3

The vast majority of Gleason pattern 3 is composed of single glands that show marked variation in size and shape (Figure 4). The neoplastic gland size is usually smaller than seen in Gleason pattern 1 or 2. Gleason pattern 3 tumor infiltrates in between non-neoplastic prostate acini (Figure 5). A disagreement with the original Gleason classification system is that "individual cells" are not allowed within Gleason pattern 3. In contrast to Gleason pattern 4, the glands in Gleason pattern 3 are distinct units so that one can mentally draw a circle around well-formed individual glands. Gleason grading as stated above has to be applied at low power objective; the presence of a few poorly formed glands at high power is still consistent with Gleason pattern 3.

A controversial area in the Gleason system is cribriform Gleason pattern 3. This issue will be discussed below.

Gleason Pattern 4

Pattern 4 has become significantly expanded beyond

Gleason's original description of tumors with clear cytoplasm that resembled renal cell carcinoma. Gleason pattern 4 today consists of large irregular cribriform glands (Figure 6) or fused, ill-defined glands with poorly formed
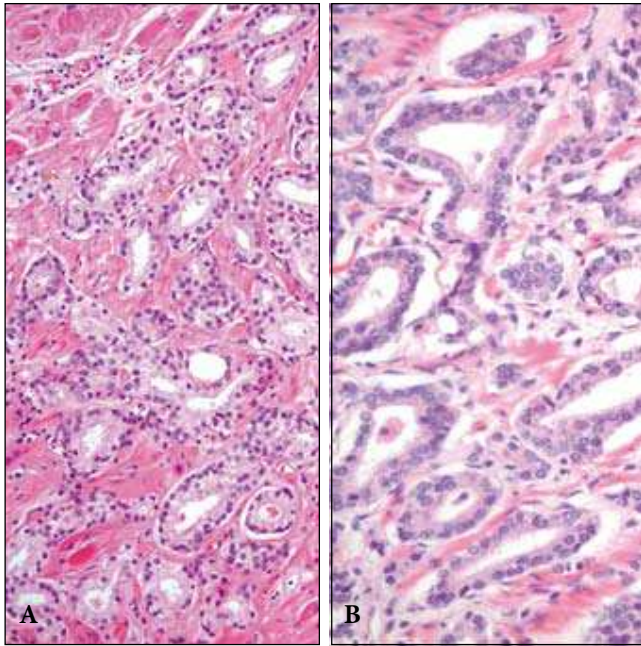

Figure 4: Prostatic adenocarcinoma - Gleason pattern 3 (**A:** H&E, x200; **B:** H&E, x400).
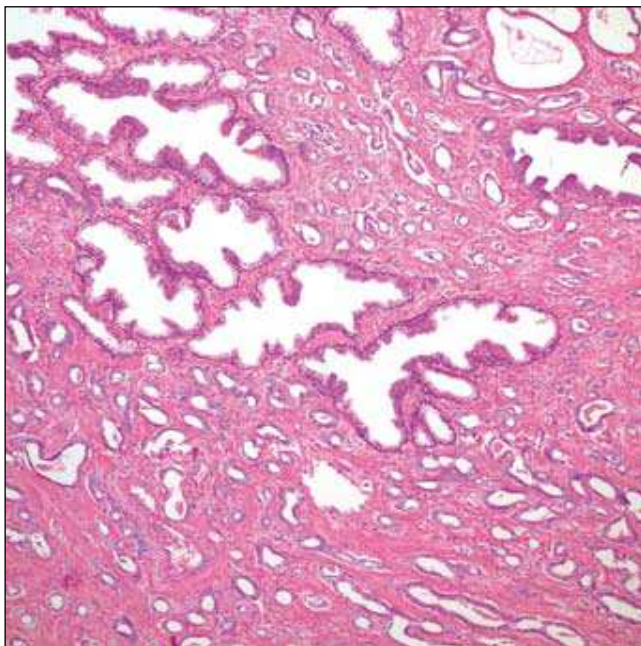

Figure 5: Prostatic adenocarcinoma - Gleason pattern 3. Neoplastic acini infiltrating in-between benign prostatic glands (H&E, x100).

glandular lumina (Figure 7). Glands are no longer single and separate as seen in patterns 1 to 3. It must be remembered that a tangential section of Gleason pattern 3 may produce a minute cluster that gives false impression of ill-defined glands with inconspicuous lumina, and thus may lead to misdiagnosis as Gleason pattern 4. Very small, but still well formed glands are within the spectrum of Gleason pattern 3.

Hypernephromatoid pattern is an uncommon variant of Gleason pattern 4 (Figure 8). Here, tumor is composed of clear cells and reminds renal cell carcinoma microscopically.

