Gleason Grading Of Prostate Cancer

A Contemporary Approach

1st Edition
Dedication

To our families, in appreciation of their silent sacrifices over the years and especially during the preparation of this book.

For my wife, Ushma, and children, Anmol and Aneri.  

M. B. A.

For my wife, Laurie, and children, Robert and Mark.  

D. J. G.

For my wife, Kay, and children, Tom and Jen.  

P. A. H.

For my wife, Sandra, and children, Jocelyn, Justin, and Jillian.  

J. R. S.
Authors

Mahul B. Amin m.d.
Director of Surgical Pathology
Professor
Departments of Pathology, Urology, Hematology, and Oncology
Emory University School of Medicine
Atlanta, Georgia

Peter A. Humphrey m.d., ph.d.
Professor
Department of Pathology and Immunology
Washington University School of Medicine
St. Louis, Missouri

David J. Grignon m.d.
Professor and Chairman
Department of Pathology
Wayne State University
Specialist-in-Chief
Detroit Medical Center
Barbara Ann Karmanos Cancer Institute
Detroit, Michigan

John R. Srigley m.d., f.r.c.p.c.
Professor
Department of Pathology and Molecular Medicine
McMaster University
Hamilton, Ontario, Canada
Chief
Department of Laboratory Medicine
The Credit Valley Hospital
mississaug, ontario, Canada
Preface

One of the most powerful histologic grading schemes that has emerged in oncologic pathology is the Gleason grading system for prostate cancer. Although the system was first proposed in the late 1960s, it was only in the late 1980s and early 1990s that there was broad consensus in North America to more widely adopt this system. Vast literature since then has established Gleason score as one of the paramount pathologic factors in predicting disease outcome. In fact, the grading scheme has now become so vital that it is often used as an integral piece of information in both management and treatment stratification of patients with prostate cancer before and after definitive therapy. Sometimes the Gleason score is used to determine whether a patient should receive any therapy at all.

Given this historic context, the objectives of this book are as follows: 1) The principles of the Gleason system were established on the basis of observations made primarily on material from 14-gauge needle biopsies, transurethral resections, and simple prostatectomies. The 18-gauge needle biopsy used almost universally today provides approximately one-third the width of the 14-gauge needle biopsy. This requires extrapolation and modification of some of the original principles of the Gleason system (which we propose in this book) in order to facilitate application in these more limited specimens while preserving the prognostic utility. 2) The practice of urology has dramatically changed with the availability of serum PSA and transrectal ultrasound to help detect cancers earlier. Consequently, the volume of cancer encountered in needle biopsies today is, on average, often significantly lower. Sextant to 12 or more core needle biopsies, as well as radical prostatectomies, are standard diagnostic and therapeutic approaches. All of this raises concerns about the application and reporting of Gleason score in contemporary clinical scenarios and specimens; hence, a contemporary approach to Gleason grading is needed. 3) Given the increasingly heavy reliance on this system for clinical management, interobserver variability in reporting must be minimized. Our aim in publishing over 300 images here is to expose practicing pathologists to the entire spectrum of possibilities, both morphologic and clinical, which should assist in attaining more robust interobserver reproducibility. The book would also be useful to pathology residents and fellows, urologists, and all interested in prostate cancer. 4) When a clinical or pathologic parameter is used for patient management, it is expected to be practiced with the “standard of care” principles and, consequently, adverse outcomes are exposed to the possibility of medicolegal litigation. We are aware of lawsuits beginning to appear for “erroneous” grading. To assist pathologists, we have outlined numerous pitfalls and provided diagnostic pearls to aid in their daily clinical practice. 5) Finally, given the incontrovertible importance of the Gleason grading system, the World Health Organization Classification (WHO, 2003) has for the first time endorsed Gleason grading as the standard, and the AJCC/UICC TNM manual (2002) has incorporated the Gleason system. These important endorsements are in synchrony with the Armed Forces Institute of Pathology fascicle (Series 3, volume 28) and the guidelines for reporting of cancer produced by the College of American Pathologists (CAP) and the Association of Directors of Anatomic and Surgical Pathology (ADASP). All of this should ensure worldwide acceptance and, hence, the timing of this book is, we believe, opportune.
Our approach in preparing this book has been unique. All authors spent over five days (over two separate long weekends) in Atlanta simultaneously reviewing several hundred cases using a multiheaded microscope (see photo). The cases were extracted from the vast clinicopathologic material we have collected over the years. Our collective experience of having used the Gleason system to grade literally thousands of cancers served as a platform for discussion and for making recommendations. A case was chosen for publication only when there was a consensus Gleason grade among all of us, at which time a representative image was captured using a digital camera. During our two meetings, we captured over 1,500 images. Our final selection of the more than 300 illustrations was influenced by the following guidelines: 1) illustration of the entire morphologic diversity and panorama of Gleason grading situations, which also encompasses special situations such as variants of prostate cancer and variations in histology, including those produced by therapy and artifact; 2) inclusion among the illustrations of not only the most classic textbook examples, but also the gray areas or “cusp” patterns that only a volume solely dedicated to the subject of grading has the luxury to reproduce; and 3) ample inclusion of examples of pitfalls in grading. Another departure from convention is the inclusion of figure legends detailed enough to serve as stand-alone text.

After completing this book, we are still amazed at how a morphologic parameter on a needle biopsy that represents approximately 0.04% of the prostate gland and often contains carcinoma in less than 10% of the sample (hence, representing less than 0.004% of the prostate) provides such powerful information that it works in almost every clinical setting—no therapy, surgical, radiation or hormonal therapy, and adjuvant or neoadjuvant therapy. In trying to preserve the prognostic validity of the Gleason system in contemporary practice and approach, we have made recommendations and modifications based on the literature and on personal experience, as well as communications with other urologic pathologists as to how they apply the Gleason system. Hence, while we are of the opinion that our approach is rather mainstream, some of it is not based on objective data, thus, future data may require the approach to be modified. Due to the inclusion of difficult or “gray zone” cases, it is also likely that not all experts will agree with every Gleason grade we have provided with our illustrations.

Finally, such a monumental task could not be achieved without the help and support of a number of individuals. We are indebted to Dr. So Dug Lim (Emory) and Dr. Rafael Cabrera and Dr. Paulo Salles (visiting pathologists to Emory from Portugal and Brazil, respectively) for their expert assistance in digital capturing and recording of images. For
their assistance in manuscript preparation, we also wish to thank Suzanne Briceño (Atlanta), Margaret Chesney (St. Louis), Lydia Cuper (Detroit), and Barbara Jones (Mississauga). We are thankful to Dr. William Alisbrook, Jr., for loaning us glass slides from an earlier interobserver reproducibility study he coordinated (see Chapter 4). We are grateful to our clinical colleagues, who contributed clinical material, and our pathology colleagues, who submitted consultation cases with specific questions that serve for us to appreciate problem areas perceived in the community.

We are grateful to Dr. Gleason for his seminal work, his astute observations, and his leadership, all of which has led to the establishment of the principles of the Gleason system and enhanced the role of the surgical pathologist as an integral participant in the multidisciplinary approach to prostate cancer management.

Mahul B. Amin
David J. Grignon
Peter A. Humphrey
John R. Srigley
Contents

Dedication

Authors

Preface

Contents

1 Background, Principles, and Overview of the Gleason System

2 Contemporary Application of Gleason Grading in 18-Gauge Needle Biopsy, Transurethral Resection, and Radical Prostatectomy Specimens

3 Gleason Scoring in Unusual Situations

4 Reproducibility of the Gleason System

5 CLINICAL SIGNIFICANCE OF GLEASON GRADING

6 REPORTING OF PROSTATE CARCINOMA BY THE GLEASON SYSTEM

subject Index
Background, Principles, and Overview of the Gleason System

BACKGROUND AND HISTORICAL PERSPECTIVES

The modern surgical pathologist's role as diagnostic oncologist mandates knowledge and skill that extends beyond that required simply to make a histologic diagnosis of cancer. Detailed information regarding tumor subtype, histologic grade, pathologic stage, and sometimes other morphologic and phenotypic parameters is required by surgeons and oncologists to properly treat patients with cancer. Indeed, the contemporary surgical pathology report on cancer specimens includes not only the diagnosis but also the relevant morphologic prognostic and predictive factors that pertain to a given tumor subtype. There has been burgeoning literature on the importance of pathologic prognostic factors in many solid tumors (1). Morphologic parameters, including tumor subtype, histologic grade, pathologic stage, and margin status often have strong and consistent correlations with patient outcome, especially in common carcinomas. Currently, basic morphologic factors have more strength in predicting patient outcome than most novel phenotypic and genotypic markers (2).

Among the morphologic prognostic factors, histologic grade has assumed immense importance, especially in common solid tumors such as breast and prostate cancer. Histologic grade coupled with variables such as clinical stage and other measurements, such as estrogen and progesterone receptor protein expression or serum prostate-specific antigen levels, are used to choose the appropriate primary or adjuvant therapies for the individual patient. Additionally, grading has strong prognostic value for groups of patients with given tumor types.

The concept of grading as applied to a histologic or cytologic tumor sample refers to the identification and grouping of morphologic attributes along a scale that conveys a range of aggressivity to the tumor. The grade is usually expressed numerically (1 to 3, 1 to 4) or qualitatively (low-grade, high-grade; well, moderately, and poorly differentiated). The histologic grade of a neoplasm generally relates to its degree of differentiation compared with the nonneoplastic tissue counterpart. Cytologic grade may incorporate microarchitectural or cytoplasmic features, but more consistently uses nuclear features, such as pleomorphism, chromatin pattern, nuclear membrane irregularity, and nucleoli and mitotic activity—all factors that generally require high-power microscopy for evaluation.

Since the early days of the microscope, it has been recognized that the morphologic grade of a neoplasm correlates with malignant biologic behavior (3). In 1920 Broders formalized the first grading system in a study of squamous cell carcinoma of the lip. He devised a four-tiered scheme based on the degree of differentiation (4). More than 80 years have passed since the original Broders publication, and there have been numerous specific grading systems based on anatomic tumor site and specific histogenetic subtypes,
such as ductal carcinoma of the breast and adenocarcinoma of the prostate. While some systems are very detailed and focused on specific criteria, others involve a more general “gestalt” approach (i.e., well differentiated versus moderately differentiated versus poorly differentiated).

In no other tumor has grading assumed a greater significance than in prostate cancer, where it is now considered a standard descriptor required for both determining individual treatment and for assessing prognosis (5) (see Chapter 5).

Prostatic adenocarcinoma lends itself particularly well to histologic grading. From the biologic perspective, there is a wide range in tumor behavior. Autopsy studies have shown a prevalence rate of 30% for histologic cancer in men over the age of 50 (6,7). Indeed, a recent study has identified “incidental” histologic tumors in as many as 16% of men in the 20 to 40 year range, 3% in the 40 to 60 year range, and 57% in the 60 to 80 year range (8). Despite these high prevalence rates for histologic cancer, it is estimated that only approximately 12% of men will actually develop clinical disease during their lifetime (9). This figure, however, is changing with the move toward increasing case detection in prostate-specific antigen (PSA) screening programs. Approximately 3.6% of men will actually die of prostatic cancer (9). These statistics underscore the biologic diversity of prostate cancer and support the truism that a man is more likely to die with prostate cancer than of it.

To deal with this biologic heterogeneity, classification systems have been devised to stratify patients into treatment and prognostic groups. Staging systems that classify on the basis of tumor extent have been widely employed. The tumor, node, metastasis (TNM) staging system [American Joint Commission on Cancer (AJCC), International Union against Cancer (UICC)] has now largely supplanted the earlier systems of the Veterans Administration Cooperative Urological Research Group (VACURG) and Whitemore-Jewett (10, 11 and 12). Staging is a powerful tool for classifying patients into relevant therapeutic and prognostic groups. However, it was recognized early on that the assessment of histologic differentiation (grade) could provide additional information above and beyond that provided by stage alone (11).

In the more than 80 years since the original grading system described by Broders, more than 40 systems for grading prostatic adenocarcinoma have been proposed (13). These schemes are based on a variety of morphologic features, including architectural pattern, degree of differentiation, mitotic activity, and various nuclear factors. Several nuclear morphometric systems have also been proposed, although they have not been widely translated into routine practice, mainly because of the extra time required for quantitative assessment (14, 15, 16, 17, 18 and 19). Selected grading approaches using routine microscopy since the initial publication of Gleason in 1966 are shown in Table 1-1 (20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36). The majority of these approaches use a combination of histologic differentiation and cytologic features. The most well known of these combined systems is probably the World Health Organization (WHO) classification (1975, 1980), which assesses the presence of both glandular differentiation and nuclear anaplasia (29,30).

The Gleason grading system (1966) is one of a relatively few number of systems that employs a low-power architectural approach (20, 21, 22 and 23). Currently, the Gleason scheme is the most widely used grading system in North America, and it is also extensively employed throughout the world (37). For the first time and in contrast to their recommendations in previous editions, both the AJCC TNM manual (2002 edition) and the most recent WHO classification (2003) have endorsed the Gleason system, undoubtedly making it more consistently practiced worldwide. Most other influential recommendations or guidelines, including those written by the Armed Forces Institute of Pathology, the College of American Pathologists, and the Association of Directors of Anatomic and Surgical Pathology, have also endorsed the Gleason system (2,7).

An immense amount of clinical, pathologic, and other research data have been published in relationship to the Gleason grading system.

In the years since the Gleason system was described, urology and surgical pathology practices have changed remarkably. In earlier decades, benign prostatic hyperplasia (BPH)
was managed mainly by surgical techniques—namely transurethral resection and simple prostatectomy. These procedures are used less commonly now, because medical and minimally invasive surgical techniques have been developed to treat BPH (38, 39 and 40). Consequently, transurethral resectates and simple prostatectomy specimens form a smaller proportion of prostatic specimens seen by the surgical pathologist.

Table 1-1. GRADING SCHEMES FOR PROSTATIC ADENOCARCINOMA USING ROUTINE MICROSCOPY*

<table>
<thead>
<tr>
<th>Study (ref no)</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason et al. (20, 21, 22 and 23)</td>
<td>1966-1974</td>
<td>Five patterns and their combination as most common and second most common pattern (score)</td>
</tr>
<tr>
<td>Jewett et al. (24)</td>
<td>1968</td>
<td>Three grades of well, moderately, and poorly differentiated cancer</td>
</tr>
<tr>
<td>Mobley &amp; Frank (25)</td>
<td>1968</td>
<td>Grades 1-3, using gland-forming ability and nuclear features</td>
</tr>
<tr>
<td>Utz &amp; Farrow (26)</td>
<td>1969</td>
<td>Grades 1-4, based on architecture, cytology, and mitoses</td>
</tr>
<tr>
<td>Jewett et al. (27, 28)</td>
<td>1972, 1977</td>
<td>Four groups based on histologic pattern, in order from best to worst prognosis: well differentiated, poorly differentiated, cribriform, solid-anaplastic</td>
</tr>
<tr>
<td>Mostofi et al. (WHO) (29, 30)</td>
<td>1975, 1980</td>
<td>Grade I-III, using capacity to form glandular spaces and nuclear atypia</td>
</tr>
<tr>
<td>Gaeta et al. (31)</td>
<td>1980</td>
<td>Grades IV, defined by gland formation and organization, amount of stroma, nuclear atypia, and mitotic count</td>
</tr>
<tr>
<td>Böcking et al. (32, 33)</td>
<td>1980, 1982</td>
<td>Grade of 1-3 based on differentiation pattern and nuclear anaplasia, using highest grade</td>
</tr>
<tr>
<td>Brawn et al. (34)</td>
<td>1982</td>
<td>MDAH system: grade 1-4, depending on % tumor that is gland-forming or non-gland-forming</td>
</tr>
<tr>
<td>Schroeder et al. (35)</td>
<td>1985</td>
<td>Scoring system with five prognostic groups, based on architecture, nuclear anaplasia and mitoses</td>
</tr>
<tr>
<td>Uchida et al. (36)</td>
<td>1988</td>
<td>Japanese General Rules of Prostatic Cancer: well, moderately, and poorly differentiated</td>
</tr>
</tbody>
</table>

*Only systems based on H&E staining and routine microscopy since the original description of the Gleason system (1966) are included in this table.

WHO, World Health Organization; MDAH, M.D. Anderson Hospital.

Needle biopsy practice has also changed dramatically. Between the 1960s and 1980s, digitally directed, thick (14-gauge) needle biopsies were commonly used. The modern, gun-type biopsy instruments were developed in the 1980s, and they were coupled with transrectal ultrasound imaging (41). Systematic sampling techniques were also developed, including the sextant and extended sextant approaches. The thin-core, 18-gauge biopsies individually produce significantly less tissue than the older, 14-gauge needles did, but the cores display much less artifact. The thin-core biopsies are less painful for the patient and have fewer complications, thus allowing more aggressive sampling of the gland (42). The Gleason system was never specifically designed with these thin prostatic cores in mind.

Another change in clinical practice over the last 20 years has been the increasing use of radical prostatectomy. Numerous developments were made in the technical aspects of the operation, including the development and refinement of the nerve-sparing technique (43). Radical prostatectomy is widely performed in academic and community centers, and the resulting specimens are commonly seen on the surgical pathology bench. The radical prostatectomy specimen provides interesting grading problems—especially with respect to the issue of multifocal disease and the handling of multiple Gleason patterns (see Chapter 6).

PRINCIPLES OF THE GLEASON SYSTEM

The Gleason grading system was developed by Dr. Donald F. Gleason in conjunction with the VACURG (20, 21 and 22). Over a 15-year period from 1960 to 1975, close to 5,000 patients with prostate cancer participated in the VACURG randomized clinical trials. Grading was performed in a large proportion of the trial cases by Dr. Gleason. There was long patient follow-up, using survival as an end point (23).

The Gleason grading system entails several basic principles. First, the system is based on classification of histologic patterns at relatively low magnification (10X to 40X, which
equates to using a 1¥ to 4¥ objective coupled with a 10¥ ocular. The low magnification makes it relatively easy for the pathologist to scan slides and assess the architectural pattern of the tumor. Very little time is added above the time required to establish a diagnosis of prostatic adenocarcinoma. The histologic patterns are characterized with respect to the “extent of glandular differentiation and the pattern of growth of tumor in the prostatic stroma” (20). Dr. Gleason identified nine basic patterns of prostatic adenocarcinoma (Fig. 1-1, Table 1-2). In initial studies, these patterns were recorded by Dr. Gleason and correlated with survival data by the VACURG study statistician. It was found that some patterns commonly occurred together and showed similar correlation rates with mortality. In total, there were two distinct patterns and three sets of related patterns that were rank ordered from 1 to 5, reflecting increasing degrees of biologic malignancy (23).

The nine patterns lumped in five grades are depicted in a simple diagram for the purpose of teaching the system to others (23). The diagram (Fig. 1-2) clearly depicts individual patterns and also shows the boundary areas between patterns and grades.

In the original cases, Gleason noted that approximately one-half of the tumors had more than one grade. In looking at the biologic malignancy of those cases, it was determined that patients with two different grades displayed mortality rates that were in between the mortality rates of the patients who had pure tumors of either of the two grades. The biologic behavior correlated better with the average of the two grades than either the best or worst grades.

FIGURE 1-1. Original hand drawings by Dr. Donald Gleason (1968) showing the nine fundamental patterns that eventually comprised the overall Gleason grading diagram. (From Yesner R, Kelly LJ, Chen YK. Minimum prostate-specific antigen (PSA) level diagnostic of prostate cancer. Conn Med 1996;60:399-404, with permission.)
Table 1-2. DESCRIPTION OF NINE BASIC PATTERNS COMPRISING THE GLEASON GRADING SYSTEM

<table>
<thead>
<tr>
<th>Tumor shape Pattern and borders</th>
<th>Stromal Invasion</th>
<th>Tumor cell arrangements</th>
<th>Gland size</th>
<th>Cytoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Nodular, well-defined, and smooth edges</td>
<td>Pushing</td>
<td>Single, round to oval, closely-packed, but separate glands</td>
<td>Small to medium</td>
<td>Clear to lightly eosinophili c, similar to benign glands</td>
</tr>
<tr>
<td>2 Masses less well-defined and less well-circumscribed</td>
<td>Some gland separation at tumor edge with limited infiltratio n</td>
<td>Single, separate, round to oval glands, with more variation in gland size and shape, and loosely-packed with stromal separation (up to one gland diameter, on average)</td>
<td>Small to medium</td>
<td>Same as pattern 1</td>
</tr>
<tr>
<td>3A Ill-defined, infiltrating edges</td>
<td>Irregular extension of variable shape and</td>
<td>Single, separate glands more clear than size, with elongated, angular and twisted forms, usually with wide stromal separation</td>
<td>Medium to large</td>
<td>More amphophil ic or patterns 1 and 2</td>
</tr>
<tr>
<td>3B Ill-defined, infiltrating edges</td>
<td>Irregular extension are smaller</td>
<td>Same as 3A but glands</td>
<td>Small to tiny</td>
<td>Same as pattern 3A</td>
</tr>
<tr>
<td>3C Masses and cylinders with smooth, rounded edges</td>
<td>Expansile</td>
<td>Papillary and cribriform epithelium, with well-defined and regular lumina, without necrosis</td>
<td>Medium to large</td>
<td>More amphophil ic than patterns 1 and 2</td>
</tr>
<tr>
<td>4A Raggedly infiltrative</td>
<td>Permeative</td>
<td>Fused, microacinar, papillary, and cribriform glands, creating masses, cords, or chains</td>
<td>Small, medium, or large</td>
<td>Amphophil ic or basophilic</td>
</tr>
<tr>
<td>4B Raggedly infiltrative</td>
<td>Permeative</td>
<td>Similar to 4A, but cells have clear cytoplasm (hypernephroid)</td>
<td>Small, medium, or large</td>
<td>Pale or clear</td>
</tr>
<tr>
<td>5A Smooth, rounded cylinders</td>
<td>Expansile</td>
<td>Papillary, cribriform, or solid masses with central necrosis = Comedocarcinoma</td>
<td>Variable</td>
<td>Variable, often amphophil ic or basophilic</td>
</tr>
<tr>
<td>5B Raggedly infiltrative</td>
<td>Diffusely permeative</td>
<td>Masses and sheets of anaplastic carcinoma, with few indistinct glands or signet ring cells</td>
<td>Small</td>
<td>Similar to 5A</td>
</tr>
</tbody>
</table>


In the early writings of Gleason, the terms “patterns” and “grades” were used almost interchangeably (20, 21, 22 and 23). However, for our purposes, pattern will be used for one or more of the original nine patterns described by Gleason, and grade will be used for a pattern or combination of patterns that are reflected in the five bands of the Gleason diagram.

In using this system, the predominant grade based on surface area of all tumor examined is defined as the primary grade; the secondary grade is the second most common one. Adding these two grades together yields the Gleason score, which ranges from 2 to 10. In the literature, other terms have been used for the Gleason score, including Gleason sum, Gleason grade, combined Gleason grade, category score, histologic pattern score, and histologic score. “Gleason score” will be used here.
The concept of averaging a primary and secondary grade is unique with respect to the grading of human tumors. In most other malignancies, it is known that the worst tumor grade determines biologic outcome.

When only a single grade is identified, this grade is doubled to arrive at the Gleason score. In the early writings of Gleason, a qualitative approach to the handling of minor secondary grades was taken. Gleason stated that:

A strong effort was made to limit the histologic grade to a single pattern in each case. A few large glands or a few tiny squeezed glands at the centre or the periphery of a mass in pattern 1 tumor did not change it to patterns 2 or 3. A few elongated glands or a few small cribriform masses did not change a pattern 2 tumor to a pattern 3. An occasional small area of fused glands did not change a pattern 3 tumor to a pattern 4. A small focus of disorganized cells did not change a pattern 3 or 4 tumor to pattern 5 (23).

In later literature, he suggested that if a secondary grade was present but only a minor component (i.e., less than 5% of the tumor), it could be ignored and the primary grade doubled to arrive at a Gleason score (44).

In the original VACURG cases, there were a number of carcinomas with more than two grades, but there were too few in the original studies to properly assess their biologic behavior. In one publication, Gleason outlined a series of somewhat complex rules for dealing with multiple grades, but some of these arbitrary rules appear to contradict one another and were not substantiated by any published data (44). It is now recognized that tertiary, high-grade patterns should be mentioned in surgical pathology reports (for reporting guidelines, see Chapter 6) (45).

The Gleason system has been used for over 35 years, and its widespread success is attributed to several factors. First, there is an immense database of publications showing strong clinical correlation between Gleason grading and numerous clinical, pathologic, and outcome parameters. Second, the Gleason system is simple. It is based on low-power microscopic assessment that adds very little time to the pathologist’s assessment of prostatic adenocarcinoma. There is recognition that many prostatic cancers contain more than one histologic pattern and that they could be classified as predominant and secondary based on surface area of involvement. Third, no histogenetic models need to be embraced to use this grading system. Finally, for the purpose of teaching, the famous Gleason drawing (Fig. 1-2) provides a simple visual aid for pathologists that they can keep
near their microscopes for assessment of individual cases. The diagram accurately reflects the wide diversity of patterns of prostatic adenocarcinoma and, as such, has stood the test of time.

**DISTRIBUTION OF GLEASON SCORES (GRADES)**

The original Gleason series was based on 2,912 cases from the VACURG studies. It consisted of a mixture of needle biopsies (60%), transurethral resectates, and prostatectomies (23). The distribution of Gleason scores is shown in Table 1-3. Of particular note is the small percentage of cases (5.5%) in the low-grade category (score 2 to 4) and the high proportion of cases (23%) in the high-grade category (score 8 to 10). Also of note is the relatively small percentage (9%) of Gleason/VACURG cases assigned a score of 7 compared with the pooled contemporary needle biopsy data for clinically localized disease (29.5% of cases) and to the unselected, prospective needle biopsy series (42% of cases) (46, 47, 48, and 49). The difference in the prevalence of Gleason score 7 is even more pronounced in the pooled radical prostatectomy data, which show close to 50% of cases with a Gleason score of 7 (46, 47, 48, and 49). There is a low percentage of high Gleason score cases in the modern needle biopsy and radical prostatectomy series compared with the early work of Gleason. To a great extent, these differences reflect the different stage distribution in the historical versus contemporary series, as well as the selection factors in choosing patients for radical prostatectomy. The higher prevalence of Gleason score 7 in more contemporary series may, in part, reflect differences in the application of criteria related to “gland fusion.” In addition, a more aggressive approach is used to grade the tiny, thin-core needle biopsy specimens, in which even tiny foci of gland fusion occupying less than 1% of the surface area of the tumor are used to derive the final Gleason score. In Gleason's original data, a minor secondary grade would have been ignored, and the primary grade would have been doubled to arrive at the Gleason score (44).

The differences in the distribution of Gleason scores between the pooled needle biopsy data for clinically localized disease and the prospective community-based needle biopsy series (Table 1-3) are accounted for by at least two major factors. First, the pooled needle biopsy data for clinically localized cancer reflect a group of selected patients deemed suitable for cancer surgery (i.e., selection bias). Second, this group of patients contains a high proportion of individuals whose tumors were detected in a screening scenario, hence the high proportion of Gleason 6 tumors. The prospective, community-based needle biopsy series displays a high proportion of Gleason score 7 tumors (42%) along with a sizeable proportion of high-grade (Gleason score 8 to 10) tumors (16.8%), reflecting the unselected nature of this population. Additionally, it reflects a Canadian (Ontario-based) practice where prostate cancer screening is not as commonplace as in the United States, and where screening programs are neither endorsed nor funded as part of the universal health care system.

**Table 1-3. COMPARISON OF DISTRIBUTION OF GLEASON SCORES AMONG HISTORIC AND CONTEMPORARY SERIES: CLINICALLY LOCALIZED CANCER**

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Original Gleason VACURG series* (n = 2,911)</th>
<th>Radiation therapyb (n = 1,954)</th>
<th>Needle biopsiesc (n = 2,004)</th>
<th>Community-based needle biopsies 1999-2002 (n = 1,517)d</th>
<th>Radical prostatectomy (n = 2,004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.5%</td>
<td>0.4%</td>
<td>-</td>
<td>0.05%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3%</td>
<td>1.7%</td>
<td>0.3%</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2%</td>
<td>5.1%</td>
<td>5.5%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19%</td>
<td>13.2%</td>
<td>13.3%</td>
<td>1%</td>
<td>11.3%</td>
</tr>
<tr>
<td>6</td>
<td>43%</td>
<td>35.4%</td>
<td>46.2%</td>
<td>40.2%</td>
<td>33.8%</td>
</tr>
<tr>
<td>7</td>
<td>9%</td>
<td>29.4%</td>
<td>29.5%</td>
<td>42.0%</td>
<td>47.1%</td>
</tr>
<tr>
<td>8</td>
<td>18%</td>
<td>10.5%</td>
<td>4.3%</td>
<td>10%</td>
<td>3.8%</td>
</tr>
<tr>
<td>9</td>
<td>2%</td>
<td>3.8%</td>
<td>0.9%</td>
<td>6.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td>10</td>
<td>3%</td>
<td>0.5%</td>
<td>-</td>
<td>0.1%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

*Based on evaluation of needle biopsies (60% of cases), transurethral resection and prostatectomy chips, and prostatectomies.


c Pooled data (1994-2000) from four large centers representing needle biopsies and corresponding radical prostatectomy cases.

d Recent experience of co-author (Srigley) with series of consecutive adenocarcinomas diagnosed in a community-based Canadian needle biopsy practice.
The radiation therapy series referred to in Table 1-3 shows a wide spread of Gleason scores, and approximately 7% of these cases have a score of 4 or less (50). This may reflect a high proportion of low-grade transition zone tumors and, perhaps, a more liberal assignment of Gleason grades 1 and 2 than would currently be used.

The correlation between primary and secondary grades from the original Gleason series is displayed in Table 1-4A (23). In summary, 1,447 cases (49.7%) displayed a single grade, and 1,464 cases (50.3%) had at least two different grades. Of particular note is the strong correlation between the primary and secondary grades. The lower grades tended to be associated with one another, as did the higher grades. No grade 1 was associated with a grade 5 or vice versa.

A similar display of primary and secondary grades derived from a contemporary needle biopsy series is shown in Table 1-4B. Of note is the absence of grade 1 tumors—a pattern that is virtually nonexistent in thin-core needle biopsies (see Chapter 2). Gleason grade 3 is the most common primary and secondary grade in both series. Interestingly, in the original work of Gleason, the second most common primary grade is 2, and the secondary grade is 5, the latter reflecting many advanced-stage tumors present in this early series. In the contemporary needle biopsy series, the second most common primary and secondary grades are 4.

### Table 1-4. PREVALENCE AND COINCIDENCE OF PRIMARY AND SECONDARY GLEASON GRADES

<table>
<thead>
<tr>
<th>A: Original Gleason data</th>
<th>Secondary grades</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary grades</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>%</td>
<td>1.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>66 (2.3%)</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>%</td>
<td>2.2%</td>
<td>10.5%</td>
<td>-</td>
<td>0.03 %</td>
<td>404 (13.9%)</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>%</td>
<td>8.6%</td>
<td>42.5%</td>
<td>2.6%</td>
<td>5.2%</td>
<td>1,722 (59.1%)</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>%</td>
<td>0.03%</td>
<td>6.1%</td>
<td>1.2%</td>
<td>1.0%</td>
<td>245 (8.4%)</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td>50 (2%)</td>
<td>370 (12.6%)</td>
<td>144 (4.9%)</td>
<td>276 (9.5%)</td>
<td>1,517 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B: Contemporary thin-core (18-gauge) biopsy seriesa</th>
<th>Secondary grades</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary grades</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.0 (15)</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>0.7%</td>
<td>-</td>
<td>-</td>
<td>0.3%</td>
<td>51.2% (775)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>0.3%</td>
<td>40.3%</td>
<td>9.4%</td>
<td>1.2%</td>
<td>-</td>
<td>39.2% (596)</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>32.5%</td>
<td>4.7%</td>
<td>-</td>
<td>2.0%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>3.8%</td>
<td>4.7%</td>
<td>-</td>
<td>0.1%</td>
<td>8.6% (131)</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td>4</td>
<td>1,174 (77.3)</td>
<td>284 (18.8)</td>
<td>55 (3.6)</td>
<td>1,517 (100%)</td>
</tr>
</tbody>
</table>

*a Recent experience of co-author (Srigley) with series of consecutive adenocarcinomas diagnosed in a community-based needle biopsy practice.*
CORRELATION BETWEEN NEEDLE BIOPSY AND RADICAL PROSTATECTOMY GLEASON SCORES

There have been several studies addressing the correlation between Gleason scores in needle biopsy and corresponding radical prostatectomy specimens. Although earlier studies used the thicker (14-gauge) needle biopsies (51, 52 and 53), more recent series reflect the typical, thin-core (18-gauge) needles used in conjunction with biopsy guns attached to transrectal ultrasound (46, 47, 48 and 49). Sextant or other modes of systematic sampling is typically performed in the more current series. In a recent compilation of data on 3,789 patients from 18 studies, Humphrey found exact correlation of Gleason scores in 43% of cases and correlation plus or minus one Gleason score unit in 77% of cases (54). Undergrading of carcinoma in needle biopsy is the most common problem, occurring in 42% of all reviewed cases. Importantly, overgrading of carcinoma in needle biopsies may also occur, but this was only found in 15% of cases (54).

The grading errors may result from different factors. Perhaps the most important factor is sampling error, which relates to the small amount of tissue removed by thin-core needle biopsies (Fig. 1-3). The average 20-mm, 18-gauge core samples approximately 0.04% of the average gland volume (40 cc). Prostatic carcinomas are commonly heterogeneous, and the higher grade component may not be represented in the core. Overgrading can also result from sampling error in cases where the high-grade pattern is selectively represented in needle biopsy. It may only occupy a very minor element in the radical prostatectomy specimen. Even the same cancer focus may have different grades depending on the area sampled (Fig. 1-3). Interestingly, recent data suggest that even minor tertiary elements of Gleason grades 4 and 5 adversely affect outcome and should be included in the surgical pathology report (45).

Undergrading may also result from difficulty in recognizing an infiltrating growth pattern or failing to recognize the presence of small areas of gland fusion. In some instances, undergrading results from an attempt to grade very tiny areas of carcinoma, so-called minimal or limited adenocarcinoma (49,55). Scores of minimal adenocarcinoma in needle biopsies show a reasonably strong correlation with radical prostatectomy scores, but the Gleason scores do not have the same power to predict extraprostatic extension and positive margin status as they do in nonminimal carcinomas (49).

FIGURE 1-3. Schematic representation of multifocal adenocarcinoma within the prostate gland demonstrating potential grade variability associated with sampling. Areas of Gleason grades 2, 3, and 4 are identified, and a focus of grade 5 remains unsampled.
The pathologists' experience in grading thin-core needle biopsies can also influence overall correlation with radical prostatectomy results. With experience, pathologists recognize grading pitfalls; in particular, the fact that Gleason scores of 4 and lower are almost nonexistent in the needle biopsy situation. Furthermore, small areas of fusion in the presence of a predominantly grade 3 background are recognized and will yield a Gleason score of 7, which often correlates well with radical prostatectomy results.

GRADE PROGRESSION

The question of whether the histologic grade of prostate cancer progresses over time is complex. Some have suggested that the hypothesis of “biologic determinism” applies to prostate cancer (56). In this theory, prostate carcinomas have an intrinsic, fixed degree of biologic malignancy. To some extent, questions related to grade progression or stability cannot be answered because complete characterization of the histologic grade of a primary tumor requires examination of the whole prostate, which in itself interferes with the natural history of the disease process. There is some data suggesting that biopsy grades may progress over time, but this may be an artifact of sampling (56,57). Additionally, it has been suggested that “dedifferentiation” may occur after radiation therapy or with metastatic spread, but this could represent high-grade clonal selection that may not have been represented in the initial biopsy sample (58, 59 and 60).

The concept of biologic determinism is somewhat attractive and in keeping with the morphologic observation that small prostatic primaries may be well differentiated, moderately differentiated, or poorly differentiated at the outset (61). Nevertheless, it is also possible that over time prostatic carcinoma may progress to a higher grade in a subset of untreated patients. This would certainly be consistent with the concept of genetic instability of a neoplastic process—especially one with malignant characteristics (62). Nevertheless, at the current time, the issue of grade progression in human prostate cancer remains unresolved.

REFERENCES


Histological typing of prostate tumours.

44. Mostofi FK, Sesterhenn I, Sobin LH. Histological typing of prostate tumours.
54. Ekman P. Maximal efficacy of finasteride is obtained within 6 months and maintained over 6 years. Eur Urol 1996;33:312-317.


Contemporary Application of Gleason Grading in 18-Gauge Needle Biopsy, Transurethral Resection, and Radical Prostatectomy Specimens

In this chapter, we outline the contemporary approach to Gleason grading in diagnostic surgical pathology based on the original Gleason system (1, 2, 3 and 4). The 18-gauge needle biopsy technique currently used yields approximately 36% of the width of the core, compared with the 14-gauge biopsy, hence providing considerably less tissue for examination (5). Although the basic principles and diagnostic criteria remain relatively unchanged, application of the system in contemporary 18-gauge needle biopsies requires extrapolation and modification of some of the principles to facilitate application in these more limited specimens while, importantly, preserving the prognostic utility of the system (see application below for each respective Gleason pattern) (6,7) (Fig. 2-1).

CRITERIA AND PITFALLS FOR THE DIAGNOSIS OF EACH GLEASON GRADE

Gleason Grade 1 ("Very Well Differentiated") (Figs. 2-2, 2-3, 2-4 and 2-5)

Original Gleason Criteria

The tumor growth pattern is that of a well-defined, circumscribed, expansile nodule in which the glands are single, separate and round; of fairly uniform, medium gland size; and closely packed such that stroma in between the glands is minimal but with distinct stromal rims. Key to its recognition is a pushing border with a very smooth, tumor-stromal interface, and monotonously replicated glands (Fig. 2-2A and Figs. 2-3, 2-4 and 2-5).

Application in Needle Biopsy Specimens

Given the narrow width of needle cores, grade 1 cannot be entirely represented in 18-gauge specimens. Grade 1 should not be diagnosed in these specimens because one needs to see the definite edges of the entire focus of carcinoma, and this is not possible in 18-gauge specimens (Fig. 2-2B).

Application in Transurethral Resection and Prostatectomy Specimens

This is the rarest of Gleason grades, and we have personally seen very few examples of Gleason grade 1. Dr. Gleason has acknowledged that his standard drawing (Fig. 2-2A) “deliberately overemphasizes the uniformity of the glands and one must allow for the variation inherent to biologic material” (4). Although the majority of the glands in grade 1
are packed back-to-back, more loosely arranged areas may be present. Plane of sectioning results in variation of gland size and shape, and one may occasionally see even more than two-fold variation in size depending on plane of sectioning (Fig. 2-3). The outline of the nodule of grade 1 cancer may not be perfectly rounded, but rather should be abrupt and relatively smooth. Unquestionable areas at the periphery where glands permeate the adjacent stroma indicate Gleason grade 2.

**Pitfalls in Grading Pattern 1**

(a) The most common pitfall, particularly in needle biopsy specimen, is when an extremely small focus of cancer (e.g., composed of 3 to 6 glands) is graded as grade 1 because stroma is appreciable on all sides of the specimen (Fig. 2-6). As mentioned above, Gleason grade 1 diagnosis should not be made in needle biopsies.

(b) Strict interpretation of Gleason 1 pattern may result in some acceptable cases being diagnosed as Gleason grade 2. Because both grades indicate prostate cancer of low biologic potential, this misclassification has little clinical relevance.
FIGURE 2-3. A: Gleason grade 1 (score 2). Sharply circumscribed proliferation of relatively uniform and closely packed acini in a transurethral resection specimen. This slide was reviewed by Dr. Gleason, and he considered this to represent the “prototypic” grade 1 (score 2) adenocarcinoma. B: Gleason grade 1 (score 2). Higher power photomicrograph illustrating the sharp circumscription of the nodule and the degree of gland shape and size accepted by Dr. Gleason within this pattern. However, the degree of size and shape variation is greater than that depicted in the stylized Gleason diagram. C: Gleason grade 1 (score 2). The edge of the nodule is sharply circumscribed with moderate variation in the size and shape of the glands (primarily due to plane of sectioning) and little intervening stroma. Strict interpretation of the case using the stylized original Gleason diagram would yield a score of 3 (1 + 2).

FIGURE 2-4. A: Gleason score 3 (1 + 2). This sharply circumscribed nodule shows features of grade 1, but in some areas, the degree of gland size and shape variability exceeds that acceptable for a pure grade 1 tumor; hence, a score of 3 is assigned. B: Gleason score 3 (1 + 2). Closer view of the edge of the nodule, highlighting the sharp circumscription and the relative uniformity of the glands. This part of the nodule represents grade 1.
FIGURE 2-5. Gleason grade 1 (score 2). Central portion of a Gleason grade 1 tumor illustrating the gland uniformity with mild variation in size and little intervening stroma.

FIGURE 2-6. Gleason grade 3 (score 6). Small foci of Gleason grade 3 adenocarcinoma should not be misgraded as grade 1 or 2 simply because of its small size or because of apparent circumscription.

Gleason Grade 2 (“Well Differentiated”) (Figs. 2-7, 2-8, 2-9, 2-10, 2-11, 2-12, 2-13, 2-14, 2-15 and 2-16)

Original Gleason Criteria

The tumor growth pattern is that of an expansile nodule that is not as well circumscribed and rounded as grade 1 (Fig. 2-7A). There is a clear-cut, limited stromal invasion, although it may be focal (Fig. 2-8). The glands are single, separate, and round to oval. Although the glands are similar in size and shape, there is greater variability between glands (beyond what is explainable as variation due to plane of sectioning) compared with Gleason grade 1. The stromal spacing between glands may be slightly more irregular than in Gleason grade 1 and up to one gland in diameter.