Gleason Pattern 5

In Gleason pattern 5, tumor shows no glandular differentiation. Instead it is composed of solid sheets, cords, trabeculae or single cells (Figures 9,10). Cribriform or solid nests of tumor with central comedonecrosis are also classified under Gleason pattern 5. One must be stringent as to the definition of comedonecrosis. Luminal eosinophilic secretions may be misinterpreted as comedonecrosis. The presence of intraluminal necrotic cells and/or karyorrhexis is required especially in the setting of cribriform glands. Tumors with comedonecrosis generally have high nuclear grade often with brisk mitotic activity. Gleason stated that "A small focus of disorganized cells did not change a pattern 3 or 4 tumor to pattern 5".
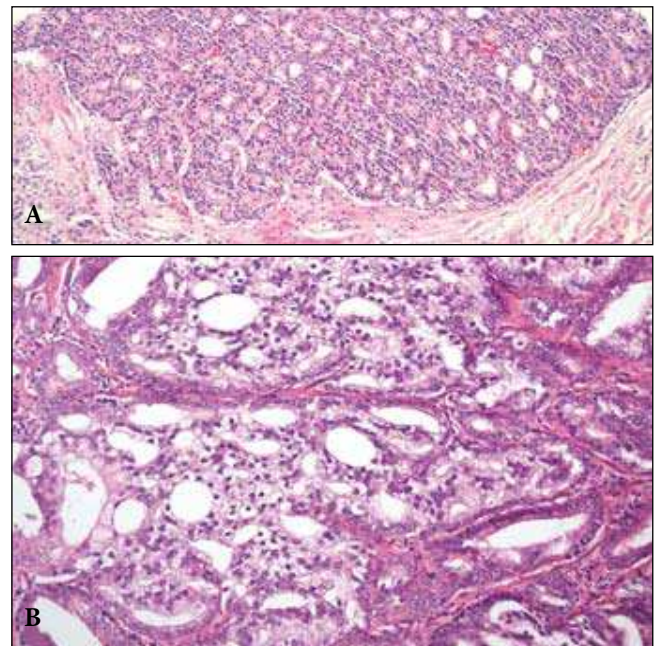

Figure 6: Large cribriform glands of Gleason pattern 4 prostatic adenocarcinoma (**A:** H&E, x100; **B:** H&E, x200).
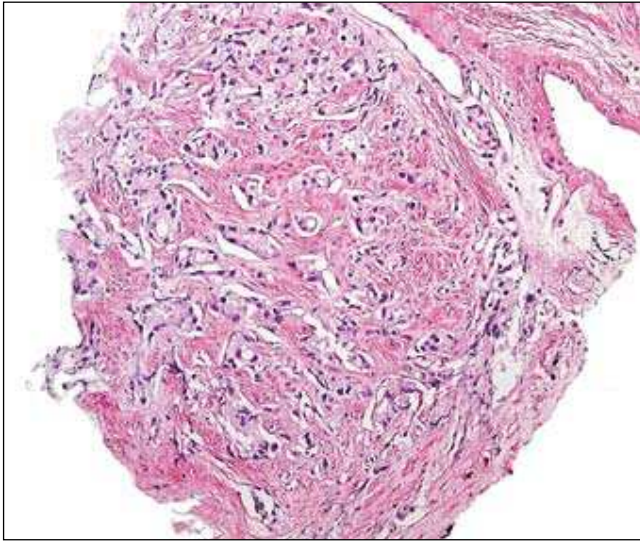
Figure 7: Incompletely formed abortive glands in pattern 4 prostatic adenocarcinoma (H&E, x400).
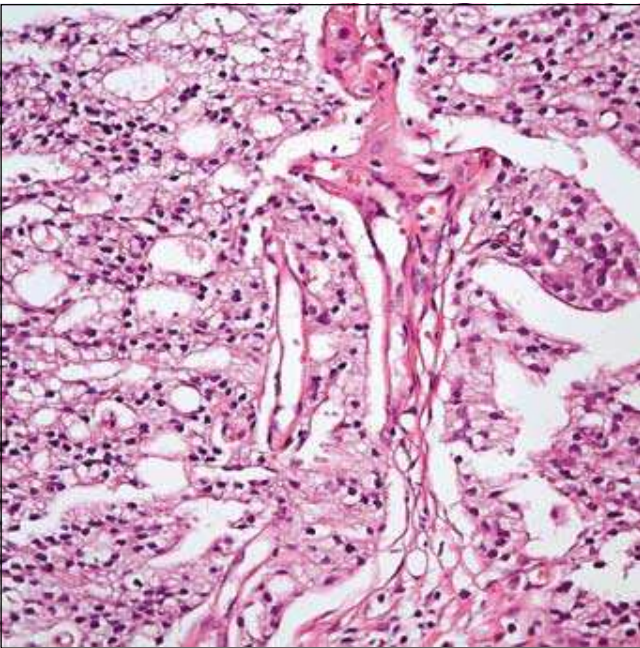

Figure 8: Hypernephromatoid prostatic adenocarcinoma, a form of Gleason pattern 4 (H&E, x400).

Figure 9: Solid islands of tumor cells with no gland formation, Gleason pattern 5 (H&E, x200).

Figure 10: Gleason pattern 5. Neoplastic cells infiltrating in the stroma singly or in cords and trabeculae (H&E, x400).

Modifications in Gleason System

Since the introduction of Gleason grading system, many aspects of prostate cancer have changed, including the use of PSA testing, transrectal ultrasound-guided prostate needle biopsy with greater sampling, immunohistochemistry for basal cells changing the classification of prostate cancer, and discovery of new prostate cancer variants (ie pseudohyperplast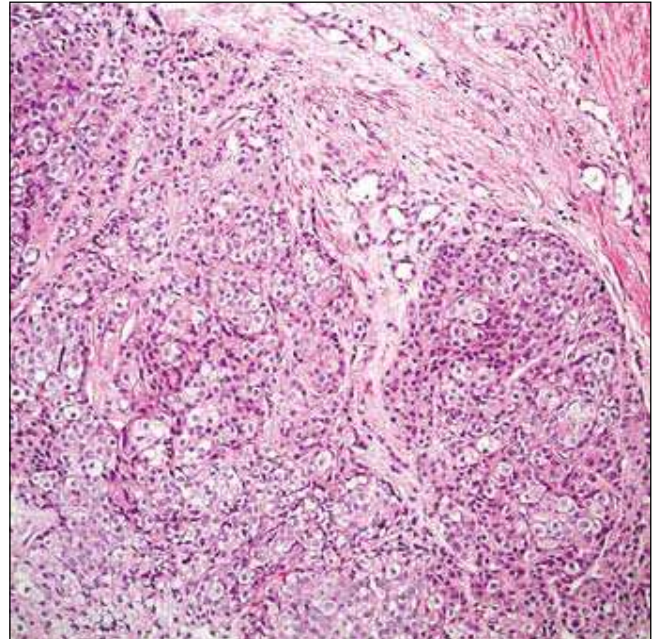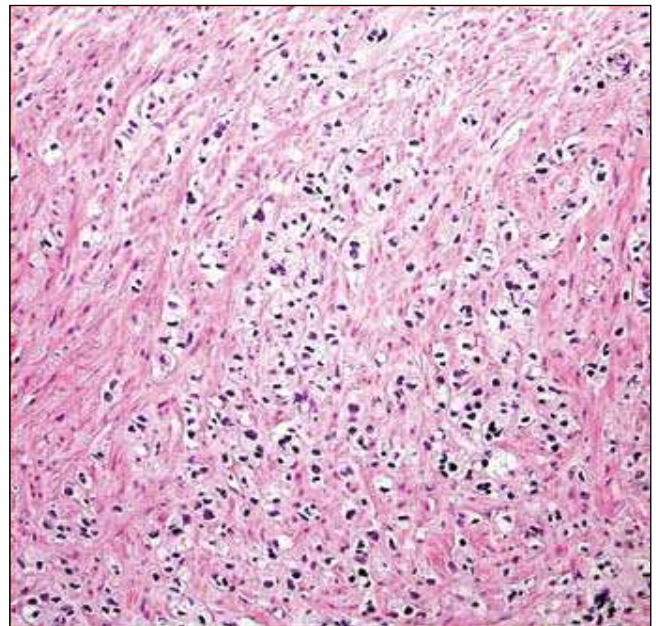ic, foamy gland, mucinous, ductal). These striking changes in prostate cancer created a need for revision of the Gleason grading system. Over the years several modifications have been proposed and certain aspects of the Gleason system are interpreted differently in surgical pathology practice today than its original description. A consensus conference of international experts in urologic

pathology was recently convened to update the Gleason grading system. 80 urological pathologists from around the world gathered in a meeting at the United States and Canadian Academy of Pathology convention in 2005 (17). They updated Gleason grading system based on data in the literature (Figure 11). In areas where there was either a lack of data or scant information as to the optimal method of grading, the consensus was based on personal and institutional experience with a large number of cases.

Below we list the major modifications to original Gleason system, mainly in reference to ISUP-2005 consensus conference outlines.

Recommendations of reporting of the Gleason score in needle biopsies

Gleason scores for each recognizable core have to reported separately irrespective of whether the cores are individually submitted (in individual container signifying specific anatomic location, or submitted together (more than one core, possibly sampling different areas of the prostate). Assigning a global (composite) score is optional and left to the pathologist.

When there are multiple cores per container, they often fragment. If tissue fragmentation makes grading of individual cores difficult, the effort should be exerted to identify and provide information on the core with the highest Gleason score. When the cores are extremely fragmented, it becomes impossible or potentially misleading to give a Gleason score on small tissue pieces. In these cases where one cannot be sure if the tumor fragments belong to one intact core, only an overall score for that container must be given.

Gleason score 3 - 4 adenocarcinoma in needle biopsy – an extremely rare diagnosis

A Gleason score 3 or 4 should be made "rarely, if ever" on needle biopsy. Such a diagnosis is usually incorrect because: 1) There is poor interobserver reproducibility even amongst urologic pathology experts; 2) The radical prostatectomy show a higher Gleason grade in almost all cases at resection; and 3) a diagnosis of Gleason score 3-4 may potentially misguide clinicians and lead patients to under-treatment or counseling as to having indolent tumor (18-19). The major microscopic limitation for rendering a diagnosis of Gleason score 4 on needle biopsy is that the entire edge of the lesion cannot be visualized to determine if it is completely circumscribed. Consequently, majority of the lesions that appear to be very low grade on needle biopsies are diagnosed by urological pathologists as Gleason score 2+3=5 or 3+2=5.
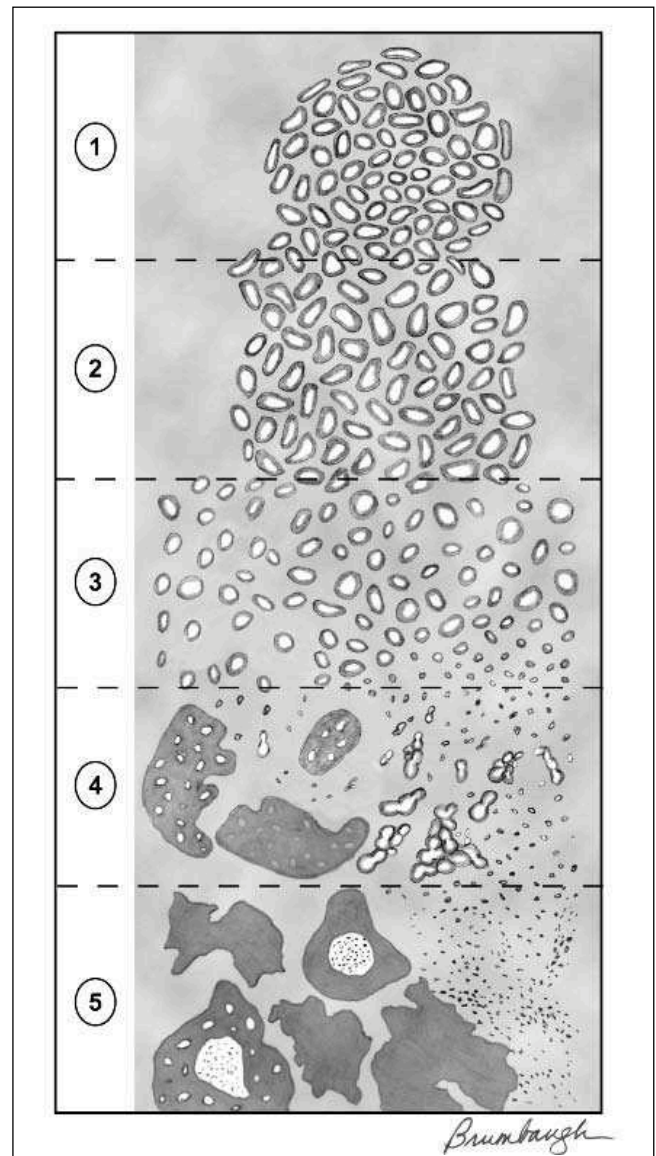