Application in Needle Biopsy Specimens

Given the narrow width of the needle cores, grade 2 cannot be entirely represented in 18-gauge needle biopsy specimens (Fig. 2-7B). This diagnosis is still tenable if the edges of a circumscribed proliferation are appreciated and if they appear relatively smooth (Figs. 2-10, 2-11, 2-12 and 2-13). Although the entire focus is not represented, grade 2 is assigned to clearly designate low-grade, partially sampled cancers that have well-defined edges and uniformly spaced glands (Fig. 2-7B). If two edges are clearly visible and well defined, a diagnosis of Gleason grade 2, score 4, is made. If one edge appears circumscribed and the other is infiltrative, the cancer is graded as Gleason score 2 + 3 or 3 + 2 = 5, depending on the relative proportion of Gleason grade 2 (Figs. 2-12 and 2-13). An important proviso is that the glands within the cancer are relatively uniform in size and shape with minimal stromal separation between the glands (not exceeding one gland in diameter) and the cytoplasm is frequently clear (Figs. 2-8, 2-9, 2-10 and 2-11, 2-13, and 2-15). Because the diagnosis of grade 2 (score 4) is made on the observation of circumscription of two edges of the cancer and the assumption that the other edges that are not sampled are also smooth, it should be understood that a higher grade may be present at prostatectomy (see Fig. 1-3). Hence, some experts have indicated that Gleason grade 2, like grade 1, should not be diagnosed in needle biopsy specimens (8); other expert urologic pathologists do occasionally make this diagnosis with needle biopsies
Assignment of Gleason grade 2 in needle biopsies represents the best opportunity to pathologically identify potentially low biologic risk prostate cancers based on the Gleason paradigm, which indicates that circumscription is the hallmark of Gleason grade 1 and 2 cancers. In the authors' collective experience, Gleason grade 2 (in Gleason scores 2 + 2, 3 + 2, or 2 + 3) is very uncommon in needle biopsies. In needle biopsy cases with a Gleason score of 4 or 5, it may be helpful to comment that the Gleason score may be higher in the prostatectomy due to the presence of unsampled higher Gleason grades; hence, any treatment planning should not be entirely influenced by the Gleason score in the needle biopsy. In patients with a minimal amount of cancer and “low” Gleason score, some recommend a repeat biopsy before the patient is considered for watchful waiting.

Application in Transurethral Resection and Prostatectomy

Specimens

Grade 2 is more commonly present in transurethral resection and prostatectomy (TURP) specimens containing "incidental" transition zone cancers and in the transition zone in radical prostatectomy specimens. A slight variation in histologic and cytologic features may be seen in a subset of cases. The cytoplasm is abundant; pale eosinophilic or clear; similar to adjacent benign glands; and the cells are tall and columnar (Figs. 2-8 and 2-16). The glands show considerable variation in size and are often large (15,16) (Fig. 2-15). This variation of prostate cancer histology is not restricted to the transition zone and may also be seen in Gleason grade 3 cancers and in cancers arising in the peripheral zone. In some cases, the architecture significantly overlaps with benign prostate hyperplasia (pseudohyperplastic pattern of prostate cancer) (see Figs. 3-24, 3-25, 3-26, 3-27 and 3-28). The overall assignment of Gleason grade 2 in TURPs and radical prostatectomy is made on architectural criteria and the glandular pattern specified in the "Original Gleason Criteria." Occasionally, the stromal planes at the advancing edge of the tumor may be quite prominent with columns of discrete, infiltrating glands, although low-power examination should demonstrate the overall circumscription with limited invasion (Figs. 2-9 and 2-14).

Pitfalls in Grading Pattern 2

(a) An extremely small focus of cancer (e.g., composed of three to six glands) is not a grade 2 simply because stroma is appreciable on all sides of the specimen. Gleason grade 2 is a relatively circumscribed, expansile nodule and, hence, this designation should not be used for a closely packed cluster of glands that are not overtly infiltrative (Fig. 2-17).

(b) Not all circumscribed prostate cancers are Gleason grade 2. Fused glands of Gleason grade 4 may be nodular in configuration with excellent circumscription (Figs. 2-18 and 2-19) in TURP or prostatectomy specimens, and evaluation at an intermediate power may be necessary to recognize gland fusion.

(c) Marked variation in gland size and shape with angulation and marked stromal separation in a circumscribed nodule indicate Gleason grade 3, not grade 2.

(d) The presence of benign glands in an otherwise well-circumscribed nodule indicates Gleason score 2 + 3 = 5 and not 2 + 2 = 4 (see Gleason grade 3 criteria) (Fig. 2-20).

(e) As elaborated in the needle biopsy application of grade 2, it is conceivable that a pattern judged as grade 2 (score 4) may actually represent a higher-grade tumor if the entire focus was available (as in the prostatectomy). This is one of the reasons for "under grading" in needle biopsies when compared with prostatectomy specimens (10, 11, 12 and 13) (see Fig. 1-3).
FIGURE 2-7. A: Gleason grade 2. Original Gleason drawing illustrating the increased variability in gland size and shape and reduced circumscription characteristic of grade 2. Note also the increased amount of stroma present between neoplastic acini within the tumor nodule. B: Gleason grade 2. Stylized drawing of Gleason grade 2 within a contemporary needle core biopsy. To assign this grade, apparent circumscription at both ends must be evident.

FIGURE 2-7. B: (Continued)

FIGURE 2-8. Gleason grade 2 (score 4). A: Transurethral resection chip containing a relatively circumscribed nodule of glands showing moderate size and shape variation with variable amounts of stroma within the tumor nodule. B: Higher power illustrating the irregularity at the periphery of the nodule, the variability in gland shape and size, and the increased amount of stroma between the glands.

FIGURE 2-8. Gleason grade 2 (score 4). B: (Continued)

FIGURE 2-9. Gleason grade 2 (score 4). A: The tumor nodule shows an overall appearance of circumscription; however, the amount of fibrous tissue forming bands and the variability in gland size and shape make this a grade 2 rather than a grade 1 pattern. B: This higher power photomicrograph of the same case illustrates the stromal separation between the neoplastic acini.

FIGURE 2-9. Gleason grade 2 (score 4). B: (Continued)
FIGURE 2-10. Gleason grade 2 (score 4). Needle biopsy containing a focus of Gleason grade 2 adenocarcinoma. Note that the circumscribed edge of the nodule is evident at the right side. The nodule otherwise consists of relatively uniform glands but has moderate amounts of stromal separation.

FIGURE 2-11. Gleason grade 2 (score 4). Needle biopsy containing a focus of Gleason grade 2 adenocarcinoma. Note the relative uniformity of the gland size and shape and the sharp circumscription of the nodule at one edge.

FIGURE 2-12. Gleason score 5 (2 + 3). One edge of the tumor nodule shows closely packed, relatively uniform glands with a sharply circumscribed border corresponding to a grade 2 pattern. The opposite edge (not illustrated) and a few of the glands in the right side had a more infiltrative pattern, leading to the assignment of a Gleason score of 5.

FIGURE 2-13. Gleason score 5 (2 + 3). A: This well-circumscribed nodule of relatively uniform glands is located between two groups of widely spaced benign glands. A sharp circumscription to most of the visible tumor justifies assignment of Gleason grade 2. Scattered, irregular glands extend into the stroma on the left side and, therefore, a secondary grade of 3 is assigned. B: Higher power illustrates the uniformity of the glands, the minimal intervening stroma, and the sharp circumscription in this particular region.

FIGURE 2-13. Gleason score 5 (2 + 3). B: (Continued)
FIGURE 2-14. Gleason grade 2 (score 4). Transurethral resection specimen containing a sharply circumscribed expansile nodule of tumor but showing moderate to marked variation in glandular size and shape, as well as increased amount of stroma, leading to assignment of a grade 2 rather than grade 1.

FIGURE 2-15. Gleason score 5 (2 + 3). In this transurethral resection chip, an expansile tumor nodule contains closely packed but variably sized and shaped glands. The overall impression is one of circumscription. Due to the lack of visualization of the complete edge, however, an overall score of 5 rather than 4 is assigned.

FIGURE 2-16. Gleason grade 2 (score 4). High-power photomicrograph taken from a Gleason grade 2 tumor showing circumscription at one edge and illustrating the variability in size and shape of the glands.

FIGURE 2-17. Gleason grade 3 (score 6). A: Small focus of closely packed glands at the edge of a needle biopsy is assigned a grade of 3 rather than 2 because it is not possible to appreciate circumscription in such a small sample of carcinoma. B: Higher power highlights the gland uniformity, including small gland size and cytoplasmic amphophilia. In this situation, we default to a grade 3.

FIGURE 2-17. Gleason grade 3 (score 6). B: (Continued)
FIGURE 2-18. Gleason score 9 (4 + 5). A: High-grade prostatic adenocarcinomas can occasionally grow in sharply circumscribed nodules, as illustrated in this case. The sharp circumscription does not indicate a low Gleason grade pattern. B: Higher power photomicrograph illustrating the fused glands with high-grade morphology despite the sharp circumscription.


FIGURE 2-20. Gleason score 5 (2 + 3). A: Although this tumor is composed of closely packed, relatively uniform glands with sharp circumscription along one edge, infiltration between benign glandular elements (arrows) is apparent and, therefore, a grade 3 component must be acknowledged. B: Higher power photomicrograph illustrating the infiltrating glands between benign glandular elements.

Original Gleason Criteria

In grade 3, there are three morphologic variations (also referred to as patterns), labeled A, B, and C in the Gleason drawing (Fig. 2-21A). Gleason patterns 3A and 3B are characterized by more severe variations in size and shape and are often accompanied by separation of discrete glandular structures by stroma exceeding one gland in diameter (Figs. 2-22 and 2-24). The glands are more elongated and angular and may be small, medium, or large in the same focus. If most of the glands are medium to large, the focus is designated 3A (Figs. 2-22 and 2-23); if the glands are small (sometimes only evident as tiny clusters of three or more cells with tiny lumina or no lumina), the focus is designated 3B (Figs. 2-24 and 2-25). Gleason pattern 3C consists of well-delineated, circumscribed masses of tumor that have rounded edges and a papillary or cribriform intraluminal proliferation (Figs. 2-50, 2-51, 2-52, 2-53 and 2-54). The rounded masses have fenestrations, resulting in a sievelike appearance (Figs. 2-26, 2-27, 2-51, and 2-52).

Application in Needle Biopsy Specimens

This is the most common grade encountered in needle biopsy specimens (Fig. 2-21B). Because there is no apparent clinical utility in subgrading patterns into 3A, 3B, or 3C, reporting subgrades is not routinely done in needle biopsies. The defining feature for Gleason patterns 3A and 3B is infiltration, which is evidenced in needle biopsies by

(a) the presence of neoplastic glands between benign glands (Figs. 2-22 and 2-23),

(b) a haphazard, random, nonlobular proliferation of irregularly shaped and sized glands (Figs. 2-28, 2-29, 2-30 and 2-31), or

(c) closely clustered glands disposed in a vertical column across the width of a needle biopsy (Figs. 2-32 and 2-33).

Because desmoplasia is not frequently evoked by prostate carcinoma, the presence of neoplastic acini between benign glands or the observation of an altered architecture (haphazard arrangement, vertical column) should be viewed as evidence of invasiveness (Figs. 2-35, 2-36, 2-37, 2-38, 2-39, 2-40, 2-41, 2-42, 2-43, 2-44, 2-45, 2-46, 2-47 and 2-48). Hence, if diagnosed as cancer and composed of discrete (nonfused) glands, even the most limited focus of cancer (composed of 2, 3, or 4 glands or more) is Gleason grade 3. If malignancy is diagnosed on the basis of a single gland (e.g., one invading or circumferentially surrounding a nerve), it is a Gleason grade 3 (score 3 + 3 = 6) by virtue of its infiltrating prostatic parenchyma into the nerve or perineural space (Fig. 2-34). Glands of pattern 3B may mimic prostatic atrophy ("atrophic pattern of prostate cancer") (see Figs. 3-29, 3-30, 3-31 and 3-32).

Although the hallmark of Gleason pattern 3C is a cribriform architecture, this feature alone does not indicate Gleason grade 3. The glandular units must be regular and evenly spaced with smooth borders, and the intraluminal spaces within them should be relatively smooth (Figs. 2-26, 2-27, 2-51, and 2-52). The intraluminal component may be papillary and/or cribriform but not solid or with irregularly fused glands; the latter two features qualify for a grade 4 designation. The intraglandular spaces in Gleason grade 3 should be of medium size; presence of very small fenestrations represents Gleason grade 4 and not grade 3. The separation of cribriform grade 3 from cribriform grade 4 is one of the most difficult and controversial issues in contemporary Gleason grading (see Chapter 4). Cribriform proliferations span a continuum from single, discrete cylindrical structures with regular, sharply punched, sievelike spaces (Gleason 3, in our opinion) to cylindrical structures with intraluminal spaces that are more irregular, appearing fused (Gleason 4) and even solid (Gleason 5) at the other end of the spectrum (Fig. 2-73). The shape and configuration of the cylinders is also important, and it varies from being discrete, smooth, and round (Gleason
3, in our opinion) to proliferations in which the outlines become irregular, scalloped, and fused with adjacent cribriform structures (Gleason 4). In this continuum of cribriform proliferations, we recommend that only those with discrete, single, round, cylindrical structures with medium-sized intraluminal proliferations that are relatively even, punched out, and distinct be designated Gleason 3. If the outer contours are round and cylindrical and the inner proliferation shows variability between even punched-out spaces and fused spaces, we are of the opinion that the fused spaces merit a grade 4 designation. Hence, employing this concept, even a single cylindrical structure can have a Gleason score 3 + 4 or 4 + 3: Gleason 3 because of a discrete, round, and smooth outer aspect and some even-punched intraluminal spaces; and Gleason 4 because of areas with intraluminal fusion (Fig. 2-73). There are no data to support this approach, but we are aware of other urologic pathologists who also practice with this philosophy (13,17). In contrast, others (18,19) recommend that most cribriform proliferations indicate grade 4 because the cribriform pattern is seen in the company of cancer that is biologically more aggressive than that seen in grade 3. This approach clearly departs from Gleason's original proposal, which is still largely endorsed (20). Our position for handling many cribriform proliferations departs from the original Gleason paradigm and is intermediate in the spectrum of opinion, but it is in keeping with the current mainstream practice of grading (13).

Application in Transurethral Resection and Prostatectomy

Specimens

As in needle biopsies, this is the most prevalent Gleason grade in radical prostatectomy specimens, and there is no known clinical value in reporting individual patterns of Gleason grade 3. Application in these specimens is based on the original Gleason criteria and features characterizing invasion in prostate cancer (defined in the section of application in needle biopsy specimens).

Pitfalls in Grading Pattern 3

(a) Neoplastic acini may branch, which often results in V- and Y-shaped configurations that are long, tortuous, and serpiginous and that raise the possibility of fusion (Figs. 2-38, 2-39, 2-41, 2-42, and 2-86, 2-87, 2-88, 2-89 and 2-90). In three dimensions, malignant neoplastic acini may have a complex branching configuration that may mimic fusion when cut randomly in two-dimensional H & E histology. Strict criteria are required for fusion (see Gleason grade 4).

(b) Not all cribriform neoplastic proliferations are Gleason grade 3. Besides the extraordinarily rare adenoid cystic carcinoma (which should not be assigned a Gleason grade), prostatic adenocarcinoma of the usual type may have a cribriform architecture that is not a Gleason 3 grade (Figs. 2-55 and 2-73). In fact, in our experience, most cribriform proliferations of prostatic adenocarcinoma are Gleason grade 4 or 5 (see below).

(c) Tightly packed or “squeezed” yet discrete and separate acini should not be interpreted as fused glands (Figs. 2-56 and 2-57). As long as an imaginary line can be drawn around each acinus, it is a Gleason grade 3. Thick sections compound this diagnostic problem.

(d) Small clusters or tiny or absent lumina of grade 3B should not be construed as a lack of, or poor evidence of, gland formation and designation as Gleason grade 4 or 5. Small-caliber glands cut tangentially may result in cords that also should not evoke a grade 4 diagnosis (Figs. 2-25 and 2-43).

(e) The mere presence of signet rings in a carcinoma does not indicate grade 5 Gleason cancer, because on rare occasions, signet rings may be seen in discrete neoplastic acini of pattern 3 (Fig. 2-58).
FIGURE 2-21. A: Original Gleason diagram illustrating the three patterns comprising grade 3. B: Stylized diagram depicting a needle biopsy to illustrate the three patterns comprising Gleason grade 3 as they may be seen in an 18-gauge needle biopsy specimen. Acini in green represent benign glands.

FIGURE 2-22. Gleason grade 3 (score 6). The tumor consists of small acini infiltrating between nonneoplastic glands and comprising Gleason pattern 3A.

FIGURE 2-23. Gleason grade 3 (score 6). Note the small, amphophilic acini infiltrating between nonneoplastic glands. This comprises Gleason pattern 3A.

FIGURE 2-24. Gleason grade 3 (score 6). The tumor consists of very small acini, many with collapsed lumina infiltrating through prostatic stroma. This indicates Gleason pattern 3B, not grade 4.

FIGURE 2-25. Gleason grade 3 (score 6). Note the tiny, amphophilic acini with atrophic features infiltrating prostatic stroma. This comprises Gleason pattern 3B, not grade 4.
FIGURE 2-26. Gleason grade 3 (score 6). Sharply circumscribed island with cribriform pattern. In this case, the tumor shows sharply punched out holes without solid areas, representing Gleason pattern 3C.

FIGURE 2-27. Gleason score 6 (3 + 3). Combination of typical infiltrating, small acinar Gleason pattern 3A with sharply circumscribed cribriform pattern 3C.

FIGURE 2-28. Gleason grade 3 (score 6). This focus of minimal (limited) adenocarcinoma consists of a few infiltrating, small acini between nonneoplastic glands, indicating Gleason grade 3.

FIGURE 2-29. Gleason grade 3 (score 6). Microfocus of infiltrating, small acini between nonneoplastic glands, indicating Gleason grade 3.

FIGURE 2-30. Gleason grade 3 (score 6). A small cluster of neoplastic acini between nonneoplastic glands, indicating Gleason grade 3.

FIGURE 2-31. Gleason grade 3 (score 6). Clusters of small, malignant acini between nonneoplastic glands, indicating Gleason grade 3.
FIGURE 2-32. Gleason grade 3 (score 6). A focus of infiltrating, small glands between nonneoplastic glands is seen in this needle biopsy, indicating Gleason grade 3.

FIGURE 2-33. Gleason grade 3 (score 6). A vertical, broad column of infiltrating, small acini invades the prostatic stroma. No gland fusion is present, indicating Gleason grade 3.

FIGURE 2-34. Gleason grade 3 (score 6). Distinct, infiltrating, small glands without fusion around a peripheral nerve. Even as an isolated finding, this is indicative of infiltration and is therefore a Gleason grade 3.

FIGURE 2-35. Gleason grade 3 (score 6). Variably sized and shaped acini infiltrating around nonneoplastic glands (Gleason pattern 3A).

FIGURE 2-36. Gleason grade 3 (score 6). Diffuse involvement of the core by infiltrating, very small acini and small-to-medium acini, comprising Gleason patterns 3A and 3B.

FIGURE 2-37. Gleason grade 3 (score 6). A minute focus of infiltrating, small acini between nonneoplastic ones. This is Gleason grade 3.
FIGURE 2-38. Gleason grade 3 (score 6). Regular branching of medium-sized glands. The degree of branching seen in this case is accepted within Gleason grade 3. No gland fusion is identified in this picture.

FIGURE 2-39. Gleason grade 3 (score 6). Note the branching, irregular glands permeating the prostatic stroma. This degree of branching is allowable for Gleason grade 3. There is no gland fusion in this picture.

FIGURE 2-40. Gleason grade 3 (score 6). A: The neoplastic acini in this case have abundant pale-to-clear cytoplasm, simulating a lower grade pattern. However, they show diffuse infiltration of the stroma and are classified as Gleason grade 3. B: Higher power highlighting the irregular infiltration of acini (some with clear cells) around a benign gland. This constitutes Gleason grade 3 and not a lower grade.

FIGURE 2-40. Gleason grade 3 (score 6). B: (Continued)

FIGURE 2-41. Gleason grade 3 (score 6). Note the complex, irregular branching of the neoplastic acini without glandular fusion.
FIGURE 2-42. Gleason grade 3 (score 6). Note the infiltration of prostatic stroma by small acini with an irregular distribution. The cleared cytoplasm does not necessarily equate with low-grade pattern 1 or 2.

FIGURE 2-43. A: Gleason grade 3 (score 6). Prototypic example of Gleason pattern 3B consisting of tiny, irregular acini permeating prostatic stroma. This should not be confused with higher grades of Gleason 4 or 5. B: Gleason grade 3 (score 6). Higher power of same case. Note the tiny microacini infiltrating the prostatic stroma. In most areas, tiny lumina are identified. In some areas, there is an appearance of single cells, but these likely represent tangential edges of small glands. The glands have atrophic features due to loss of cytoplasmic volume. C: Gleason grade 3 (score 6). Radical prostatectomy specimen. Low-power photomicrograph showing infiltrating microacini of Gleason pattern 3B. D: Gleason grade 3 (score 6). Higher power of example in (C). Note the very small and discrete microacini infiltrating glands of high-grade prostatic intraepithelial neoplasia. The pattern is typical of Gleason pattern 3B.
FIGURE 2-44. Gleason grade 3 (score 6). A: Note the infiltrating, nonlobular, and irregular small acini comprising Gleason grade 3. B: At higher power, no fusion is apparent.

FIGURE 2-45. Gleason grade 3 (score 6). A: Needle biopsy showing infiltrating, small-to-medium sized acini with foamy gland appearance. In the absence of fusion, this is indicative of Gleason grade 3. B: Higher power shows lack of fusion between acini.

FIGURE 2-46. Gleason grade 3 (score 6). This needle biopsy shows infiltration by variably sized glands—some of which appear atrophic and others more cystically dilated. Although no nonneoplastic glands are identified, this widely infiltrative pattern would be indicative of Gleason grade 3.
FIGURE 2-47. Gleason grade 3 (score 6). A: This needle biopsy is extensively involved by irregular, small acini of Gleason grade 3. B: Higher power demonstrating that the glands are tightly spaced in areas, but there is no evidence of fusion in this case.

FIGURE 2-48. Gleason grade 3 (score 6). Note the tightly packed glands, many with clear cytoplasm. Despite the close packing, this does not constitute glandular fusion, and this would be graded as Gleason grade 3.

FIGURE 2-49. A: Gleason grade 3 (score 6). This unusual pattern of prostatic carcinoma shows prominent retraction artifact around acini. This is graded as a Gleason grade 3 because each of the neoplastic acini is single and surrounded by retracted stroma. B: Gleason grade 3 (score 6). Another area of the same case as (A) showing tiny microacini, many of which have retraction artifacts around the edges. This does not constitute a higher grade pattern but is given a Gleason grade of 3 because the glands are discrete and not fused.
FIGURE 2-50. Gleason grade 3 (score 6). Rounded, regular islands of tumor with cribriform architecture but no solid areas. This histology falls within Gleason pattern 3C.

FIGURE 2-51. Gleason score 6 (3 + 3). Needle biopsy showing infiltrating, small acinar pattern 3A (right side), with a single, sharply circumscribed cribriform tumor island representing pattern 3C (left side).

FIGURE 2-52. Gleason score 7 (4 + 3). Most of the cribriform structures in this picture represent Gleason cribriform grade 4; however, some of the intraluminal spaces are evenly and sharply punched indicating a Gleason pattern 3C.

FIGURE 2-53. Gleason score 6 (3 + 3). Unusual large gland grade 3 pattern with prominent pseudostratification and tufting, simulating high-grade prostatic intraepithelial neoplasia. A more typical pattern 3A is present on the left side.
FIGURE 2-54. Gleason grade 3 (score 6). A: Unusual papillary architecture with enlarged glandular structures is considered a part of pattern 3C in a needle biopsy specimen. B: Higher power photomicrograph illustrating the micropapillary architecture. C, D: Examples of similar unusual papillary architecture of 3C in a radical prostatectomy specimen.

FIGURE 2-54. Gleason grade 3 (score 6). B: (Continued)

FIGURE 2-54. Gleason grade 3 (score 6). C: (Continued)

FIGURE 2-54. Gleason grade 3 (score 6). D: (Continued)

FIGURE 2-55. Gleason score 8 (4 + 4). The cribriform structures contain fused glands, indicating grade 4.
FIGURE 2-56. Gleason grade 3 (score 6). Infiltrating, small acini with scant cytoplasm and inapparent central lumina. This pattern can be confused with grade 4; however, there is no glandular fusion. The lack of obvious lumina could be artifactual distortion.

FIGURE 2-57. Gleason grade 3 (score 6). Small, infiltrating acinar pattern 3A at the edge of a needle biopsy. The glands are squeezed together mimicking a 4, which could result in overgrading. This compression artifact is not an infrequent finding at a needle biopsy edge.

FIGURE 2-58. Gleason grade 3 (score 6). Note the vacuolated cytoplasm within individual cells lining these infiltrating, well-formed glands. This is not considered to represent signet ring cell differentiation and does not alter the assignment of Gleason grade.

Gleason Grade 4 ("Poorly Differentiated") (Figs. 2-59, 2-60, 2-61, 2-62, 2-63, 2-64, 2-65, 2-66, 2-67, 2-68, 2-69, 2-70, 2-71, 2-72, 2-73, 2-74, 2-75, 2-76, 2-77, 2-78, 2-79, 2-80, 2-81, 2-82, 2-83 and 2-84)

Original Gleason Criteria

Although the architecture may be microacinar, cribriform, or papillary (as in Gleason grades 1 through 3), the masses of tumor have irregular, obvious, infiltrative edges, and the tumor grows in a “ragged spongework of epithelium, having lost the simple entwined tubular structures of Gleason grade 1, 2, 3A, and 3B” (1, 2, 3 and 4) (Figs. 2-59A, 2-60, 2-61, and 2-64, 2-65, 2-66, 2-67, 2-68, 2-69, 2-70, 2-71 and 2-72). Few tiny glands or signet ring cells may be present (4). The cytology may be paradoxically bland. Fusion may be so extreme that the appearance is that of solid sheets of epithelium punctuated by multiple glandular lumina of variable size and shape. Also included in this grade are tumors with very pale cytoplasm resembling renal cell carcinoma, hence called hypernephroid pattern or hypernephromatoid pattern (Gleason pattern 4B) (Figs. 2-62 and 2-63). One form of Gleason grade 4 shows an arrangement of chains and cords (Fig. 2-71) that appears to be a transition from well-formed, separate glands of Gleason pattern 3B to undifferentiated cords and sheets of cancer (grade 5).
Application in Needle Biopsy Specimens

Gland fusion is the defining feature of Gleason grade 4. Fusion and ill-defined glandular formation (in contrast to the discrete, separate glands of grade 3) are often apparent at low power (Figs. 2-59B, 2-60, 2-61, and 2-67, 2-68, 2-69 and 2-70). Gleason grade 4 is biologically, prognostically, and often therapeutically critical (see Chapter 5); hence, strict criteria are required to prevent overdiagnosing or underdiagnosing this grade. Gland fusion should be obvious, unquestionable, and clear-cut. It may be focal (Fig. 2-64); therefore, in a predominant background of discrete, single glands of grade 3, we suggest that at least two distinct, fused glandular units are recognizable within a focus before assigning a Gleason grade 4. Care should be exercised to discount branching and tortuous glands and tangentially sectioned, small-caliber glands of Gleason 3B that appear as cords (Fig. 2-43). Cribriform structures with irregular, ragged outlines or containing irregularly sized and shaped or very small fenestrations are Gleason grade 4 (Figs. 2-74, 2-75, 2-76, 2-77 and 2-78). In the description of Gleason grade 3, we have elaborated on the controversy of grading cribriform proliferations. In addition to the criterion of the outer contours of the cribriform or papillary structures, we believe that the intraluminal proliferation may be composed of variably sized and shaped fenestrations with fused areas that should be graded as Gleason grade 4 (Figs. 2-74 and 2-75). The continuum of cribriform proliferations from grade 3 to grade 5 is depicted schematically in Fig. 2-73. Extracellular mucin is most often associated with fused glands floating within mucinous pools (see discussion on mucinous carcinoma, Chapter 3), and this histology is a grade 4 by virtue of fusion (Figs. 2-80 and 2-81). The amount of Gleason grade 4 may be extremely small, but the quantity should not dissuade from designation as a high-grade tumor (Fig. 2-64).

Application in Transurethral Resection and Prostatectomy Specimens

In these specimens, application is usually straightforward. The amount of tumor and architecture varies. Carcinoma is usually extensive but may be extremely focal, and forms sheets, cribriform aggregates or, rarely, is nodular in configuration (Figs. 2-18 and 2-19).

Pitfalls in Grading Pattern 4

(a) Problems lie in both undergrading [failure to recognize subtle fusion, resulting in misclassification as Gleason grade 3 (Fig. 2-83), or classifying nodular forms as Gleason grade 2 (Figs. 2-18 and 2-19)], and overgrading (cords and chains of poorly formed, tangentially sectioned glands of Gleason grade 4 as grade 5). Branched V- and Y-shaped configurations are not equivalent to fused glands (Figs. 2-85, 2-86, 2-87, 2-88, 2-89 and 2-90). Isolated single cells in a background of predominantly grade 4 should most likely be interpreted as tangentially cut cords, resulting in single cell appearance (hence Gleason 4) rather than Gleason 5. The distinction between the latter two is not of significant clinical relevance and may be difficult, as the distinction along a continuum of poor differentiation is rather arbitrary.

(b) Xanthomatous (lipid-rich or foamy gland) grade adenocarcinoma should not be mistaken for hypernephroid Gleason 4 grade (Fig. 2-84). Xanthomatous carcinoma may be Gleason grade 3 or 4 based on the presence of absence of fusion (see Figs. 3-33, 3-34, 3-35 and 3-36); whereas, by definition, hypernephroid Gleason 4 is comprised of architecturally fused glands.

(c) Foci of comedonecrosis in irregular cribriform, solid, or papillary aggregates may be focal and indicate Gleason grade 5.

(d) The mere presence of signet rings does not suggest Gleason grade 4. Signet rings may be seen in discrete nonfused glands (grade 3), fused glands (Fig. 2-82), and in solid sheets.

(e) Occasionally, marked luminal distention by mucin may mimic pools of extracellular mucin with associated glands. This is still grade 3 and not grade 4, which requires pools of extracellular mucin containing fused glandular elements.
FIGURE 2-59. A: Gleason grade 4. Original Gleason diagram illustrating the complex fused glands and chains of glands comprising patterns A and B. B: Stylized schematic of Gleason grade 4 patterns within a prostate needle biopsy, illustrating fused glands, complex, irregular papillary cribriform architecture, and hypernephroid patterns.

FIGURE 2-59. B: (Continued)

FIGURE 2-60. Gleason grade 4 (score 8). Needle core biopsy extensively involved by large, anastomosing islands of fused glands typical of pattern 4A.

FIGURE 2-61. Gleason grade 4 (score 8). Near solid mass of fused glands of Gleason grade 4A. Although lumina are not prominent, the nuclei are clearly lined up in a glandular pattern.

FIGURE 2-62. Gleason grade 4 (score 8). A: Typical hypernephroid pattern with nests of cells that have the abundant pale cytoplasm and small, hyperchromatic nuclei characteristic of hypernephroid grade 4 pattern. B: Higher power photomicrograph highlighting the hyperchromatic, small nuclei in cells with abundant pale cytoplasm.

FIGURE 2-62. Gleason grade 4 (score 8). B: (Continued)
FIGURE 2-63. Gleason grade 4 (score 8). A: Typical example of the hypernephroid pattern of Gleason grade 4. B: Higher power of hypernephroid pattern 4 with cells that have small, hyperchromatic nuclei and abundant pale cytoplasm.

FIGURE 2-65. Gleason grade 4 (score 8). Small focus of fused glands with some lumina noted but little to no intervening stroma within this tumor island.


FIGURE 2-64. Gleason grade 4 (score 8). A: Small focus of poorly formed, fused glands and infiltrating cords of cells typical of

FIGURE 2-64. Gleason grade 4 (score 8). B: (Continued)
FIGURE 2-66. Gleason grade 4 (score 8). A: Large, complex masses of fused glands of Gleason grade 4A in a needle biopsy. B: Higher power of an interanastomosing complex cribriform tumor mass with irregular outlines. Within the mass, the fused glands do not have punched-out holes typical of pattern 3C cribriform carcinoma.

FIGURE 2-66. Gleason grade 4 (score 8). B: (Continued)

FIGURE 2-67. Gleason score 7 (4 + 3). The central portion of this needle biopsy consists of a relatively circumscribed aggregate of fused glands with pale cytoplasm (Gleason grade 4). At both ends of the biopsy, infiltrating, single, separate glands represent Gleason pattern 3A.

FIGURE 2-68. Needle core biopsy extensively involved by broad masses of fused glands of Gleason pattern 4A. B: Higher power photomicrograph illustrating the distinctive irregular masses of fused glands of Gleason grade 4A.

FIGURE 2-68. Gleason grade 4 (score 8). B: (Continued)
FIGURE 2-69. Gleason score 7 (4 + 3). A: A complex lesion consisting of fused glands (grade 4) with glands at the edge that are infiltrating and separated by intervening stroma (grade 3). B: Higher power photomicrograph illustrates both the predominantly fused glands, as well as some discrete separate glands, justifying inclusion of a minor grade 3 component.

FIGURE 2-70. Gleason grade 4 (score 8). A: The core biopsy is extensively involved by a ragged spongework of epithelium (grade 4). Although rare isolated glands are seen, these are insufficient to warrant inclusion of grade 3 in the score. B: Higher power photomicrograph illustrating the fused gland pattern.

FIGURE 2-71. Gleason score 7 (3 + 4). This needle biopsy illustrates infiltrating, well-formed acini. Focally, the acini are fused into chains, generating a grade 4 pattern (arrow); elsewhere, the glands are distinct from one another, indicating a grade 3 component as well (arrowheads). (See also Figs. 2-119B and 2-121.)
FIGURE 2-72. Gleason grade 4 (score 8). High-power photomicrograph illustrating fused glands. Note that although the glands are well formed, stroma do not intervene between any of the glandular profiles.

FIGURE 2-73. A schematic drawing illustrating the spectrum of morphologies possible within prostate cancer. The drawing exhibits cribriform morphology ranging from cribriform pattern 3C through solid pattern 5 with or without comedonecrosis. More solid areas in otherwise internally fused cribriform proliferations indicate Gleason score 4 + 5.

FIGURE 2-74. Gleason score 8 (4 + 4). The bulk of the tumor consists of large, circumscribed but irregularly shaped masses of fused glands with a cribriform appearance. This is considered to represent pattern 4A. Note also the presence of a minor fused gland component (arrow) of the typical grade 4A type.

FIGURE 2-75. Gleason score 8 (4 + 4). The tumor predominantly consists of large, somewhat irregular islands of fused glands with cribriform architecture that we consider to represent grade 4A. The outer contours of the cribriform glands are focally irregular, and the intraluminal spaces vary considerably in size and shape.
FIGURE 2-76. Gleason grade 4 (score 8). The outer contour of the cribriform proliferation is partially scalloped, and the intraluminal spaces are irregular and poorly formed.

FIGURE 2-77. Gleason grade 4 (score 8). Irregular, extensive interanastomosing cribriform aggregates contain fused intraluminal glands.

FIGURE 2-78. A: Gleason grade 4 (score 8). The outer contour of the cribriform proliferation exhibits indentation, and the intraluminal spaces are irregular and collapsed. In contrast to Fig. 2-76, the outer contour in this example is more irregular. B: Gleason grade 4 (score 8). Although the overall profiles of the cribriform proliferation in this example are more rounded, the intraluminal proliferation is composed of fused glands, and some of the intraluminal spaces are very tiny; hence, the designation of grade 4.

FIGURE 2-78. B: (Continued)
FIGURE 2-79. Gleason grade 4 (score 8). Irregular, fused, small acini (center) are seen amidst complex, interanastomosing, fused glands with slight papillary folding.

FIGURE 2-80. Gleason grade 4 (score 8). Adenocarcinoma with mucinous features. Irregularly fused glands lie within and adjacent to pools of extracellular mucin.


FIGURE 2-81. B: (Continued)
Although vacuolated signet ringlike cells are present, these are in the context of a gland-forming carcinoma; this focus of carcinoma is graded as a Gleason grade 4 + 3 based on the combination of fused and distinct separate glands.

Distinct glands with surrounding stroma (grade 3—right half) contrast with areas with fused microacini (grade 4—left half).

A: Low power. B: Intermediate power.

FIGURE 2-82. Gleason score 7 (4 + 3). Although vacuolated signet ringlike cells are present, these are in the context of a gland-forming carcinoma; this focus of carcinoma is graded as a Gleason grade 4 + 3 based on the combination of fused and distinct separate glands.

Distinct glands with surrounding stroma (grade 3—right half) contrast with areas with fused microacini (grade 4—left half).

A: Low power. B: Intermediate power.

FIGURE 2-83. Gleason score 7 (3 + 4). Distinct glands with surrounding stroma (grade 3—right half) contrast with areas with fused microacini (grade 4—left half).

A: Low power. B: Intermediate power.

FIGURE 2-83. B: (Continued)

Foamy gland adenocarcinoma of the prostate. The foamy gland pattern of adenocarcinoma of the prostate should be distinguished from the hypernephroid pattern, which is considered grade 4 by definition. In this example, discrete, separate glands are grade 3 and fused glands (arrow) represent grade 4.

FIGURE 2-84. Gleason score 7 (3 + 4). Foamy gland adenocarcinoma of the prostate. The foamy gland pattern of adenocarcinoma of the prostate should be distinguished from the hypernephroid pattern, which is considered grade 4 by definition. In this example, discrete, separate glands are grade 3 and fused glands (arrow) represent grade 4.

FIGURE 2-85. Gleason score 6 (3 + 3). The neoplastic glands exhibit prominent branching. This should not be interpreted as evidence of fusion.

FIGURE 2-85. Gleason score 6 (3 + 3). The neoplastic glands exhibit prominent branching. This should not be interpreted as evidence of fusion.
FIGURE 2-86. Gleason score 6 (3 + 3). The neoplastic glands in this example also exhibit prominent branching, simulating fusion. This should not be overinterpreted as grade 4.

FIGURE 2-87. Gleason score 6 (3 + 3). The neoplastic glands exhibit prominent branching, resulting in a complex appearance. This should not be interpreted as evidence of fusion.

FIGURE 2-88. Gleason score 6 (3 + 3). The neoplastic glands are closely packed and exhibit prominent branching. This should not be interpreted as evidence of fusion.

FIGURE 2-89. Gleason score 6 (3 + 3). The neoplastic glands exhibit prominent branching, resulting in a complex appearance. This should not be construed as evidence of fusion. The individual glands are still surrounded by stroma.

FIGURE 2-90. Gleason score 6 (3 + 3). A: Adenocarcinoma shows Gleason patterns 3A and 3B. The branching and the small acini of Gleason pattern 3B should not be interpreted as Gleason grade 4. B: A higher power view demonstrating an extreme example of branching in the center that, in our opinion, does not represent fusion.

FIGURE 2-90. Gleason score 6 (3 + 3). B: (Continued)
Gleason Grade 5 ("Very Poorly Differentiated") (Figs. 2-91, 2-92, 2-93, 2-94, 2-95, 2-96, 2-97, 2-98, 2-99, 2-100, 2-101, 2-102, 2-103, 2-104, 2-105, 2-106, 2-107 and 2-108)

Original Gleason Criteria

This includes two patterns: 5A and 5B. Pattern 5A is pattern 3C or cribriform 4 pattern cancer with comedonecrosis (Figs. 2-91A and 2-92). Pattern 5B is almost solid or rounded masses with ragged infiltration, sheets, cords, and single cells (Figs. 2-93, 2-94 and 2-95). There is minimal to absent gland formation.

Application in Needle Biopsy (Fig. 2-91B) and Transurethral Resection and Prostatectomy Specimens

Involvement is invariably extensive (Figs. 2-96, 2-97, 2-98, 2-99, 2-100, 2-101, 2-102, 2-103, 2-104, 2-105, 2-106, 2-107 and 2-108) with rare exceptions (Fig. 2-107B). Comedonecrosis in cribriform, papillary, and solid proliferations may be focal and should be suspected in the presence of high-grade cytologic atypia. It may be conspicuous and accompanied by microcalcifications.

Pitfalls in Grading Grade 5

(a) The presence of pyknotic tumor nuclei or focal punctate necrosis in intraluminal eosinophilic secretions should not be interpreted as comedonecrosis (Figs. 2-109 and 2-110). We have also observed such changes in Gleason grades 3 and 4 and in cribriform/papillary proliferations associated with a histiocytic response.

(b) Poorly preserved and thick sections may result in tumors appearing more solid and glands appearing as cords and trabeculae, resulting in overgrading.

(c) Small cell carcinoma of the prostate stands on its own as a diagnostic entity; in our opinion, it should not be graded as grade 5 (Fig. 2-111) based on the diffuse solid growth architecture (see Chapter 3).


FIGURE 2-91. B: (Continued)

FIGURE 2-92. A: Gleason score 9 (5 + 4). Cribriform glands show central comedonecrosis (pattern 5A). A few cribriform glands also show irregularly fused intraluminal proliferation with small lumina without comedonecrosis (grade 4). B: Gleason grade 5 (score 10). This single focus of adenocarcinoma from another case shows a cribriform architecture with central comedonecrosis. Although the carcinoma is focal, this is the only tumor present in this core; hence, the Gleason score is 10.

FIGURE 2-92. B: (Continued)
FIGURE 2-93. Gleason grade 5 (score 10) in a needle biopsy. Solid, sheetlike architecture with only rare glandular lumina.

FIGURE 2-94. Gleason grade 5 (score 10) in a radical prostatectomy. Solid, sheetlike architecture with only rare glandular lumina.

FIGURE 2-95. Gleason grade 5 (score 10). Haphazard, infiltrative, single cell pattern with no evidence of glandular differentiation. A: Low power. B: High power.

FIGURE 2-96. Gleason grade 5 (score 10). Solid nodules (grade 5) and irregular cribriform aggregates with central comedonecrosis (grade 5) are seen. A: Low power. B: Intermediate power.

FIGURE 2-96. B: (Continued)
FIGURE 2-97. Gleason score 9 (5 + 4). Complex cribriform and fused gland aggregates (grade 4) show areas of comedonecrosis (grade 5).

FIGURE 2-98. Gleason score 10 (5 + 5). The cylindrical cores of tumor show solid intraluminal proliferation and comedonecrosis. Both features are grade 5.


FIGURE 2-100. Gleason grade 5 (score 10). Neoplastic cells are arranged in irregular clusters and strands with minimal evidence of glandular differentiation.

FIGURE 2-101. Gleason grade 5 (score 10). The cytoplasm of the carcinoma cells shows two distinctive tinctorial qualities. The overall architecture is that of solid sheets with minimal glandular differentiation. A: Low power. B: Intermediate power.

FIGURE 2-101. B: (Continued)
FIGURE 2-102. Gleason grade 5 (score 10). Solid groups of neoplastic cells infiltrate periprostatic adipose tissue (extraprostatic extension) in a needle biopsy specimen.

FIGURE 2-103. Gleason grade 5 (score 10). A: Solid growth of single neoplastic cells extensively effacing the normal prostatic architecture. B: Higher power shows that the cells have a plasmacytoid appearance.