Figure 11: Updated Gleason scheme.

Low grade prostate cancers (Gleason score 3-4 adenocarcinomas) do exist and may be diagnosed on TURP (transurethral resection of prostate). However they are rarely seen on needle biopsy because well differentiated cancers are predominantly located anteriorly in the prostate within the transition zone and they tend to be small.

Tertiary pattern in needle biopsies

The typical scenario with tertiary patterns on biopsy is related to a tumor with patterns 3, 4, and 5 in various proportions. As being different than radical prostatectomy, these tumors on needle biopsy should not be graded simply

by summing the primary and secondary pattern with a note relating to the tertiary pattern. The tables and nomograms clinicians use, incorporate the Gleason score with no regard to a tertiary pattern mentioned in a note. When the worst Gleason grade is the tertiary pattern, it should influence the final Gleason score and must replace the secondary grade in the Gleason score calculation formula. Example: a case with primary Gleason pattern 3, secondary pattern 4, and tertiary pattern 5 should be assigned a Gleason score of 8 (3+5=8) (the primary pattern + the highest grade = score). The rationale is that the presence of both Gleason patterns 4 or 5 on needle biopsy most likely indicates an overall high grade tumor, and that its limited extent reflects a sampling issue. In cases where three patterns consist of grades 2, 3, and 4, one should ignore the pattern 2 and the biopsy would be called Gleason score 3+4=7 or Gleason score 4+3=7, depending on whether pattern 3 or pattern 4 is more prevalent.

Tertiary pattern in radical prostatectomies

In the radical prostatectomy, the approach to the tertiary pattern is not the same with that applied on needle biopsy, since the entire nodule will be available for examination. The consensus conference has recommended that pathologists assign the Gleason score based on the primary and secondary patterns with a comment as to the tertiary pattern.

A difference between tertiary patterns on needle biopsy and prostatectomy exists for the definition of "tertiary" patterns. "Tertiary" on needle biopsy means simply the presence of a tumor grade pattern that is the third most common. On the other hand, the definition of tertiary pattern in terms of its extent is controversial in radical prostatectomy specimens. The authors of this article describe the tertiary pattern on radical prostatectomy as *"the presence of a third component of a Gleason pattern higher than the primary and secondary grades, where the tertiary component is visually estimated to be <5% of the whole tumor"*. When the 3rd most common component is the highest grade and occupies >5% of the tumor, we record it as the secondary pattern. The prognosis of a tumor with a large amount of tertiary high grade carcinoma is not analogous to cases where the tertiary component is much more limited. When a tumor has a sizeable (>5%) amount of high grade tumor, it is reasonable to consider that this highest grade component should be factored into the Gleason score itself and not counted as only a tertiary component. However, this definition is not universally accepted.

The consensus conference recommends that one should assign a separate Gleason score to each dominant tumor nodule; the dominant nodule with the highest stage and highest grade is designated as the "index tumor".

Reporting secondary patterns of higher grade when present to a limited extent in needle biopsies

Whatever the quantity of a high grade pattern detected on a needle biopsy, it should be included within the Gleason score. Example: A needle biopsy which is involved by cancer with 98% Gleason pattern 3 and 2% Gleason pattern 4 would be diagnosed as Gleason score 3+4=7. The rationale for this is: even a small amount of high grade tumor sampled on needle biopsy will most likely indicate a more significant amount of high grade tumor within the prostate.

Reporting secondary patterns of lower grade when present to a limited extent in needle biopsies

In the setting of high grade cancer, lower grade patterns must be ignored if they occupy less than 5% of the tumor area. Example: A biopsy core, 100% involved by cancer, with 98% Gleason pattern 4 and 2% Gleason pattern 3 would be diagnosed as Gleason score 4+4=8. The same 5% cut off rule for excluding lower grade cancer also applies for prostatic carcinomas detected in transurethral resections.

Percent pattern 4-5

The value of information regarding the percentage pattern 4/5 both on biopsy or TURP is controversial. Percent pattern 4/5 has been found only very predictive for prognosis in radical prostatectomy specimens at the extremes of the percentages (20). Classifying tumors based on the percent pattern 4-5 is not more predictive than Gleason score 2-4, 5-6, 3+4, 4+3, or 8-10. Consequently, percent pattern 4-5 is not required or recommended as a method of Gleason grading. It remains optional if one wants to include this information in addition to the routine Gleason score.

Cribriform carcinoma behaves more like Gleason pattern 4 than Gleason 3

The cribriform pattern described in Gleason's original schema as pattern 2 and 3 would today be considered higher grade. Many of the cases in 1966 diagnosed as cribriform prostate carcinoma would probably be referred to as cribriform high grade prostatic intraepithelial neoplasia today, if labeled with basal cell markers (21). Most cancer in prostate with cribriform architecture is Gleason pattern 4 rather than 3 by consensus conference criteria.