FIGURE 2-104. Gleason grade 5 (score 10). Although the prostatic architecture is not extensively effaced, the carcinoma is arranged in sheets with no discernible glandular differentiation.

FIGURE 2-105. Gleason grade 5 (score 10). Although some preservation of the architecture is found, extensive infiltration of the stroma between the benign glands by a single cell proliferation can be seen (grade 5), which may be missed on scanning magnification examination.
FIGURE 2-106. Gleason grade 5 (pattern 10). Undifferentiated pattern of prostatic carcinoma shows solid, sheetlike growth. The degree of nuclear pleomorphism is slightly greater than is usually encountered in adenocarcinoma of the prostate.

FIGURE 2-107. Gleason grade 5 (score 10). A: Sheets of signet-ring cell carcinoma. The vacuolated cells mimic grade 4 fused gland architecture, but in reality, these are solid sheets; hence, Gleason grade 5. Carcinomas as illustrated in (A) can rarely be focal with limited involvement of a needle biopsy (B), but are still designated as Gleason score 10.

FIGURE 2-108. Gleason grade 5 (score 10). A: Closely packed, solid nests of cells have a nodular configuration on low power. B: Higher power shows a compact, solid proliferation; despite the nested architecture, it is still designated as Gleason grade 5.
FIGURE 2-109. A: Gleason grade 3 (score 6). Discrete, small acini contain eosinophilic secretions with occasional pyknotic nuclei. True ghostlike outlines of necrotic tumor cells are not evident, and this should be distinguished from comedonecrosis. B, C: Gleason grade 3 (score 6). The acini show a neutrophilic infiltrate associated with eosinophilic secretions. Neutrophils should not be misinterpreted as necrotic tumor cells.

FIGURE 2-109. B: (Continued)

FIGURE 2-109. C: (Continued)

FIGURE 2-110. Gleason grade 4 + 3 (score 7). Irregular, fused acini (Gleason grade 4) contain proteinaceous secretions with apoptotic cells. This should be distinguished from the ghostlike architecture of necrotic cells in comedonecrosis (grade 5).
FIGURE 2-111. Small cell carcinoma of the prostate. Despite the solid, sheetlike architecture, this tumor histology should not be graded because small cell carcinoma has distinct biologic and therapeutic implications. A: Low power. B: High power.

COMBINATION OF GLEASON GRADES

Because the Gleason grading system represents a morphologic continuum of architectural dedifferentiation and because prostate cancer is commonly multifocal, it is not unusual to see multiple different grades in separate foci of carcinoma in the prostate, within the same focus, and, rarely, within the same cribriform gland (Figs. 2-73 and 2-112, 2-113, 2-114, 2-115, 2-116, 2-117, 2-118, 2-119, 2-120, 2-121, 2-122, 2-123, 2-124, 2-125, 2-126, 2-127, 2-128, 2-129, 2-130, 2-131, 2-132, 2-133, 2-134, 2-135, 2-136, 2-137, 2-138, 2-139, 2-140, 2-141, 2-142, 2-143 and 2-144). The assignment of the Gleason score is performed per the guidelines for handling multiple patterns outlined in the recommendations for reporting prostate cancer of Gleason grades (Chapter 6). The presence of multiple patterns in a needle biopsy is often a source of interobserver variability in reporting (Chapter 4).

The combination of multiple grades is usually numerically adjacent (e.g., Gleason score 1 + 2, 2 + 1, 2 + 3, 3 + 2, 3 + 4, 4 + 3, 4 + 5, 5 + 4), although infrequently one may note a skipping of grades (3 + 5, 5 + 3, 2 + 4, 4 + 2, etc.) or the presence of noncontinuous grades in the same case (e.g., grade 2, 4, and 5 without grade 3). Obviously, virtually any and every conceivable mathematical permutation and combination within reason may be possible in a given case.

FIGURE 2-112. A, B: Gleason score 3 (1 + 2). The uniform, nodular configuration of this carcinoma indicates a low-grade carcinoma. Excellent circumscription of uniformly sized glands is consistent with Gleason grade 1; focally, however, limited permeation is seen in the adjacent stroma (indicating Gleason grade 2).
FIGURE 2-113. A-C: Gleason score 5 (3 + 2). The neoplastic acini are closely packed, and one edge is circumscribed [right side, (B), higher power] (grade 2). The other edge [(C), left side] shows irregular glands infiltrating the stroma (grade 3).

FIGURE 2-114. Gleason score 5 (3 + 2). A needle core biopsy showing two foci of adenocarcinoma separated by a band of fibromuscular stroma. The focus on the right side shows good circumscription (indicative of Gleason grade 2); the focus on the left side, however, shows a broad columnlike growth across the needle core (Gleason grade 3).

FIGURE 2-115. Gleason score 5 (2 + 3). The overall circumscribed nature of the proliferation (left edge) indicates a Gleason grade 2. However, toward the center, infiltration of the small acini between benign glands can be seen (Gleason grade 3). We have frequently observed infiltrating grade 3 glands in association with an overall low-power configuration of Gleason grade 2.
FIGURE 2-116. Gleason score 5 (3 + 2). There are several foci of carcinoma adjacent to one another. The focus on the left side shows sharp circumscription with slight variation in gland size and shape and with stromal separation indicating Gleason grade 2. The focus in the center and right side shows infiltration between the benign glands (right lower half) indicating a Gleason grade 3. The infiltration between benign glands occurs in several areas, and we consider this to be a greater component of grade 3 than grade 2.

FIGURE 2-117. Gleason score 7 (3 + 4). Nonfused, occasionally branching acini (grade 3) are in sharp contrast to fused acini at the bottom (grade 4).

FIGURE 2-118. Gleason score 7 (3 + 4). Round to oval, discrete glands (grade 3) (left and center) contrast with fused glands (grade 4) (right and center). A: Low power. B: High power.

FIGURE 2-118. B: (Continued)
FIGURE 2-119. Gleason score 7 (3 + 4). A needle core biopsy showing an intermingling of the glands of Gleason grade 3 and Gleason grade 4. A: Low power. B: Intermediate power. The fused glands are arranged in irregular chains of interconnected acini (arrows).

FIGURE 2-120. Gleason score 7 (4 + 3). The fused glands of grade 4 (left side) are in sharp contrast to the discrete glands of grade 3 (right side).

FIGURE 2-119. B: (Continued)

FIGURE 2-121. Gleason score 7 (4 + 3). Although the predominant architecture is that of irregularly fused glands (grade 4) (right and center), a sufficient number of single, discrete glands (grade 3) are present (left and bottom) to be included in the score.

FIGURE 2-122. Gleason score 7 (3 + 4). In contrast to the previous illustration (Fig. 2-121), the dominant pattern here is that of small, discrete acini (grade 3) with only a few fused acini associated with mucin at the top (grade 4).

FIGURE 2-123. Gleason score 7 (4 + 3). Same case as Fig. 2-121, highlighting the fused gland (grade 4) component on the right.
FIGURE 2-124. Gleason score 7 (3 + 4). Branched yet nonfused, small acini (grade 3) coexist with a cribriform proliferation of fused glands (grade 4).

FIGURE 2-125. Gleason score 7 (4 + 3). Fused glands (left side) of Gleason grade 4 contrast with the discrete acini of Gleason grade 3 (right side).

FIGURE 2-126. Gleason score 7 (4 + 3). A nodular focus of fused glands (left side, grade 4) is juxtaposed with single, discrete, occasionally branched glands of grade 3 (right side).

FIGURE 2-127. Gleason score 7 (4 + 3). The central cribriform structure has a smooth outer contour with evenly punched-out intraglandular spaces and meets our criteria for cribriform grade 3. A greater proportion of the tumor is composed of cribriform glands that show intraluminal fusion and fused noncribriform glands arranged in small chains (grade 4).
FIGURE 2-128. Gleason score 7 (4 + 3). This focus shows a pure cribriform architecture of the carcinoma. There is a single cribriform gland with a smooth outer contour and sharply punched, evenly spaced intraluminal spaces (arrow), indicating a grade 3 component. Most of the remaining cribriform structures show more irregularly fused intraluminal spaces (grade 4).

FIGURE 2-129. Gleason score 7 (4 + 3). Irregularly fused cribriform structures (grade 4) are dominant in this focus. A few single discrete glands of grade 3 are also evident.

FIGURE 2-130. Gleason score 7 (4 + 3). Cribriform structures have intraluminal spaces that vary in size and shape (grade 4). The top right corner shows discrete, nonfused glands of Gleason grade 3. The carcinoma in this focus is seen to invade the seminal vesicle (lower right).

FIGURE 2-131. Gleason score 7 (4 + 3). This focus of carcinoma shows a dominant cribriform architecture. The fused, irregular intraluminal spaces (arrows) indicate Gleason grade 4. Intraluminal spaces that are more even in size and shape and that are sharply punched out as well as a rare individual discrete gland are grade 3.
FIGURE 2-132. Gleason score 7 (4 + 3). The infiltrating, discrete, small acini represent grade 3. The larger intraluminal proliferations superficially resemble benign prostatic hyperplasia (pseudohyperplastic pattern). In this case, the latter is considered grade 4 due to the fused intraluminal proliferation.

FIGURE 2-133. Gleason score 7 (4 + 3). Complex cribriform glands with irregularly spaced and sized spaces (grade 4) predominate over a few single, small acini (grade 3).

FIGURE 2-134. Gleason score 7 (4 + 3). Gleason grade 4 is evidenced by the area with mucinous differentiation (right side). This is associated with a Gleason grade 3 component with discrete, infiltrating glands (left top side).

FIGURE 2-135. Gleason score 7 (3 + 4). The predominant component is that of single, discrete glands (grade 3). Occasional larger acini show an irregularly shaped and fused intraluminal proliferation (grade 4).

FIGURE 2-136. Gleason score 8 (3 + 5). Small, discrete acini (left) of Gleason grade 3 merge with single cells and solid cords of tumor (grade 5).

FIGURE 2-137. Gleason score 8 (5 + 3). Solid, sheetlike signet-ring cell carcinoma (right side, grade 5) separated from small acinar grade 3 (left side) by a large, benign gland in the center.
FIGURE 2-138. Gleason score 8 (5 + 3). Diffusely infiltrating, single cells (grade 5) intermingled with well-formed, discrete, small acini (grade 3).

FIGURE 2-139. Gleason score 8 (5 + 3). Solid, sheetlike architecture (grade 5) is punctuated by discrete, neoplastic glands with foamy gland pattern (grade 3).

FIGURE 2-140. Gleason score 9 (5 + 4). Irregularly infiltrating sheet of tumor (grade 5) along with raggedly fused cords (grade 4).

FIGURE 2-141. Gleason score 9 (4 + 5). Irregularly fused glands (grade 4, left side) are seen along with high-grade carcinoma with single-cell arrangement (grade 5).

FIGURE 2-142. Gleason score 6 (2 + 4). A: Well-circumscribed, nodular growth with glands varying slightly in size and shape (grade 2) is associated with a small focus of irregularly fused glands (grade 4), which is better appreciated in the high-power image (B).
FIGURE 2-143. Gleason score 8 (3 + 5). A: Both needle cores are extensively involved by adenocarcinoma with predominant pattern of single, discrete glands (grade 3). B, C: A secondary pattern of sheets and single cells (grade 5). B: A smaller, tertiary component of grade 4 (center) is also present.

FIGURE 2-143. Gleason score 8 (3 + 5). B: (Continued)

FIGURE 2-144. Gleason score 9 (5 + 4). The predominant pattern is sheets of cells (grade 5), [(A), lower left and (B), left side]. The next most common pattern is irregularly fused acini (grade 4), [(A), top and right]. A minor component of Gleason grade 3 is also evident [(B), right side].

FIGURE 2-144. B: (Continued)
REFERENCES


Gleason Scoring in Unusual Situations

The Gleason scoring system reflects the wide range of histologic patterns that prostatic adenocarcinoma can assume. Some unusual patterns often considered as variants or subtypes of prostatic adenocarcinoma, such as mucinous and signet-ring cell types, are not specifically dealt with in the Gleason system, although others are, such as the ductal ("endometrioid") type. Some authors have assigned Gleason grades to practically all unusual variants and patterns of prostatic carcinoma (1), although others have not assigned a Gleason grade in some or all of these (2). We have attempted to apply an evidence-based approach as best as possible for all such variants and patterns. In the following sections, a few brief comments concerning these distinct variants related to grading and prognosis are provided. In addition, recommendations are made for handling more recently described patterns of adenocarcinoma (such as atrophic or pseudohyperplastic) that are not specifically dealt with in the Gleason system. Finally occasional histologic findings that have uncertainties regarding appropriate handling in terms of grading (such as collagenous micronodules and glomerulations) are also covered in this chapter. Grading of these variants and patterns of prostatic adenocarcinoma is summarized in Table 3-1.

VARIANTS OF PROSTATIC ADENOCARCINOMA

Prostatic Ductal Adenocarcinoma

This tumor accounts for less than 1% of prostatic adenocarcinomas (as a dominant pattern), and has been referred to under several different names, including "endometrioid" and "papillary" carcinoma.

Clinically, ductal adenocarcinoma often involves the central ducts of the gland and may present as an exophytic papillary lesion in the prostatic urethra (3, 4 and 5). For this reason, they are often seen in transurethral resection specimens and at radical prostatectomy, and are less often found in needle biopsies. Most cases coexist with a variable proportion of acinar prostatic carcinoma. The majority of studies have indicated that ductal carcinoma has a poor prognosis (3,6,7), although some have reported a better outcome for this pattern (8). In the only study looking at outcome for patients with ductal adenocarcinoma diagnosed on needle biopsy, Brinker et al. (7) reported that in patients undergoing radical prostatectomy, 65% had tumor extension beyond the prostate (55% pT3a and 10% pT3b), which is a significantly higher rate than for acinar adenocarcinoma. In terms of biochemical disease-free survival, the actuarial rate was 50% at 5 years for ductal adenocarcinoma compared with 95% for Gleason scores 5 and 6, 66% for Gleason score 7, and 35% for Gleason scores 8 to 10 (7).

Histologically, the tumor grows in a mixture of papillary and cribriform patterns with and without central (comedo) necrosis (Figs. 3-1, 3-2, 3-3, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10 and 3-11). The papillary fronds are covered by a pseudostratified epithelium that may closely resemble...
endometrial adenocarcinoma, or the cells may have cleared cytoplasm. In some cases, the morphology closely mimics urothelial carcinoma. Gleason included tumors with so-called ductal or endometrioid features in the grade 3 category (or grade 5 with necrosis) (9), and this has been followed by some authorities (1). Others have not applied Gleason grading to ductal carcinomas, but only to any associated acinar component (2,6). Given the clinical reliance on Gleason score, we do assign a Gleason score in ductal adenocarcinoma; in our hands, the great majority are assigned a Gleason grade of 4 (for the irregular papillary cribriform masses) or 5 (when comedonecrosis is present) (10). Thus, a pure ductal adenocarcinoma without necrosis would be assigned a Gleason score of 8 (4 + 4). The grade 4 designation much more closely reflects the biologic behavior of these tumors than grade 3. Not withstanding the latter, in a few cases, grade 3 (cribriform or well-circumscribed papillary cribriform nests) can be included (9).

**TABLE 3.1 GLEASON GRADING OF PROSTATE CARCINOMA SUBTYPES**

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Gleason grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatic ductal adenocarcinoma</td>
<td>Grade 4, 5 with necrosis, some 3</td>
</tr>
<tr>
<td>Mucinous (colloid) adenocarcinoma</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
<td>Grade 5</td>
</tr>
<tr>
<td>Adenosquamous and squamous cell carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Basaloid and adenoid cystic carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>Grade 5 (glands graded separately)</td>
</tr>
<tr>
<td>Lymphoepithelioma-like carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Urothelial (transitional cell) carcinoma</td>
<td>Not graded</td>
</tr>
<tr>
<td>Undifferentiated carcinoma, not otherwise specified</td>
<td>Not graded</td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
<td>Grade 2 or 3, very rarely 4</td>
</tr>
<tr>
<td>Xanthomatous (foamy gland)</td>
<td>Most grade 3 or 4</td>
</tr>
<tr>
<td>Atrophic</td>
<td>Grade 3, occasionally 2</td>
</tr>
</tbody>
</table>

**Mucinous (Colloid) Carcinoma**

Pure mucinous carcinomas of the prostate are exceedingly rare; therefore, most authors have used this designation if more than 25% of the tumor volume consists of extravasated mucin (11,12). No clinical features distinguish mucinous carcinoma from usual acinar adenocarcinoma. These tumors cause elevated prostate-specific antigen (PSA), metastasize in the usual manner, and respond to hormonal therapy.

Histologically, pools of extravasated mucin are seen in the stroma with suspended nests and groups of carcinoma cells (Figs. 3-12, 3-13 and 3-14). Cytoplasmic mucin is usually not demonstrable. Because of the fused nature of most glands suspended in the mucin, mucinous carcinoma is considered to be Gleason grade 4 (10); as such, this variant is considered to be associated with a worse prognosis than usual acinar adenocarcinoma (11, 12, 13 and 14). In a literature review of 60 mucinous carcinomas, Saito and Iwaki (15) found 3- and 5-year survival to be 50% and 25%, respectively.

**Signet-ring Cell Carcinoma**

Pure signet-ring cell carcinoma of the prostate gland is vanishingly rare. Designation as a signet-ring cell carcinoma is restricted to those cases where the signet ring cells constitute over 25% to 50% (different criteria by different authors) of the tumor volume (16). Clinically, these tumors are often of advanced stage at the time of diagnosis (16, 17 and 18). No other specific features are associated with these tumors. In a review of 17 cases from the literature, Saito and Iwaki (15) found a 3-year survival of only 27%.
In most cases, the signet ring cells represent a minority population in an otherwise typical, although high-grade, carcinoma (Figs. 3-15, 3-16, 3-17 and 3-18). The cells are characterized by a clear cytoplasmic vacuole displacing the nucleus to one side. In most cases, the vacuole represents intracytoplasmic lumen formation, and the cells are mucin-negative; a minority of cells is mucin-positive. The tumor cells are PSA- and prostatic acid phosphatase (PAP)-positive. Signet-ring cell areas are considered grade 5, depending on whether the cells are present in solid sheets or as single cells infiltrating the stroma in a pattern reminiscent of limitis plastica (1,10). These must be distinguished from vaculated cells that can have signet ring morphology in well-formed glands of Gleason grade 3 or in fused glands of grade 4. In these settings, we do not use the term signet ring carcinoma (see Figs. 2-58 and 2-82).

**Sarcomatoid Carcinoma (Carcinosarcoma)**

Sarcomatoid carcinoma, or carcinosarcoma, refers to a tumor with mixed epithelial and mesenchymal differentiation. These tumors are rare but do occur in the prostate gland. Clinically, these patients tend to be older and, in half of cases, have a history of prostatic adenocarcinoma treated by radiation (19,20). The tumors produce bladder outlet obstruction and often require repeated transurethral resections to control local symptoms. Serum PSA levels are usually lower than expected for the tumor volume. They are associated with a very poor prognosis, often with local recurrence and uncontrollable disease in the pelvis (19, 20 and 21).

Pathologically, a mixture of epithelial and mesenchymal elements is found (Figs. 3-19 and 3-20). The epithelial component is usually high grade and of the acinar type. The mesenchymal component is almost always a high-grade spindle cell tumor without specific differentiation. Heterologous elements can be present, with osteosarcoma and chondrosarcoma more commonly found. The appropriateness of assigning a Gleason score to these is uncertain. Most authors consider these at the high end of the grading scale and assign a Gleason grade of 5. If a grade were assigned, the sarcomatoid component would appropriately be grade 5, with the glandular component graded in the usual fashion. In reporting these tumors, we assign a Gleason score with the sarcomatoid component as grade 5 and the glandular component graded appropriately. Given the distinctive clinical behavior, we would also specifically include the term “sarcomatoid carcinoma” or “carcinosarcoma” in the diagnostic line.

**VARIANTS AND CANCERS NOT TO BE GRADED**

**Adenosquamous and Squamous Cell Carcinoma**

Primary squamous cell carcinoma of the prostate is exceedingly rare and is not graded using the Gleason system because it is not an adenocarcinoma. Adenosquamous carcinoma refers to those cases with a mixture of glandular and squamous differentiation (Fig. 3-21). This is also a rare neoplasm, and it is most often seen in association with hormonal therapy for prostate cancer (22, 23 and 24). Depending on the presence of therapy-related changes (see Chapter 6), a Gleason score can be assigned to the glandular component, although insufficient experience with these tumors disallows any specific comments regarding prognosis and treatment responsiveness.

**Basaloid and Adenoid Cystic Carcinoma**

Basal cell lesions in the prostate gland span a wide range—from obviously benign basal cell hyperplasia, through varying ranges of atypia, to lesions that have been described
under the terms basal cell carcinoma and adenoid cystic carcinoma (Fig. 3-22) (25). It remains an area of considerable uncertainty without well-defined criteria for predicting the behavior of these lesions. Most experts do acknowledge the presence of a malignant end to the spectrum, although criteria for the diagnosis of malignancy in basal cell lesions remain unclear (10). Although some (1) consider these grade 5, these tumors are presumed to arise from the basal cells and, because they are not adenocarcinomas in the usual sense, are not effectively addressed in the Gleason system. Further, given the very limited outcome data available, we find no practical way to determine an appropriate approach to Gleason scoring of these rare tumors, and we personally do not recommend assigning a Gleason grade to them (26,27).