Urological pathologists require extremely stringent criteria for the diagnosis of cribriform pattern 3. They have to be

rounded, well circumscribed glands within the same size range of normal glands. Even slight irregularities of the outer border of cribriform glands typically results in upgrading as pattern 4. Some experts additionally require for pattern 3 uniformly spaced lumina and that the cellular bridges within the cribriform glands are of uniform thickness and no thicker than the width of the luminal spaces. Thus, only rare cribriform lesions can satisfy diagnostic criteria for cribriform pattern 3 while the vast majority will be designated as Gleason pattern 4.

The authors of this review believe that Gleason cribriform pattern 3 carcinoma should almost never be diagnosed. This is based on: 1) the rarity of even candidates for cribriform Gleason pattern 3; 2) within these rare candidates, the lack of interobserver reproducibility amongst experts on assessing the diagnostic criteria proposed to distinguish cribriform Gleason pattern 4 from Gleason pattern 3; 3) candidate cribriform pattern 3 cancers almost always occur in association with typical Gleason pattern 4 cancer elsewhere in the case; and 4) conceptually, one would expect the change in grade from pattern 3 to pattern 4 to be reflected in a distinct architectural paradigm shift, rather than merely a subjective continuum of differences in size, shape and contour of cribriform glands. Diagnosing all cribriform prostate cancer as Gleason pattern 4 will remove any elements of subjectivity in the assessment of cribriform prostate cancer glands, by this way general pathologists' grading of these lesions will now better correlate with genitourinary pathologists, and genitourinary pathologists will better agree with each other.

Gleason grading of carcinoma with glomerulations on needle biopsy remains controversial (22). Glomerulations are dilated glands containing intraluminal cribriform structures with a single point of attachment, resembling a renal glomerulus (Figure 12). On a biopsy, they are considered pathognomonic for invasive prostate carcinoma. Some urological pathologists do not assign a grade to glomeruloid patterns and rather just grade the surrounding tumor. According to some experts for the rare case where the entire tumor is composed of glomeruloid glands, a grade of 3+3=6 is assigned as long as the glomeruloid structures are small. Larger glomeruloid structures are uniformly accepted by urological pathologists as Gleason pattern 4. Other experts in the field feel that all glomeruloid structures should be assigned a Gleason pattern 4. In a recent study by TL Lotan and JI Epstein on 45 prostate needle biopsies containing carcinoma with glomeruloid features, glomerulations have been found overwhelmingly associated with Gleason pattern 4 or higher grade carcinoma, both on the same core, as well as on additional cores in the same case (23). Authors have

observed transitions between small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer in several cases. This data suggests that glomerulations represent an early stage of cribriform pattern 4 cancer and until follow-up data is available, are best graded as Gleason pattern 4.

Grading after therapy (radiation or androgen deprivation)

Tumors showing treatment effect of radiotherapy or hormone depletion are atrophic and shrunken; glands are closely packed and artificially appear to be fused or in cords; or single vacuolated histiocyte like tumor cells are prevalent. These features give deceptive impression of Gleason pattern 4 or 5 to the tumor (24). At this time of the clinical course of the disease, the biologic potency or tumor viability is more critical than the histologic grade of the tumor, which was presumably assigned at the time of primary diagnosis. Gleason system is applied only to the tumor or a part of tumor if it does not reflect prominent therapy related secondary changes.

Grading histologic variants and variations of prostate cancer

It is obvious that the original Gleason system can not answer how to grade newly described variants and patterns of prostatic adenocarcinoma. Although being not a formal
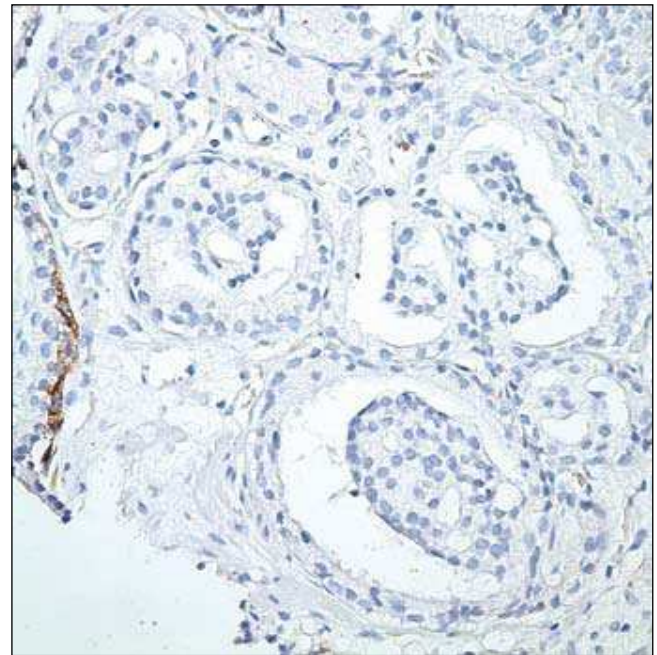

Figure 12: Prostatic adenocarcinoma with glands forming glomeruloid structures (Immunohistochemistry, anti-34bE12 Ab, x 400).

approach, the Gleason system principles can be extrapolated and employed in the grading of histologic variants of prostate cancer to fill in this defect. The outcome of patients with these variants appears to correlate with the proposed Gleason system application; although the experience with many of the variants is limited.