Lymphoepithelioma-like Carcinoma

Tumors that morphologically resemble lymphoepithelioma of the nasopharynx have been reported in numerous anatomic sites, including the prostate gland. These are extremely rare; only a single isolated case has been described (28). In that report, the lymphoepithelioma-like carcinoma was admixed with a typical small acinar adenocarcinoma. Although a Gleason grade of 5 (score 10) has been recommended based on this single case (1), the clinical significance and appropriate Gleason grading of this morphology in the prostate is unknown.

Small Cell (Neuroendocrine) Carcinoma

The term “small cell carcinoma” is restricted to those cases, either pure or admixed with an adenocarcinoma component, where the cells fulfill the light microscopic criteria for small cell carcinoma in the lung (and elsewhere) (Fig. 3-23). As in the lung, large cell neuroendocrine carcinoma can also be seen. Clinically, small cell carcinoma may arise de novo and be identified at the time of initial diagnosis. More often, the small cell component manifests itself late in the course of disease in a patient with documented metastatic prostate cancer (29,30). Soft tissue and lymph node metastases are characteristic, and bone metastases are osteolytic (31). Prognosis is very poor, and the patient will usually be offered cisplatin-based chemotherapy as part of the treatment plan (32,33). Median survival is less than 12 months after identification of small cell carcinoma (31).

Although Gleason has indicated that some grade 5 carcinomas may resemble small cell carcinoma (9), and other authors have also designated small cell carcinoma as grade 5 (1), given the distinctive behavior and treatment, we concur with others (2) and do not assign a Gleason score to small cell carcinoma of the prostate, whether a glandular component is or is not present. The diagnosis of small cell carcinoma stands on its own as predicting behavior and determining therapeutic approach.

Urothelial (Transitional Cell) Carcinoma

Urothelial (transitional cell) carcinoma is not an adenocarcinoma and is not graded using the Gleason system.

UNUSUAL HISTOLOGIC PATTERNS

Pseudohyperplastic

Some cases of prostatic adenocarcinoma grow in nodules and are composed of complex or cystic glands, resulting in an appearance that, at first glance, closely mimics nodular
prostatic hyperplasia (Figs. 3-24, 3-25, 3-26, 3-27 and 3-28) (34,35). These cases are graded as 2 or 3 depending on the degree of circumscription and complexity of the glands (10). In general, the principles outlined in Chapter 2 are followed, with the exception that if the glands are highly complex, a grade of 3 is assigned rather than 2, despite circumscription of the nodule. In other cases, individual pseudohyperplastic glands occur in an infiltrative pattern 3A carcinoma and are graded as 3 to reflect the infiltrative nature. Only rarely do these glands show features making the assignment of grade 4 appropriate.

Atrophic

In some cases of adenocarcinoma, the malignant glands are ectatic or dilated and lined by cells with scant cytoplasm, resulting in an atrophic appearance (Figs. 3-29, 3-30, 3-31 and 3-32) (36, 37 and 38). This is almost always a focal change in the context of Gleason pattern 3A and more common in pattern 3B (10). Less often, this atrophy-like change occurs in a Gleason grade 2 tumor.

Xanthomatosus (Foamy Gland)

In some cases of prostatic adenocarcinoma, the individual tumor cells have abundant, finely vacuolated or foamy cytoplasm (Figs. 3-33, 3-34, 3-35 and 3-36). These tumors have been designated as the “foamy gland” or “xanthomatosus” variant of prostatic adenocarcinoma (39, 40, 41 and 42). These tumors are graded based on the usual Gleason criteria and not on the cytoplasmic character per se. Most of these cases have either a fused gland (grade 4) or an infiltrating, discrete gland (grade 3) pattern, or a mixture of the two. They should be distinguished from the hypernephroid variant that, by definition, is considered Gleason grade 4.

Carcinoid-like (Organoid)

Prostatic adenocarcinoma occasionally contains areas where the tumor cells are arranged in organoid nests or islands, producing a superficial resemblance to carcinoid tumors (Figs. 3-37 and 3-38) (10). In most, the nuclei retain the characteristic macronucleoli; although in some, the nuclei are uniform and round, with finely stippled chromatin, further enhancing this impression. Despite the appearance, these stain for PSA and PAP and are nonreactive for neuroendocrine markers in most. This pattern has been described in metastatic sites (43,44). In most cases, the glands are fused or arranged as solid nests and are assigned a grade of 4 or 5; if the glands remain discrete, a grade of 3 is assigned.

Paneth Cell-like and Oncocytic Change

The presence of chromogranin-positive neuroendocrine cells is common in prostatic adenocarcinoma. In a small percentage of cases, the neuroendocrine cells have prominent areas of large, cytoplasmic eosinophilic granules, resulting in a Paneth cell-like appearance (Figs. 3-39, 3-40 and 3-41) (45, 46 and 47). In other cases, cells with granular eosinophilic cytoplasm more closely resemble oncocytes (48). The presence of these cells does not alter the assignment of Gleason grade, which should be based on the standard criteria.

Sclerosing Adenosis-like

Occasional cases of prostatic adenocarcinoma are characterized by small acini separated by a cellular stroma, resulting in a pattern that has been termed “sclerosing adenosis-like”
(Figs. 3-42 and 3-43) (10). These should be graded according to the usual criteria and are most often considered grade 3 or grade 4, depending on the presence or absence of fused glands.

**Histologic Features**

**Glomerulations**

An infrequent finding in prostatic adenocarcinoma is an intraluminal proliferation of cells forming fused glands within a dilated acinus, producing a glomeruloid structure (Figs. 3-44, 3-45 and 3-46) (49). We consider this a grade 4 pattern based on the fused gland architecture, although no outcome data specific to this histologic feature prove that it is associated with the expected behavior of a grade 4 pattern (10). This finding should be distinguished from the rare gland-in-gland or tunneling pattern that can be found in grade 3 tumors (Fig. 3-47) (10).

**Collagenous Micronodules (Mucinous Fibroplasia)**

Based on the evaluation of radical prostatectomy specimens, collagenous micronodules have been reported in up to 13% of prostatic carcinomas (Figs. 3-48 and 3-49) (50). They are most often seen in association with abundant mucin production and, to date, have not been found in benign conditions (13,50,51). In most cases, they are associated with grade 4 areas, but can be seen in association with grade 3 carcinoma; thus, they do not indicate a specific grade, and the tumor should be graded on other features.

**Perineural Invasion**

The appropriate grade to assign in cases with perineural invasion can occasionally be uncertain, particularly in the setting of gland-forming tumors. They are assigned a grade of 3 or 4 depending on the presence or absence of gland fusion (Figs. 3-50, 3-51, 3-52, 3-53, 3-54 and 3-55). Grade 3 cancers most often show involvement of a small percentage of the nerve circumference, although a single gland may wrap around a nerve to involve the majority of the circumference. This latter pattern may be seen rarely in Gleason pattern 3C with papillary architecture (Figs. 3-52 and 3-53).

FIGURE 3-1. Ductal adenocarcinoma, Gleason grade 4 (score 8).

FIGURE 3-2. Ductal adenocarcinoma, Gleason grade 4 (score 8).
FIGURE 3-3. Ductal adenocarcinoma, Gleason grade 4 (score 8).

FIGURE 3-4. Ductal adenocarcinoma, Gleason grade 4 (score 8).

FIGURE 3-5. Ductal adenocarcinoma, Gleason grade 4 (score 8).

FIGURE 3-6. Ductal adenocarcinoma, Gleason grade 4 (score 8).


FIGURE 3-7. Ductal adenocarcinoma, Gleason score 8 (4 + 4). B: (Continued)
FIGURE 3-8. Ductal adenocarcinoma, Gleason grade 4 (score 8).

FIGURE 3-9. A, B: Ductal adenocarcinoma, Gleason grade 5 (score 10). All of the individual masses contain areas of comedonecrosis, indicating pattern 5A.

FIGURE 3-9. B: (Continued)

FIGURE 3-10. Ductal adenocarcinoma, Gleason grade 5 (score 10). A: Unusual example of a ductal adenocarcinoma showing extensive comedonecrosis, resulting in a pseudopapillary architecture. B: Higher power photomicrograph illustrating the pseudopapillary growth with the intervening areas of comedonecrosis.

FIGURE 3-10. Ductal adenocarcinoma, Gleason grade 5 (score 10). B: (Continued)
FIGURE 3-11. Ductal adenocarcinoma, Gleason grade 3 (score 6). Although the vast majority of ductal adenocarcinomas are considered grade 4 or 5, in this unusual example, the tumor shows well-defined papillary architecture with individual papillae covered by a pseudostratified epithelium. For this reason, it is considered to represent a grade 3C pattern.

FIGURE 3-12. Adenocarcinoma with mucinous features, Gleason grade 4 (score 8).

FIGURE 3-13. Adenocarcinoma with mucinous features, Gleason score 7 (4 + 3). Predominant pattern is that of mucinous adenocarcinoma, indicating a primary Gleason grade of 4. Note the focal presence of well-defined infiltrating glands (arrow), indicating a minor grade 3 component.

FIGURE 3-14. Adenocarcinoma with mucinous features, Gleason grade 4 (score 8).

FIGURE 3-16. Signet-ring cell adenocarcinoma, Gleason score 9 (5 + 4). The tumor includes a typical signet-ring cell adenocarcinoma that is assigned a Gleason grade of 5. A component of fused glands in which some of the cells contain vacuolated cytoplasm is also seen, and this is assigned a Gleason grade of 4 (arrows).

FIGURE 3-17. Signet-ring cell adenocarcinoma, Gleason grade 5 (score 10).

FIGURE 3-18. Signet-ring cell adenocarcinoma, Gleason grade 5 (score 10). The tumor consists of a solid mass with a combination of sheets of cells, as well as cells with signet-ring cell morphology. A: Low power. B: Higher power of the signet ring cells.
FIGURE 3-19. Sarcomatoid carcinoma, Gleason score 9 (5 + 4). The sarcomatoid component is assigned a Gleason grade of 5, and the fused gland component is assigned a Gleason grade of 4.

FIGURE 3-20. Sarcomatoid carcinoma, Gleason grade 5 (score 10) in a needle biopsy.

FIGURE 3-21. Adenosquamous carcinoma of the prostate. This variant is not graded.

FIGURE 3-22. A, B: Adenoid cystic carcinoma of the prostate. This tumor is not graded.

FIGURE 3-22. B: (Continued)
FIGURE 3-23. Small cell carcinoma. A: Although a juxtaposed small cell and glandular pattern is seen, a Gleason score is not assigned in the presence of small cell carcinoma. B: Higher power photomicrograph illustrating the small cell carcinoma element. C: Higher power photomicrograph illustrating glandular component.

FIGURE 3-24. Pseudohyperplastic carcinoma, Gleason score 5 (3 + 2). A: The tumor is assigned a Gleason grade 3 for the complex architecture of the individual glands and a Gleason grade of 2 for the circumscribed nature of the nodule. B: Intermediate power photomicrograph illustrating the complex glandular architecture and the sharply circumscribed nature of the nodule.

FIGURE 3-23. Small cell carcinoma. B: (Continued)

FIGURE 3-24. Pseudohyperplastic carcinoma, Gleason score 5 (3 + 2). B: (Continued)

FIGURE 3-23. Small cell carcinoma. C: (Continued)
FIGURE 3-25. Pseudo-hyperplastic carcinoma, Gleason grade 3 (score 6) in a needle biopsy. A: The infiltrating glands have a predominantly dilated appearance and are infiltrating between benign glandular elements. B: Higher power photomicrograph.

FIGURE 3-26. Pseudo-hyperplastic carcinoma, Gleason score 5 (2 + 3), a relatively well-circumscribed nodule of predominantly dilated glands. A grade of 3 is included in this score due to infiltration between benign glandular elements (left and right sides).

FIGURE 3-27. Pseudo-hyperplastic carcinoma, Gleason score 6 (3 + 3). The predominant pattern is that of a complex, pseudo-hyperplastic carcinoma composed of intermediate to large glands that are discrete and not fused. A small component of more typical infiltrating acinar grade 3 is present in the lower right.

FIGURE 3-28. Pseudo-hyperplastic carcinoma, grade 3 (score 6). A: In this example, the predominant pattern is composed of large glands with a papillary architecture, giving an overall appearance of pattern 3C. B: Higher power photomicrograph illustrating the predominantly complex papillary architecture.
FIGURE 3-29. Adenocarcinoma with atrophic features, Gleason grade 3 (score 6). A: Glands mimicking atrophic glands are diffusely infiltrating the stroma between occasional nonneoplastic glandular elements. B: Higher power photomicrograph illustrating the cytologic features of this tumor.

FIGURE 3-29. Adenocarcinoma with atrophic features, Gleason grade 3 (score 6). B: (Continued)

FIGURE 3-30. Adenocarcinoma with atrophic features, Gleason grade 3 (score 6). A: The atrophic-appearing glands are widely infiltrating between benign glandular elements. B: Higher power photomicrograph illustrating the cytologic features of the neoplastic acini.

FIGURE 3-30. Adenocarcinoma with atrophic features, Gleason grade 3 (score 6). B: (Continued)

FIGURE 3-31. Adenocarcinoma with atrophic features, Gleason grade 3 (score 6). Acini are dilated by mucin without associated mucin extravasation. This is a grade 3 pattern and should not be overgraded as grade 4 mucinous.

FIGURE 3-31. Adenocarcinoma with atrophic features, Gleason grade 3 (score 6). B: (Continued)

FIGURE 3-32. Adenocarcinoma with atrophic features, Gleason score 7 (4 + 3). The tumor shows an “atrophic” appearance in part and has a grade of 3 in this area. Grade 4 tumor is also present.
FIGURE 3-33. Xanthomatous (foamy gland) adenocarcinoma, Gleason grade 3 (score 6). No evidence of fusion is seen in this case.

FIGURE 3-34. Xanthomatous (foamy gland) carcinoma, Gleason score 7 (3 + 4). A: The predominant pattern is infiltrating, discrete glands consistent with grade 3, with focal areas of fusion consistent with grade 4. B: Higher power photomicrograph illustrating both discrete and fused acini.

FIGURE 3-35. Xanthomatous (foamy gland) carcinoma, Gleason score 7 (4 + 3). A: The tumor shows a predominantly fused gland grade 4 pattern with a minor grade 3 pattern. B: Higher power photomicrograph illustrating the fused gland grade 4 component.

FIGURE 3-34. Xanthomatous (foamy gland) carcinoma, Gleason score 7 (3 + 4). B: (Continued)

FIGURE 3-35. Xanthomatous (foamy gland) carcinoma, Gleason score 7 (4 + 3). B: (Continued)
FIGURE 3-36. Xanthomatous (foamy gland) carcinoma, Gleason grade 3 (score 6). The tumor consists of discrete glands only. This pattern should not be misinterpreted as hypernephroid (Gleason 4B) pattern.

FIGURE 3-37. Adenocarcinoma with carcinoid-like pattern, score 8 (4 + 4). A: The carcinoid-like area has a grade 4 morphology. B: Higher power photomicrograph illustrating the cytologic features in this tumor. The carcinoid-like pattern can also be seen in association with other grades.

FIGURE 3-38. Adenocarcinoma with carcinoid-like features, Gleason grade 5 (score 10). A: The tumor grows as solid sheets but focally shows cytologic features similar to a carcinoid tumor. B: At higher power, the tumor shows a solid architecture consistent with grade 5.

FIGURE 3-38. Adenocarcinoma with carcinoid-like features, Gleason grade 5 (score 10). B: (Continued)
FIGURE 3-39. A: Adenocarcinoma with Paneth cell-like cells, Gleason grade 3 (score 6). In this otherwise typical infiltrating acinar adenocarcinoma, scattered individual cells (arrows) with abundant granular eosinophilic cytoplasm are seen. B: Adenocarcinoma with Paneth cell-like change, Gleason score 7 (3 + 4). Individual glands, as well as fused glands, contain Paneth-like cells. The presence of Paneth cell-like change does not influence the assignment of Gleason score.

FIGURE 3-39. B: (Continued)

FIGURE 3-40. Adenocarcinoma with Paneth cell-like change, Gleason score 7 (3 + 4). A: The tumor shows a combination of patterns 3A and 4A. B: Higher power photomicrograph showing the Paneth cell-like change (arrows). The presence of Paneth cell-like change does not influence the assignment of Gleason score.

FIGURE 3-40. Adenocarcinoma with Paneth cell-like change, Gleason score 7 (3 + 4). B: (Continued)
FIGURE 3-41. Adenocarcinoma with Paneth cell-like change, Gleason grade 4 (score 8). A: In this tumor with complex cribriform architecture of grade 4, scattered Paneth-like cells are present. B: Higher power photomicrograph highlighting the Paneth cell-like change within complex cribriform masses, showing perineural invasion. The presence of Paneth cell-like change does not influence the assignment of Gleason grade.

FIGURE 3-42. Sclerosing adenosis-like adenocarcinoma, Gleason grade 3 (score 6). A: This is an exaggerated Gleason 3B pattern. Note the tiny microacini and cords within sclerotic stroma and single cells that result from tangential cutting of tiny acini. Care should be taken not to overgrade these areas as grade 5. B: Higher power photomicrograph showing that the acini are discrete and not fused.

FIGURE 3-43. A: Sclerosing adenosis-like adenocarcinoma, Gleason grade 3 (score 6).

FIGURE 3-43. B: (Continued)
FIGURE 3-44. Adenocarcinoma with glomerulations, Gleason score 7 (4 + 3). A: The tufted glomerular areas are assigned a Gleason grade of 4 based on the fusion of glands forming the glomeruloid structure; the individual, infiltrating microacini (arrows) are assigned a Gleason grade of 3. B: Higher power photomicrograph of the glomerulations.

FIGURE 3-45. Adenocarcinoma with glomerulations, Gleason score 7 (4 + 3). Most of the field shows glomerulations, which are assigned a Gleason grade of 4. A few individual, infiltrating acini (Gleason grade 3) are also seen.

FIGURE 3-46. Adenocarcinoma with glomerulations, Gleason score 7 (4 + 3). Most of the field shows glomerulations, which are assigned a Gleason grade of 4. A few individual, infiltrating acini (Gleason grade 3) are also seen.

FIGURE 3-47. Adenocarcinoma, Gleason grade 3 (score 6). Note the neoplastic acini, many of which show telescoping intraglandular protrusions mimicking glomerulations. A lack of complex fusion is seen; hence, this case is given a Gleason grade 3 (score 6).
FIGURE 3-48. Adenocarcinoma with collagenous micronodules, Gleason score 7 (4 + 3). A: Areas of gland fusion (Gleason grade 4) and individual infiltrating acini (grade 3) are identified. B: Higher power magnification (arrow, grade 4 acini). Collagenous micronodules do not on their own define a specific grade.

FIGURE 3-48. Adenocarcinoma with collagenous micronodules, Gleason score 7 (4 + 3). B: (Continued)

FIGURE 3-49. Adenocarcinoma with collagenous micronodules, Gleason score 7 (4 + 3). Collagenous micronodules are seen in association with fused glands and mucinous carcinoma patterns. Occasional individual infiltrating acini are also noted (lower right) and more are present in the vicinity (not shown).

FIGURE 3-50. Adenocarcinoma with perineural invasion, Gleason grade 4 (score 8). Note the circumferential involvement of a nerve by fused glandular pattern of adenocarcinoma (Gleason grade 4).
FIGURE 3-51. Adenocarcinoma with perineural invasion, Gleason score 7 (4 + 3). A: Individual and fused acini are seen surrounding a large nerve. B: Higher power photomicrograph showing the fused glandular area. Note also the Paneth cell-like change.

FIGURE 3-52. Adenocarcinoma with perineural invasion, Gleason grade 3 (score 6). Note the complex papillary gland encircling a small, centrally located nerve (arrow). The gland is well defined, which is indicative of Gleason pattern 3C.

FIGURE 3-53. Adenocarcinoma with perineural invasion, Gleason grade 3 (score 6). Note the small nerve toward the bottom of field (arrow). The gland displays tufting and micropapillation and is best categorized as Gleason pattern 3C.

FIGURE 3-54. Adenocarcinoma with perineural invasion, Gleason grade 3 (score 6). Note the partial encirclement of nerve fibers by single malignant acini without fusion.

FIGURE 3-55. Adenocarcinoma with perineural invasion, Gleason grade 3 (score 6). Although only a single gland involves a nerve fiber, this is best graded as Gleason grade 3 (even if it is the only tumor present in a biopsy).
REFERENCES


Reproducibility of the Gleason System

Reproducibility may be defined as “the extent to which consistent results are obtained when produced repeatedly” (1). Several studies have assessed intraobserver and interobserver reproducibility of the Gleason grading system (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24) (Table 4-1). Overall, reasonably consistent results have been obtained, but a wide range of levels of observer agreement has been reported (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23) (Tables 4-1, 4-2, and 4-3). It should be recognized that all histologic grading schemes, including the Gleason grading system, are inherently subjective (12,25,26). It is remarkable that despite the interpretive nature of Gleason grade assignment, Gleason histologic grade is one of the most powerful prognostic indicators for patients with prostate cancer.