Vacuoles: Clear vacuoles may occur in adenocarcinomas of the prostate (Figure 13) and these should be distinguished from true signet-ring carcinomas containing mucin. Gleason's original scheme describes vacuoles under pattern 5 as signet cells. In fact, vacuoles are typically seen within Gleason pattern 4 cancer. Nevertheless they may also be observed within Gleason pattern 5 and even Gleason pattern 3 tumors. Tumors should be graded, as if the vacuoles were not present, by taking only the underlying architectural pattern into consideration.

Foamy Gland Carcinoma: Similar to way of handling cancers with vacuoles, the foamy cytoplasm must be disregarded and grading should be based on the architectural features of the tumor (25-26). Most foamy gland carcinomas are Gleason score 3+3=6 (Figure 14). But higher grade foamy gland carcinomas do exist and should be graded accordingly in the view of the pattern.

Ductal Adenocarcinoma: Ductal adenocarcinomas of the prostate most commonly are composed of either papillary fronds or cribriform structures (27) (Figure 15). Less frequently, there exists a pattern consisting of individual

glands lined by tall pseudostratified columnar cells resembling high grade prostatic intraepithelial neoplasia (PIN-like ductal adenocarcinoma) (Figure 16). Ductal adenocarcinomas are recognized as being aggressive tumors with most studies showing comparable behavior to acinar cancer with a Gleason score 4+4=8. Ductal adenocarcinomas should be graded as Gleason score 4+4=8, while retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathological findings. This can be achieved by diagnosing such a tumor as "Prostatic ductal
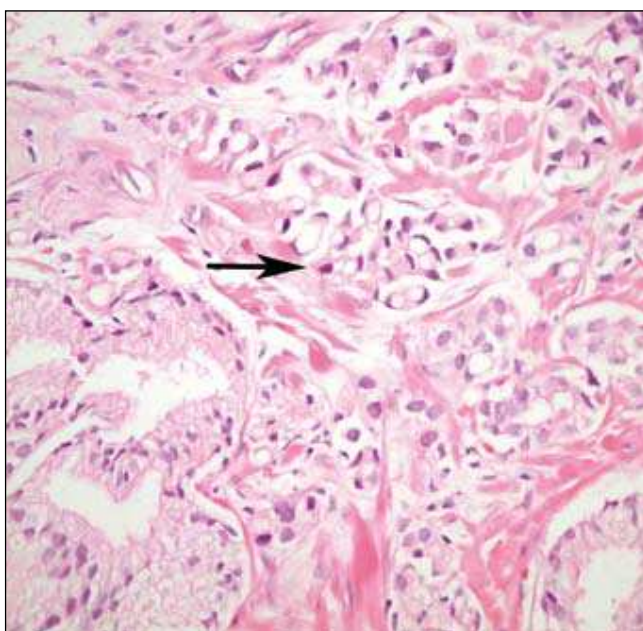

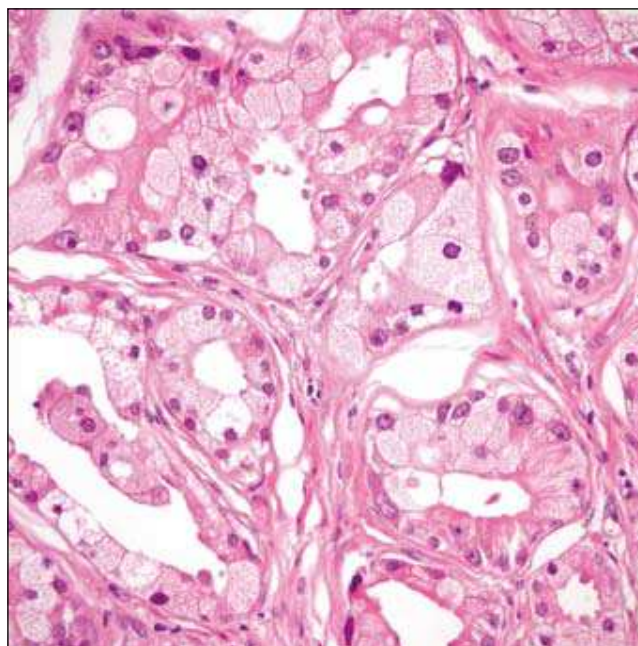**Figure 14:** Prostatic adenocarcinoma "foamy gland" variant (H&E, x 400).

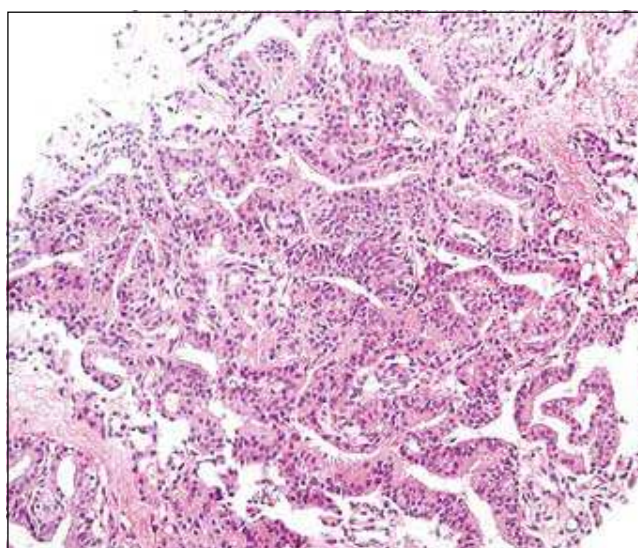**Figure 13:** Prostatic adenocarcinoma with vacuolated cells (H&E, x 400).

Figure 15: Ductal type prostatic adenocarcinoma (H&E, x 200).

adenocarcinoma (Gleason score 4+4=8)". In cases with mixed ductal and acinar patterns, the ductal patterns should be assigned Gleason pattern 4. The exception appears to be for PIN-like ductal adenocarcinomas, which have a prognosis more similar to Gleason score 6 (28).

Colloid (Mucinous) Carcinoma: The majority of cases with colloid carcinoma consist of irregular cribriform glands floating within a mucinous matrix which would be scored Gleason score 4+4=8 (29-30) (Figure 17). However, uncommonly one may see individual round discrete glands floating within mucinous pools. There is no consensus in these cases whether such cases should be diagnosed as Gleason score 4+4=8 or Gleason score 3+3=6. Some urological pathologists consider by definition all colloid carcinomas as Gleason score 8, while others ignore the extracellular mucin and grade the tumor based on the underlying architectural pattern. Given the lack of consensus, either method is acceptable for practicing pathologists until future data indicates which method is correct.

Small Cell Carcinoma: Small cell carcinoma of the prostate has unique histological, immunohistochemical, and clinical features (Figure 18). Comparable to its more common pulmonary counterpart, chemotherapy is the mainstay of therapy for prostatic small cell carcinomas in contrast to hormonal therapy for Gleason pattern 5 prostatic acinar carcinoma, such that small cell carcinoma should not be assigned a Gleason grade.

Adenocarcinoma with Focal Mucin Extravasation: Adenocarcinomas of the prostate with focal mucinous extravasation (Figure 19) should not be by default graded as Gleason score 4+4=8. Rather, one should ignore focal mucinous extravasation and grade the tumor based on the underlying architecture of the glands. The distinction between focal mucinous extravasation and colloid carcinoma is the presence in colloid carcinoma of epithelial elements floating within the mucinous matrix as opposed to mucinous extravasation where there is only focal acellular mucin adjacent to cancer.

Mucinous Fibroplasia (Collagenous Micronodules): The delicate ingrowth of fibrous tissue seen with mucinous fibroplasia can result in glands appearing to be fused resembling cribriform structures although the underlying architecture is often that of individual discrete rounded glands invested by loose collagen (31-32) (Figure 20). One should try to subtract away the mucinous fibroplasia and grade the tumor based on the underlying glandular architecture. The majority of these cases would accordingly be graded as Gleason score 3+3=6.
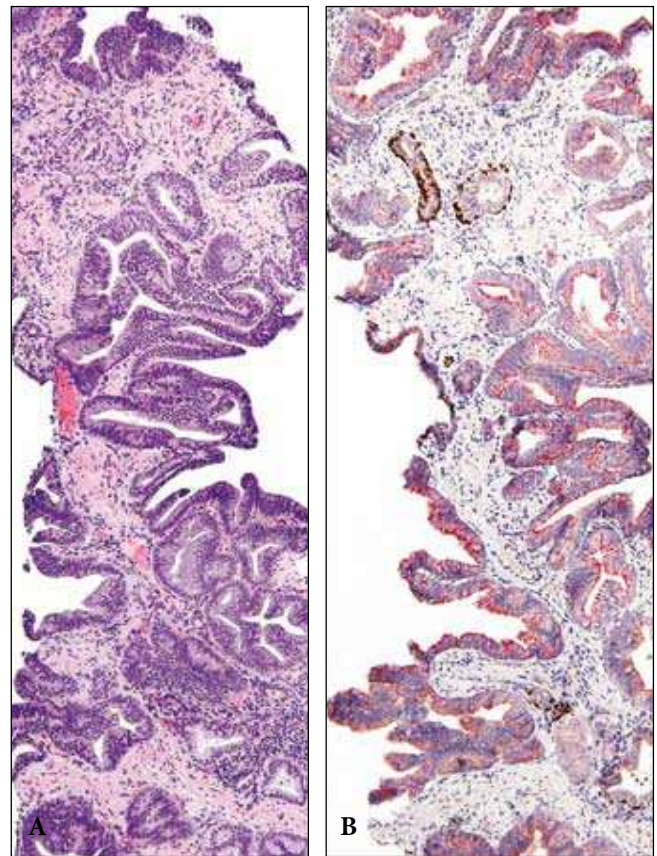

Figure 16: PIN-like ductal prostate adenocarcinoma (**A:** H&E, x100; **B:** Immunohistochemistry, triple stain, anti-34bE12+anti-p63+anti-AMACR Ab's, x100).
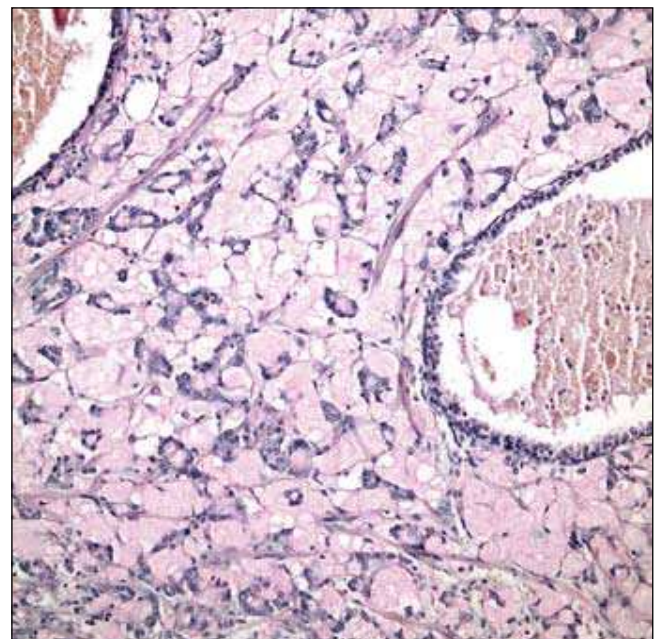