Reproducibility studies can be categorized as intraobserver or interobserver. For investigations of intraobserver agreement of Gleason grades, exact agreement was reported in 42% to 78% of cases (2,6,11,12 and 13), and agreement within plus or minus one Gleason score unit (range 2 to 10) was reported in 72% to 87% of cases (2,6,11,12) (Table 4-2). Gleason wrote that he duplicated exactly his previous histologic scores approximately 50% of the time (12). It is difficult to compare the different intraobserver study agreement figures because they employed different (or not specified) tissue samples, including needle biopsy tissue, transurethral resection and prostatectomy chips, and open prostatectomy tissue sections. Unfortunately, no study has focused on intraobserver reproducibility of Gleason grading solely of carcinoma in needle biopsy tissue, which is critical in the current era. Also, only two studies (6,11) specified number of slides examined. Another problematic aspect of attempts to compare these intraobserver agreement data is that teaching sessions on Gleason grading were held prior to performance of one large study (2), but it is unknown if such a program was undertaken prior to initiation of other studies. One of the highest exact intraobserver agreement rates (71%) was obtained when two conferences were held with Dr. Gleason prior to beginning the study (2). This highlights the importance of educational sessions in enhancing intraobserver reliability in Gleason grading. The durability of intraobserver agreement over time is unknown, because almost all studies assessed agreement at only two separate time points.

Limited data exist on the comparative intraobserver agreement rates for the Gleason grading system versus other grading schemes (6,11,13). In two publications, the Gleason system was noted to have lower intraobserver reproducibility than the Böcking (6,11) and Mostofi (11) grading methods; whereas, in a third comparison, the Gleason and World Health Organization (WHO) systems exhibited an essentially equivalent intraobserver agreement level (13).

Highly variable levels of interobserver agreement on Gleason grading have also been reported, with a range of 36% to 81% (median = 61%) for exact agreement (2-4,6,7,9,10,13,17) and 69% to 86% of observers within plus or minus one Gleason score unit (2,4,6,10) (Tables 4-1 and 4-3). Use of another measure of interobserver agreement,
the kappa coefficient, similarly generated a wide range of values—from 0.13 to 0.78 (15,16,22, 23 and 24). This represents slight to substantial agreement (22) (Table 4-1). The basis for these disparate degrees of interobserver agreement in different studies is likely multifactorial (as it is in the intraobserver agreement studies). Potentially confounding factors include different study designs with use of different tissue samples, examination of a variable number of slides or cases, comparison with other single observers versus consensus scores, variable numbers of participants, the use of “lumped” versus the full range of Gleason scores, and perhaps most critically, the amount of observer experience and instruction given to the particular observers (27).

Table 4.1. REPRODUCIBILITY OF GLEASON GRADING

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Ref no.</th>
<th>No. of patients</th>
<th>Type tissue sample</th>
<th>Intraobserver variability</th>
<th>Interobserver variability</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harada et al.</td>
<td>1987</td>
<td>9</td>
<td>3</td>
<td>NG</td>
<td>71% exact agreement</td>
<td>38% exact agreement</td>
<td>Reasonable accuracy</td>
</tr>
<tr>
<td>Guille &amp; al.</td>
<td>1988</td>
<td>9</td>
<td>3</td>
<td>Autopsy prostate</td>
<td>NA</td>
<td>81% exact agreement</td>
<td>2 observers (pathologists)</td>
</tr>
<tr>
<td>Bain et al.</td>
<td>1989</td>
<td>9</td>
<td>3</td>
<td>49 TURP chips; f/ needle biopsies</td>
<td>1 pathologist with correlations of 0.86, 0.90, and 0.94; on three occasions</td>
<td>55% exact agreement for consensus score; 86% ± 1 unit</td>
<td>7 pathologists self-taught Gleason system; agreement level viewed as satisfactory</td>
</tr>
<tr>
<td>Babian et al.</td>
<td>1988</td>
<td>8</td>
<td>3</td>
<td>13 TURP chips; f/ needle biopsies; 1 birth</td>
<td>Difference for one observer: 0.63 Gleason units, correlation coefficient = 0.89</td>
<td>NA</td>
<td>Suggested accurate reproducibility</td>
</tr>
<tr>
<td>Swahn et al.</td>
<td>1989</td>
<td>9</td>
<td>3</td>
<td>96% TURP chips</td>
<td>42.45% exact agreement; 87% ± 1 unit</td>
<td>36% exact agreement; 86% ± 1 unit</td>
<td>For two observers, blocking system more reproducible than Gleason system</td>
</tr>
<tr>
<td>Ten Kate et al.</td>
<td>1988</td>
<td>8</td>
<td>3</td>
<td>Radical prostatectomy</td>
<td>NA</td>
<td>36% exact agreement among five observers</td>
<td>Low reproducibility, with weighted kappa = 0.3; for three Gleason score tiers: 2-4, 5-5, and 6-10</td>
</tr>
<tr>
<td>Humprey et al.</td>
<td>1989</td>
<td>8</td>
<td>3</td>
<td>TURP chips</td>
<td>NA</td>
<td>Media difference for two observers &gt;1 score unit</td>
<td>Determining extent of tumor showed better interobserver agreement than Gleason grade</td>
</tr>
<tr>
<td>De la Moren et al.</td>
<td>1989</td>
<td>9</td>
<td>3</td>
<td>NG</td>
<td>NA</td>
<td>66% exact agreement for three pathological grade</td>
<td>HUHN (88%) and blocking (73%) systems exhibited better agreement</td>
</tr>
</tbody>
</table>

Table 4-1. REPRODUCIBILITY OF GLEASON GRADING
Table 4.1. REPRODUCIBILITY OF GLEASON GRADING

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Methodology</th>
<th>Agreement</th>
<th>Study Restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'I Loreto et al.</td>
<td>14</td>
<td>Needle biopsy, TURP chips, radical prostatectomy</td>
<td>68.7%</td>
<td>Perfect agreement for three Gleason patterns.</td>
</tr>
<tr>
<td>Cost and B. Billis</td>
<td>11</td>
<td>TURP and open prostatectomy cases</td>
<td>63%</td>
<td>NA</td>
</tr>
<tr>
<td>Gleason et al.</td>
<td>9</td>
<td>NA</td>
<td>70%</td>
<td>Perfect agreement for three Gleason patterns with 85% ± 1 unit.</td>
</tr>
<tr>
<td>Özdamar et al.</td>
<td>9</td>
<td>NA</td>
<td>78%</td>
<td>Two observers' agreement was 71% for two Gleason patterns.</td>
</tr>
<tr>
<td>Grignon et al.</td>
<td>9</td>
<td>NA</td>
<td>79%</td>
<td>Concordance of Gleason grades from 75% to 80%.</td>
</tr>
<tr>
<td>McLellan et al.</td>
<td>9</td>
<td>NA</td>
<td>79%</td>
<td>Concordance of Gleason grades from 75% to 80%.</td>
</tr>
<tr>
<td>Lessie et al.</td>
<td>9</td>
<td>Needle biopsies</td>
<td>79%</td>
<td>Concordance of Gleason grades from 75% to 80%.</td>
</tr>
<tr>
<td>Steinberg et al.</td>
<td>9</td>
<td>Needle biopsies</td>
<td>62%</td>
<td>Concordance of Gleason grades from 75% to 80%.</td>
</tr>
<tr>
<td>Iczkowski &amp; Bostwick</td>
<td>9</td>
<td>Needle biopsies</td>
<td>95%</td>
<td>Concordance of Gleason grades from 75% to 80%.</td>
</tr>
</tbody>
</table>
The highest levels of interobserver agreement (up to 70% to 80%) were reported in Gleason grading of whole prostate glands. In one study on interobserver reproducibility of Gleason grading by general pathologists, the most significant demographic factor associated with better interobserver agreement was if the observer had learned the system at a meeting or course (23). Experience with two web-based tutorials (Table 4-4) has shown that using a small set (n=24 cases prior to teaching) correlated with improved interobserver agreement since low (7) to high (3) levels of interobserver reproducibility have been reported for Gleason grading of carcinomas in whole prostate glands. These findings clearly substantiate the importance of both experience and educational sessions in better reproducibility of Gleason grading.

Educational programs on Gleason grading improve the accuracy of Gleason grading. In one study on interobserver reproducibility of Gleason grading by general pathologists, the most significant demographic factor associated with better interobserver agreement was if the observer had learned the system at a meeting or course (23). Experience with two web-based tutorials (Table 4-4) has shown that using a small set (n=24 cases prior to teaching) correlated with improved interobserver agreement since low (7) to high (3) levels of interobserver reproducibility have been reported for Gleason grading of carcinomas in whole prostate glands. These findings clearly substantiate the importance of both experience and educational sessions in better reproducibility of Gleason grading.

Specific problem areas that are major targets for improvement in reproducibility of Gleason grading include the undergrading of prostatic carcinoma, low-grade carcinomas (Figs. 4-1, 4-2 and 4-3), cribriform proliferations (Figs. 4-4 and 4-5), borderline patterns that bridge the interface between two grades, and large tumors with more than two patterns (Figs. 4-6 and 4-7) (4,17,18,22,23) (Table 4-5).

Undergrading prostatic carcinoma is a significant cause of poor interobserver reproducibility (14,17,18,23). In one study of 360 prostate needle biopsies, a web-based differentiated grade of Gleason score 2 to 4 was reviewed by contributing institutions in 61% (22).
cases compared with 4 (1%) cases by the tertiary referral hospital (17). Of note is that none of these cases was Gleason score 2 to 4 carcinoma in the matched whole prostate gland in radical prostatectomy specimens (17). Well-differentiated Gleason score 2 to 4 should be a rare to nonexistent grade in needle biopsy tissue from the peripheral zone of the prostate (17,18,28). A minimal amount of carcinoma should not be equated with well-differentiated Gleason score 2 to 4 adenocarcinoma (29). Undergrading can also occur at higher Gleason grades. For example, 46% of Gleason score 5 to 6 carcinomas and 39% of Gleason score 7 carcinomas are undergraded by general pathologists (23). Failure to recognize fused glands as pattern 4 and failure to identify necrosis in pattern 5 have been listed as specific examples of undergrading in reproducibility studies (4).

Table 4.3. SUMMARY OF INTEROBSERVER REPRODUCIBILITY FOR GLEASON GRADING

<table>
<thead>
<tr>
<th>Agreement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exact interobserver agreement</td>
<td>36-81%</td>
</tr>
<tr>
<td>Interobserver agreement ± 1 score unit</td>
<td>69-86%</td>
</tr>
<tr>
<td>Kappa values (slight to substantial agreement)</td>
<td>0.13-0.78</td>
</tr>
</tbody>
</table>

Table 4.4. WEBSITES FOR GLEASON GRADING TUTORIALS

- http://www.pathology.jhu.edu/prostate
- http://www.pathology.ks.se/egevad/gleason.html

Even among urologic pathologists, difficult “nonconsensus” cases exist, where less than 70% agreement on the correct Gleason grade is found. In a recent investigation on interobserver agreement by 10 urologic pathologists (22), these constituted 8 of 46 (17%) cases. Two of the eight problematic cases were cribriform proliferations, with a nearly even split between a grade assignment of 6 and 7 (Figs. 4-4 and 4-5) (22). Here, the disagreement likely stems from the conception of what constitutes cribriform Gleason grade 3 (22) and the difficulty in assessing a raggedly infiltrative cribriform, fused-gland architecture (grade 4) versus smooth, rounded cylinders with cribriform epithelium (grade 3) in the limited tissue sampled by needle core biopsy. Three “nonconsensus” cases were lower grade carcinomas; for two of these cases, the Gleason score by urologic pathologists was divided mainly between 4 and 5 (Figs. 4-1, 4-2 and 4-3) (22). Here, the issue is whether an infiltrative, small acinar component is found. Because prostatic carcinoma uncommonly evokes a stromal response, such infiltration can be difficult to appreciate and consistently diagnose in needle biopsy tissue sections. Three cases presented difficulty due to a large amount of tumor with multiple patterns and areas at the border between two patterns (Figs. 4-6 and 4-7) (22). For these cases, the Gleason score range was 7 to 9, which reflected differences in interpretation of pattern 3 vs. 4 and 4 vs. 5 (22).

In a few published studies, a comparison of interobserver agreement levels for the Gleason grading system with other prostatic carcinoma grading systems has shown better agreement for the M. D. Anderson Hospital (7,9), Böcking (6,9), and Broders (7) grading systems. The WHO (Mostofi) grading system exhibited worse (7,11) or equivalent (9) agreement, and the Mostofi-Schroeder system displayed slightly better interobserver agreement (9).

In summary, the Gleason grading system demonstrates a reasonable degree of intradobserver and interobserver reproducibility, and can reach a substantial level of agreement. Improvements in Gleason grading reproducibility can be achieved by recognizing problematic areas (Table 4-5) and educating physicians via meetings, courses, website tutorials, and publications that specifically focus on the Gleason grading system.

Table 4.5. MAJOR PROBLEM AREAS WITH LOWER INTEROBSERVER AGREEMENT IN GLEASON GRADING

- Undergrading of prostatic carcinoma
- Circumscribed cribriform proliferations
- Lower-grade carcinomas
- Borderline patterns bridging the interface between two grades
- Large tumors with more than two patterns
FIGURE 4-1. Gleason score 5 (3 + 2). Study reference case A was graded by six urologic pathologists as Gleason score 4, by three as Gleason score 5, and by one as Gleason score 6. In our consensus opinion, this case represents a Gleason pattern score 5 (3 + 2) tumor. Left side: The carcinoma is relatively well circumscribed (pattern 2). Right side: It is infiltrative (pattern 3A). In addition to the circumscription at one edge, this proliferation is low grade because of the minimal stromal separation between acini. A: Low power. B: Intermediate power with reasonable circumscription. C: High power showing infiltrative edge.

FIGURE 4-2. Gleason score 6 (3 + 3). Study reference case B was graded by one urologic pathologist as Gleason score 3, by two as Gleason score 4, by two as Gleason score 5, by four as Gleason score 6, and by one as Gleason score 7. Our consensus grade is Gleason score 6 (3 + 3). Despite a somewhat nodular configuration (A, B), considerable variation in the size and shape of the acini that have amphophilic cytoplasm is found. C, D show greater variation in size and shape of the acini, with stromal separation and an infiltrative growth pattern.

FIGURE 4-1. B: (Continued)

FIGURE 4-1. C: (Continued)

FIGURE 4-2. B: (Continued)

FIGURE 4-2. C: (Continued)

FIGURE 4-2. D: (Continued)
FIGURE 4-3. A: Gleason score 5 (3 + 2). Study reference case C was graded by one urologic pathologist as Gleason score 2, by three as Gleason score 4, and by six as Gleason score 5. Our consensus grade is Gleason score 5 (3 + 2). B: The acini are closely packed with minimal stromal separation and are circumscribed at one edge (right side), in keeping with grade 2. C: The acini show infiltrative growth (grade 3) on the left side, as seen at intermediate power.

FIGURE 4-4. A: Gleason score 7 (4 + 3). Study reference case D was graded by six urologic pathologists as Gleason score 6 and by four as Gleason score 7. Our consensus grade is Gleason score 7 (4 + 3). This case highlights the controversy over the grading of tumors that have cribriform architecture. B: The cribriform structures have irregular, scalloped outlines with stromal bands extending into most of the large nests. C: In many areas, the spaces are irregular in size and shape, and some of the cribriform nests show small gland fusion with an irregular outer contour (grade 4). A few discrete, single separate glands are noted, indicating a minor grade 3 component.
FIGURE 4-5. A: Gleason score 7 (4 + 3). Study reference case E was graded by four urologic pathologists as Gleason score 6, by five as Gleason score 7, and by one as Gleason score 9. In our consensus opinion, this cancer represents Gleason score 7 (4 + 3). Most of the cribriform glands have a scalloped, irregular outer contour that shows intraluminal spaces with small, fused microacini (grade 4). B, C: Some discrete, single microacini are visible at the periphery (grade 3), and occasionally, the intraluminal spaces are even, punched out, and regular (grade 3) within the cribriform glands (arrow).

Gleason score 9. In our consensus opinion, this tumor is best graded as Gleason score 9 (4 + 5), based on the predominant Gleason grade 4 and the tertiary grade 5 components (seen in A and between fused acini as single cells in B). This tumor has multiple patterns, and no data regarding the handling of multiple grades in 18-gauge needle biopsy tissue are available. The predominant pattern is composed of irregularly fused glands (grade 4). The secondary grade is discrete, infiltrating glands (grade 3). B, C: A tertiary component of solid growth with single cells (grade 5) is also found. The score is assigned based on the College of American Pathologists recommendation (30) that the tertiary grade should be included in such cases. An alternative approach to grading this carcinoma would be Gleason score 8 (4 + 4), acknowledging lesser components of grades 3 and 5 in a comment.
FIGURE 4-7. Gleason score 8 (3 + 5). Study reference case G was graded by six urologic pathologists as Gleason score 7, by two as Gleason score 8, and by two as Gleason score 9. In our consensus opinion, this is a Gleason score 8 (3 + 5) carcinoma. A: The primary pattern is that of single, infiltrating, discrete glands (grade 3). B, C: Although the secondary pattern is composed of irregularly fused glands (pattern 4) (arrows), a tertiary, high-grade pattern of single infiltrating cells (grade 5) (C, D) is also seen (arrowhead). As in the prior example, using current College of American Pathologists recommendations, the predominant grade and the highest grade need to be factored in to arrive at the Gleason score; hence, this case is Gleason score 8 (3 + 5).

ACKNOWLEDGMENT

All figures in this chapter are cases selected from Allsbrook WC Jr, Mangold KA, Johnson MH, et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: Urologic pathologists. Hum Pathol 2001;32:74-80. The authors are grateful to William C. Allsbrook, Jr., M.D., for loaning us the glass slides from which we obtained the images for this work.

REFERENCES


CLINICAL SIGNIFICANCE OF GLEASON GRADING

Numerous reports have confirmed the significance of Gleason score in predicting outcome for patients with prostate cancer. This includes patients receiving no immediate therapeutic intervention, therefore reflecting the natural history of the disease (1,2), and patients treated with radical prostatectomy (3, 4 and 5), radiation therapy (6, 7 and 8), and other treatment modalities. Numerous nomograms have been developed to predict pathologic stage and clinical outcome in different clinical situations (9). The following sections briefly highlight the most common clinical scenarios in which Gleason score has been repeatedly demonstrated to have an important role in prognostication and therapeutic decision making.

PREDICTION OF PATHOLOGIC STAGE

Many studies have been published that consistently demonstrate the independent value of biopsy Gleason score in predicting pathologic stage at radical prostatectomy (Table 5-1) (10, 11, 12 and 13). Based on these studies of needle biopsies and radical prostatectomy specimens, several groups have developed nomograms for predicting pathologic stage based on clinical stage, serum prostate-specific antigen (PSA), and needle biopsy Gleason score (5). The best known of these are the “Partin tables” (14,15), which use clinical stage, serum PSA, and biopsy Gleason score to predict the likelihood of various pathologic stages. For example, a patient with a serum PSA of 4.0, a Gleason score of 6, and a clinical stage of T2a has a 2% (95% CI, 1% to 3%) chance of seminal vesicle invasion. In contrast, a patient with a PSA of 11, Gleason score of 8, and clinical stage T2b has a 19% (95% CI, 12% to 29%) chance of seminal vesicle involvement, an almost 10-fold increase (15).

Although inconsistent, several recent studies have demonstrated that in Gleason score 7, a significant prognostic difference in the 3 + 4 and 4 + 3 subgroups has been found (16, 17 and 18). In an updated prostate cancer staging nomogram (Partin table), Gleason score 7 has been divided into two subgroups based on whether the primary pattern is 3 or 4 (15). For example, in a patient with a PSA of 5, clinical stage T1c, and Gleason score of 7, the probability of extraprostatic extension increases from 32% (95% CI, 27% to 36%) for score 3 + 4 to 42% (95% CI, 35% to 50%) for score 4 + 3.

PREDICTING OUTCOME AFTER DELAYED TREATMENT

Gleason score is also an important predictor of the natural history of untreated prostate cancer (1,2,19), In the Egevad et al. series (19), men diagnosed at transurethral resection with clinically benign disease received hormonal therapy at the time of development of symptomatic local or metastatic disease. The most powerful
predictor of death from prostate cancer was the presence and amount of Gleason grade 4 or 5 adenocarcinoma; for patients with 0%, less than 5%, 5% to 50%, and greater than 50% grade 4 or 5, the cause of death was prostate cancer in 8%, 28%, 38%, and 65%, respectively. Many groups have included the presence of any Gleason grade 4 or 5 as a contraindication for conservative (no treatment) or delayed treatment (1,2).

Table 5.1. PREDICTION OF PATHOLOGIC STAGE BASED ON NEEDLE BIOPSY GLEASON SCORE

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Pathologic stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pT2, margin negative</td>
</tr>
<tr>
<td>&lt;7</td>
<td>59%</td>
</tr>
<tr>
<td>7</td>
<td>44%</td>
</tr>
<tr>
<td>&gt;7</td>
<td>26%</td>
</tr>
</tbody>
</table>

aBased on 668 patients.


PREDICTING OUTCOME AFTER RADICAL PROSTATECTOMY

The power of Gleason score in predicting outcome after radical prostatectomy has been repeatedly demonstrated in numerous reports (Tables 5-2, 5-3, and 5-4) (3, 4 and 5,12,20, 21, 22 and 23). The prognostic value is independent of race (24). Nomograms using the radical prostatectomy Gleason score and other variables are widely available (9,25,26). In patients with organ-confined, margin-negative tumors, the data are particularly compelling—patients with Gleason score 6 tumors infrequently fail (27).

More recently, data have emerged that demonstrate the value of the needle biopsy Gleason score in predicting biochemical failure after radical prostatectomy (4,5). In one report, the needle biopsy Gleason score was an independent predictor when the model also included the radical prostatectomy Gleason score (12). Nomograms using the preoperative needle biopsy Gleason score have also been created, and their usefulness has been confirmed in large, multi-institutional studies (Tables 5-5 and 5-6) (28,29). Biopsy Gleason score has also been shown to be a powerful predictor of death due to prostate cancer in men treated with radical prostatectomy (30).