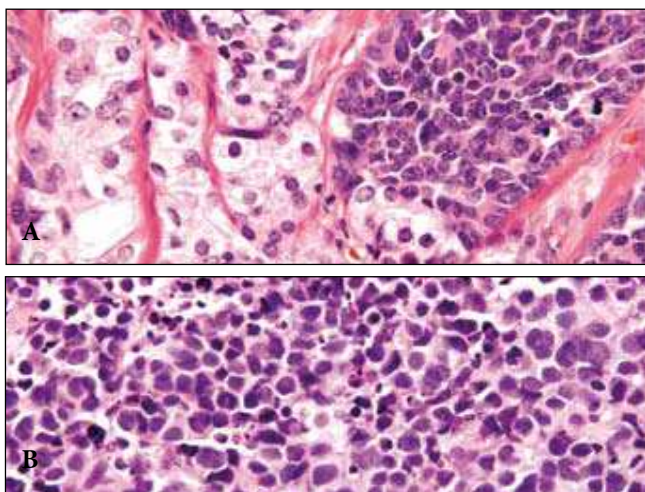**Figure 17:** Mucinous prostatic adenocarcinoma (Mucicarmine, x200).

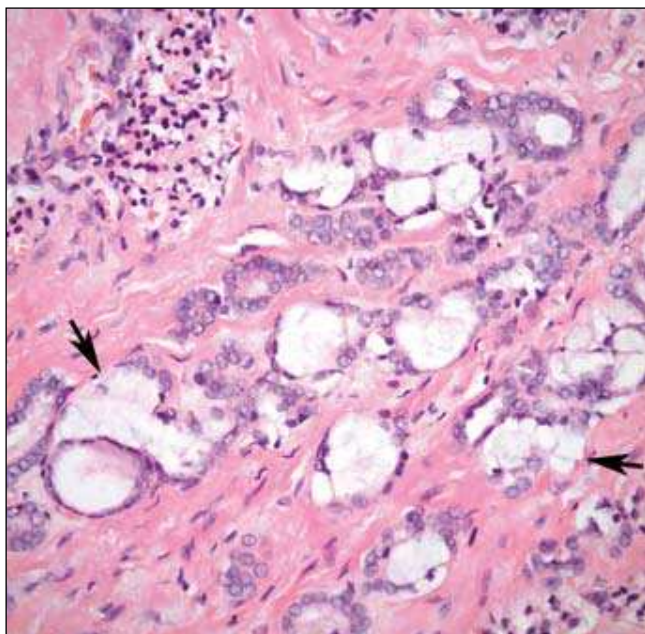**Figure 18:** Small cell carcinoma accompanying conventional prostatic adenocarcinoma (**A:** H&E, x400; **B:** H&E, x400).

Figure 20: Mucinous fibroplasia (H&E, x400).

Figure 19: Prostatic adenocarcinoma with mucin extravasation in some glands (H&E, x400).
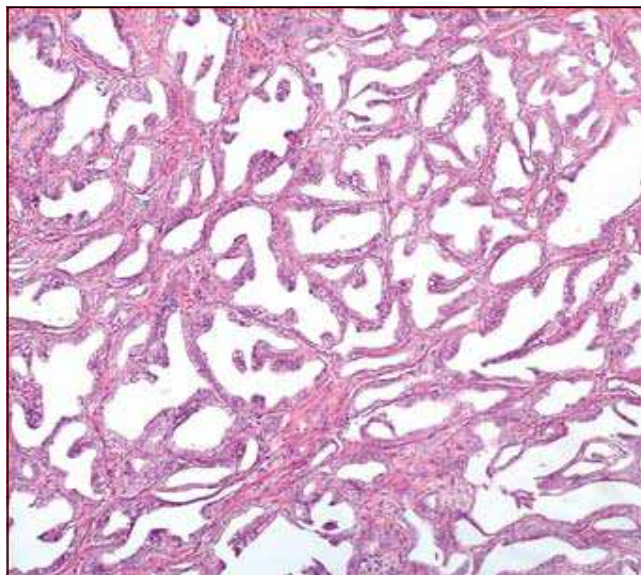
Figure 21: Pseudohyperplastic type prostatic adenocarcinoma (H&E, x100).

Pseudohyperplastic Adenocarcinoma: These cancers should be graded as Gleason score 3+3=6 with pseudohyperplastic features (33-34) (Figure 21). This is in large part based on the recognition that they are most often accompanied by more ordinary Gleason score 3+3=6 adenocarcinoma.

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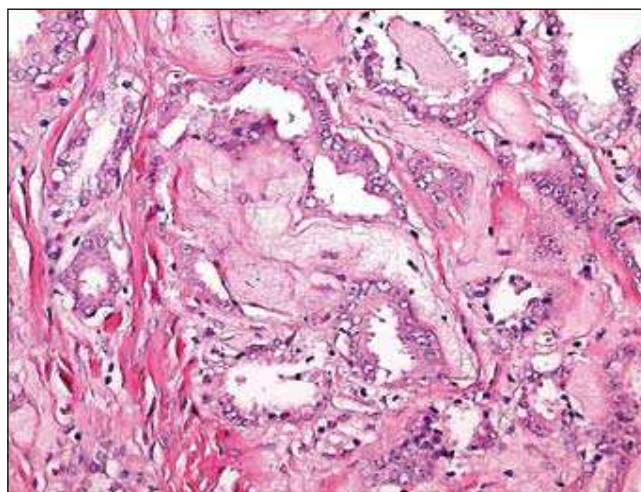3. *Gleason DF:* Histological grading and staging of prostatic carcinoma. In Tannenbaum M (Ed): The Prostate. Philadelphia, Lea and Febiger, 1977, 171
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