Table 5.2. 5-YEAR PROGRESSION-FREE SURVIVAL (PFS) AFTER RADICAL PROSTATECTOMY WITH pT2/3N0M0 ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>5-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>89%</td>
</tr>
<tr>
<td>5</td>
<td>85%</td>
</tr>
<tr>
<td>6</td>
<td>71%</td>
</tr>
<tr>
<td>7</td>
<td>68%</td>
</tr>
<tr>
<td>8-10</td>
<td>43%</td>
</tr>
</tbody>
</table>

aBased on 2,518 patients.

### Table 5.3. FIVE-YEAR PROGRESSION-FREE SURVIVAL (PFS) AFTER RADICAL PROSTATECTOMY WITH pT2N0M0 ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>5-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>98%</td>
</tr>
<tr>
<td>4</td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>82%</td>
</tr>
<tr>
<td>7</td>
<td>65%</td>
</tr>
<tr>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>9</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Based on 904 patients.


### Table 5.4. TWENTY-YEAR CUMULATIVE RATE OF DEATH FROM PROSTATE CANCER AFTER RADICAL PROSTATECTOMY FOR CLINICALLY LOCALIZED ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Age group (years)</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td></td>
<td>7%</td>
<td>7%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>12%</td>
<td>13%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>18%</td>
<td>19%</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>34%</td>
<td>35%</td>
<td>30%</td>
<td>29%</td>
</tr>
<tr>
<td>8-10</td>
<td></td>
<td>42%</td>
<td>43%</td>
<td>37%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*Based on 751 patients.


### Table 5.5. EFFECT OF BIOPSY GLEASON SCORE ON ESTIMATED PROGRESSION-FREE SURVIVAL (PFS) IF TREATED WITH RADICAL PROSTATECTOMY

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Serum PSA (ng/ml)</th>
<th>Gleason score</th>
<th>Estimated PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1c</td>
<td>6</td>
<td>4</td>
<td>96%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>5</td>
<td>92%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>6</td>
<td>91%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>7</td>
<td>85%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>8</td>
<td>84%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>9</td>
<td>83%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>4</td>
<td>91%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>5</td>
<td>82%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>6</td>
<td>81%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>7</td>
<td>68%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>8</td>
<td>66%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>9</td>
<td>63%</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.

Table 5.6. TEN-YEAR PROGRESSION-FREE SURVIVAL (PFS) AFTER RADICAL PROSTATECTOMY BASED ON CLINICAL STAGE, BIOPSY GLEASON SCORE, AND SERUM PROSTATE-SPECIFIC ANTIGEN (PSA)*

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>PSA 0-4</th>
<th>PSA 4.1-10</th>
<th>PSA 10.1-20</th>
<th>PSA &gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage T1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>99%</td>
<td>97%</td>
<td>94%</td>
<td>87%</td>
</tr>
<tr>
<td>6</td>
<td>97%</td>
<td>95%</td>
<td>90%</td>
<td>81%</td>
</tr>
<tr>
<td>7 (3 + 4)</td>
<td>95%</td>
<td>91%</td>
<td>84%</td>
<td>73%</td>
</tr>
<tr>
<td>7 (4 + 3)</td>
<td>89%</td>
<td>83%</td>
<td>74%</td>
<td>62%</td>
</tr>
<tr>
<td>8-10</td>
<td>79%</td>
<td>71%</td>
<td>61%</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical stage T2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7 (3 + 4)</td>
</tr>
<tr>
<td>7 (4 + 3)</td>
</tr>
<tr>
<td>8-10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical stage T2b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7 (3 + 4)</td>
</tr>
<tr>
<td>7 (4 + 3)</td>
</tr>
<tr>
<td>8-10</td>
</tr>
</tbody>
</table>

*Based on 2,091 cases.


PREDICTING OUTCOME AFTER RADIATION THERAPY

For radiation therapy, the significance of Gleason score in predicting outcome holds true whether the patient is treated with external beam photon therapy (including conformal treatment planning), photons combined with neutron therapy, or brachytherapy (Tables 5-7 and 5-8) (31). Many groups have used Gleason score as the criteria for brachytherapy eligibility. Risk models or nomograms based on serum PSA and Gleason score (with or without inclusion of clinical stage) for predicting the risk of progression after treatment.
with radiation therapy are available (Table 5-9) (7,8,32, 33, 34 and 35). For example, Ennis et al. (8) used serum PSA and Gleason score to group patients into four prognostic categories with hazard ratios for biochemical failure ranging from 1.0 (Gleason score 2 to 7 and PSA 0 to 4.0 ng/ml) to 18.2 (Gleason score 7 and PSA greater than 50 ng/ml or Gleason score 8 to 10 and PSA greater than 15 ng/ml).

Table 5.7. ACTUARIAL OUTCOME BY GLEASON SCORE FOR PATIENTS WITH CLINICAL STAGES T1-4 PROSTATE ADENOCARCINOMA TREATED WITH EXTERNAL BEAM RADIATION THERAPY

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Local recurrence</th>
<th>Distant metastases</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-year</td>
<td>10-year</td>
<td>5-year</td>
</tr>
<tr>
<td>2-3</td>
<td>8%</td>
<td>21%</td>
<td>88%</td>
</tr>
<tr>
<td>4-6</td>
<td>14%</td>
<td>31%</td>
<td>87%</td>
</tr>
<tr>
<td>7</td>
<td>17%</td>
<td>24%</td>
<td>78%</td>
</tr>
<tr>
<td>8-10</td>
<td>31%</td>
<td>36%</td>
<td>69%</td>
</tr>
</tbody>
</table>

*Based on 648 patients.


Table 5.8. FAILURE-FREE SURVIVAL AFTER BRACHYTHERAPY AND EXTERNAL BEAM RADIATION THERAPY (RT)

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Brachytherapy 5-year</th>
<th>Brachytherapy 7-year</th>
<th>External beam RT 5-year</th>
<th>External beam RT 7-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>78%</td>
<td>68%</td>
<td>78%</td>
<td>69%</td>
</tr>
<tr>
<td>5-6</td>
<td>74%</td>
<td>68%</td>
<td>72%</td>
<td>64%</td>
</tr>
<tr>
<td>7</td>
<td>49%</td>
<td>45%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>8-10</td>
<td>28%</td>
<td>ND</td>
<td>52%</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, no data point available.

*Based on 695 brachytherapy patients and 1,527 external beam RT patients.


Application of such models allows for selection of high-risk patients for more aggressive treatment approaches, such as dose intensification and the use of adjuvant or neoadjuvant treatments (36). In those patients treated primarily with radiation therapy but receiving neoadjuvant or adjuvant hormonal ablation, Gleason score has also been found to be an independent predictor of biochemical failure (37, 38 and 39).

PREDICTING OUTCOME AFTER OTHER TREATMENTS

Several other treatment options are available to patients with localized prostate cancer who are being treated for potential cure, including cryosurgery and the addition of neoadjuvant and adjuvant hormonal therapy, chemotherapy, and even dietary supplements. In most of these situations, data are less robust than in those previously described, but Gleason score remains a relatively constant significant prognostic parameter in all of them (40, 41 and 42). In many of the adjuvant and neoadjuvant situations, Gleason score is one of the primary determinants of recurrence risk that stimulates the discussion of additional therapy.
Table 5.9. EFFECT OF BIOPSY GLEASON SCORE ON ESTIMATED PROGRESSION-FREE SURVIVAL (PFS) IF TREATED WITH THREE-DIMENSIONAL CONFORMAL EXTERNAL BEAM RADIATION THERAPY

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Serum PSA (ng/ml)</th>
<th>Gleason score</th>
<th>Estimated PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1c</td>
<td>6</td>
<td>4</td>
<td>95%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>5</td>
<td>95%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>6</td>
<td>94%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>7</td>
<td>92%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>8</td>
<td>91%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>9</td>
<td>88%</td>
</tr>
<tr>
<td>T1c</td>
<td>6</td>
<td>10</td>
<td>84%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>4</td>
<td>83%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>5</td>
<td>83%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>6</td>
<td>82%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>7</td>
<td>78%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>9</td>
<td>67%</td>
</tr>
<tr>
<td>T2a</td>
<td>10</td>
<td>10</td>
<td>58%</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.


Table 5.10. EXAMPLES OF CLINICAL DECISIONS WHERE GLEASON SCORE MAY PLAY A MAJOR ROLE IN THE DECISION-MAKING PROCESS

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Role of Gleason score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision to opt for no immediate (delayed) therapy</td>
<td>In general, delayed or no therapy is not offered to patients with Gleason scores of 7 or higher</td>
</tr>
<tr>
<td>Selection of radical prostatectomy as the primary treatment</td>
<td>Gleason score is used in part to determine the likelihood of advanced or metastatic disease— if this is high, other approaches may be favored</td>
</tr>
<tr>
<td>Decision to do frozen sections during lymph node dissection at radical prostatectomy</td>
<td>Many surgeons elect to do frozen sections of lymph nodes during radical prostatectomy only in cases with high risk of nodal involvement, including cases with Gleason scores of 8-10</td>
</tr>
<tr>
<td>Selection of standard versus high-dose external beam radiation therapy</td>
<td>High Gleason score (7 or more) combined with other factors may lead to a dose intensified treatment</td>
</tr>
<tr>
<td>Suitability for brachytherapy</td>
<td>For some groups, the presence of a grade 4 component has been considered a relative contraindication to brachytherapy</td>
</tr>
<tr>
<td>Use of neoadjuvant and/or adjuvant hormonal therapy with radiation therapy</td>
<td>The presence of Gleason score 7 or higher, in combination with other factors, may lead to combination therapy</td>
</tr>
<tr>
<td>Use of neoadjuvant and/or adjuvant chemotherapy</td>
<td>Many studies are ongoing in patients at high risk for metastatic disease (partially determined by Gleason score) for the role of chemotherapy.</td>
</tr>
</tbody>
</table>

For patients who have failed locally, Gleason score is a powerful predictor of outcome when salvage therapy is used (43). Gleason score is also an important predictor of survival in patients treated primarily with hormonal therapy, whether for locally advanced or metastatic disease (44,45).

POTENTIAL ROLE OF GLEASON SCORE IN CLINICAL DECISION MAKING

For patients with prostate cancer, the Gleason score remains one of the most important parameters, impacting all aspects of their disease to include, potentially, the therapeutic stratification or approach (Table 5-10). The importance placed by clinicians and patients on the many nomograms available cannot be overemphasized.

REFERENCES

Percent Gleason grade 4/5 as prognostic factor.


REPORTING OF PROSTATE CARCINOMA BY THE GLEASON SYSTEM

Gleason grade should be reported for prostatic carcinoma in all tissue samples of the prostate from patients with no prior radiation or hormonal therapy (Table 6-1) (1, 2, 3, 4, 5, 6, 7, 8, 9 and 10). Another grading scheme may be employed and reported in addition to the Gleason grade, if desired, but the Gleason grade should always be included in the report. The primary (most predominant) Gleason grade and the secondary (second most predominant) Gleason grade should both be given, along with their sum, which is the Gleason score (Table 6-2) (5, 6, 7, 8, 9 and 10). If only one Gleason grade is assigned, then the grade is doubled to yield the Gleason score. It is important to provide all three numbers, because merely reporting a carcinoma as Gleason grade 4 may be misinterpreted as a Gleason score of 4 (3).

GRADE HETEROGENEITY: REPORTING OF MORE THAN TWO GRADES

The Gleason grading system allows for two separate grades in an individual tissue sample, but the histomorphologic appearance of prostatic carcinoma is very often more heterogeneous than this. Indeed, in one study (11), an average of 2.7 Gleason grades (range 1 to 5) was found in carcinomas in whole prostate glands. Two additional papers reported that 14% to 18% of patients had more than two grades in sections of their prostatic carcinoma (12,13). In one of these reports (13), 3% of cases had four different Gleason grades. The number of grades assigned depends on the tumor sample size and the size of the tumor in the whole gland (11, 12 and 13). Hence, more than two grades are more often observed in transurethral resection chips (TURP) and simple prostatectomy (28% of cases) compared with needle biopsies (4% of cases) (12), and tumors greater than 1 to 2 cm3 in size tended to have more than two grades (11,13).

Limited data are available on how to grade carcinomas with more than two grades. Gleason wrote that he was unable to acquire enough three-grade tumors to evaluate their behavior and proposed an algorithm to provide a Gleason score in cases with more than two grades (9). Recent data on radical prostatectomy specimens indicate that a high-grade Gleason pattern 4 or 5 that is a tertiary component occupying less than 5% of the tumor influences pathologic stage and progression rates (14). Therefore, any tertiary high-grade pattern should be mentioned in surgical pathology reports on radical prostatectomy cases. Comparable data do not currently exist for carcinoma in needle biopsy tissue, but recommendations have been made. In 1990, Gleason recommended that the two highest grades should be recorded for needle biopsies (9). [Note that this does not follow the general Gleason approach, which was established in publications from the 1960s and 1970s (5, 6, 7 and 8), and which was devised in large
part (60% of cases) on needle biopsies. In another recommendation for needle biopsy tissue in which more than two patterns are present and the worst grade is neither the predominant nor the secondary grade, the predominant and highest grade should be chosen to arrive at a score (1, 4). Clearly, more data and analyses are needed before establishment of a definitive approach to Gleason grading when more than two patterns are present. However, because it is also abundantly clear that any amount of high-grade Gleason pattern 4 or 5 is significant, this should be incorporated into the Gleason score in needle biopsy tissue in some fashion and should be noted in a comment in reports on radical prostatectomies.

Table 6.1. RECOMMENDATIONS FOR REPORTING GLEASON HISTOLOGIC GRADE

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report Gleason grade of carcinoma for all prostate tissue samples.</td>
</tr>
<tr>
<td>Report primary Gleason pattern and secondary pattern = score</td>
</tr>
<tr>
<td>If one pattern present, double to yield Gleason score</td>
</tr>
<tr>
<td>Provide grade for each separately submitted sample (container)</td>
</tr>
<tr>
<td>For needle biopsy cases, provide composite Gleason score for all cores</td>
</tr>
<tr>
<td>For needle biopsy cases, note Gleason score of core with highest score</td>
</tr>
<tr>
<td>For needle biopsy cases in which more than two patterns are present and the worst grade is neither the predominant nor the secondary grade, the predominant and highest grade should be chosen to arrive at a score</td>
</tr>
<tr>
<td>For radical prostatectomy cases in which more than two patterns are present and the worst grade is neither the predominant nor the secondary grade, mention the tertiary worst grade in a comment</td>
</tr>
<tr>
<td>Provide Gleason grade for adenocarcinoma histologic variants—ductal, signet ring, and mucinous</td>
</tr>
<tr>
<td>Do not provide Gleason grade for small cell carcinoma of the prostate</td>
</tr>
<tr>
<td>Provide Gleason grade for adenocarcinoma growth/cytologic variants, such as hypernephroid, atrophic, and pseudohyperplastic patterns</td>
</tr>
<tr>
<td>Additional grading schemes may be used, if desired</td>
</tr>
<tr>
<td>Do not report Gleason grade in metastatic deposits</td>
</tr>
<tr>
<td>Do not report Gleason grade after hormonal therapy</td>
</tr>
<tr>
<td>Report Gleason grade after radiation therapy of carcinoma that shows no treatment effect</td>
</tr>
<tr>
<td>Avoid lumping of Gleason scores</td>
</tr>
</tbody>
</table>

*Lumping (Grade Compression)*

“Lumping” or “grade compression” by combining Gleason scores in an attempt to translate to other grading systems should be avoided in reports (10). Such grouping often results in loss of information, with the risk of combining grades of different biologic aggressiveness into one larger category. Many different approaches to the lumping of Gleason scores have been published (Table 6-3) (8, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 and 26). As compared with the nine groups of Gleason score 2 to 10, groupings of two, three, and four categories have been used (Table 6-3). A common practice has been to translate Gleason score 2 to 4 carcinoma as well differentiated, Gleason score 5 to 7 as moderately differentiated, and Gleason score 8 to 10 as poorly differentiated. Yet, Gleason score 7 carcinoma harbors an element of high-grade pattern carcinoma, and it is intermediate in clinical aggressiveness between patterns 5 to 6 and 8 to 10 (27, 28) and should not be included in a moderately differentiated category. If lumping is necessary due to low patient numbers in a research setting, the 2 to 6 versus 7 versus 8 to 10 lump or 2 to 4 versus 5 to 6 versus 7 versus 8 to 10 lump seems most appropriate.
Table 6.2. EXAMPLES OF GLEASON GRADE REPORTING: MULTIPLE SCENARIOS

I. One Grade
Gleason grade (pattern) + same Gleason grade = Gleason score
Example with only grade = Gleason grade 3: ADENOCARCINOMA, GLEASON GRADE 3 + 3 = SCORE OF 6

II. Two Grades
Predominant grade + second most predominant grade = Gleason score
Example with predominant grade = 3 and second most predominant grade = 4: ADENOCARCINOMA, GLEASON GRADE 3 + 4 = SCORE OF 7

III. Multiple Grades
A. Needle biopsy case
Predominant grade = 3, second most predominant grade = 4, tertiary grade = 5
ADENOCARCINOMA, GLEASON GRADE 3 + 5 = SCORE OF 8

B. Radical prostatectomy case
Predominant grade = 3, second most predominant grade = 4, tertiary grade = 5
ADENOCARCINOMA, GLEASON GRADE 3 + 4 = SCORE OF 7 (SEE COMMENT)
COMMENT: A tertiary pattern of high-grade Gleason grade 5, comprising less than 10% of the tumor is noted

IV. Multiple Needle Biopsy Cores with Different Gleason Scores
A. Submitted as separate, single cores in six containers
1. PROSTATE, LEFT APEX, NEEDLE BIOPSY—ADENOCARCINOMA, GLEASON GRADE 3 + 3 = SCORE OF 6, IN ONE OF ONE CORE, AND INVOLVING 30% OF NEEDLE CORE TISSUE
2. PROSTATE, LEFT MID, NEEDLE BIOPSY—ADENOCARCINOMA, GLEASON GRADE 3 + 4 = SCORE OF 7, IN ONE OF ONE CORE, AND INVOLVING 60% OF NEEDLE CORE TISSUE
3. PROSTATE, LEFT BASE, NEEDLE BIOPSY—BENIGN PROSTATIC TISSUE
4. PROSTATE, RIGHT APEX, NEEDLE BIOPSY—ADENOCARCINOMA, GLEASON GRADE 3 + 3 = SCORE OF 6, IN ONE OF ONE CORE, AND INVOLVING LESS THAN 5% OF NEEDLE CORE TISSUE
5. PROSTATE, RIGHT MID, NEEDLE BIOPSY—ADENOCARCINOMA, GLEASON GRADE 3 + 4 = SCORE OF 7, IN ONE OF ONE CORE, AND INVOLVING LESS THAN 5% OF NEEDLE CORE TISSUE
6. PROSTATE, RIGHT BASE, NEEDLE BIOPSY—BENIGN PROSTATIC TISSUE
COMMENT: The composite Gleason score for this case based on evaluation of all needle core biopsies is 3 + 4 = score of 7

B. Submitted in two containers
PROSTATE, LEFT, NEEDLE BIOPSY—BENIGN PROSTATIC TISSUE
PROSTATE, RIGHT, NEEDLE BIOPSY—ADENOCARCINOMA, GLEASON GRADE 3 + 4 = SCORE OF 7, IN FOUR OF SIX CORES, INVOLVING 40% OF NEEDLE CORE TISSUE (SEE COMMENT)
COMMENT: One core has a Gleason grade 4 + 4 = score of 8

Table 6.3. DIFFERENT APPROACHES TO LUMPING OF GLEASON SCORES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Lumping approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>15, 16</td>
<td>2 to 6 versus 7 to 10</td>
</tr>
<tr>
<td>17</td>
<td>2 to 5 versus 6 to 7 versus 8 to 10</td>
</tr>
<tr>
<td>18, 19</td>
<td>2 to 4 versus 5 to 7 versus 8 to 10</td>
</tr>
<tr>
<td>20</td>
<td>2 to 4 versus 5 to 6 versus 7 to 10</td>
</tr>
<tr>
<td>21</td>
<td>2 to 6 versus 7 versus 8 to 10</td>
</tr>
<tr>
<td>22</td>
<td>2 to 5 versus 6 versus 7 versus 8 to 10</td>
</tr>
<tr>
<td>23</td>
<td>2 to 3 versus 4 to 6 versus 7 versus 8 to 10</td>
</tr>
<tr>
<td>24-26</td>
<td>2 to 4 versus 5 to 6 versus 7 versus 8 to 10</td>
</tr>
<tr>
<td>8</td>
<td>2 to 3 versus 4 to 5 versus 6 versus 7 to 8 versus 9 to 10</td>
</tr>
</tbody>
</table>
REPORTING IN PROSTATIC FINE NEEDLE ASPIRATES

Attempts have been made to apply Gleason grading to fine needle aspiration biopsy samples of prostatic carcinoma (29, 30, 31, 32 and 33), but because epithelial-stromal relationships are not preserved in these specimens, this is not advisable. Rather, traditional cytologic grading, as well, moderately or poorly differentiated is recommended (33).

REPORTING IN NEEDLE CORE BIOPSY TISSUE

Gleason grade should be reported for all needle core biopsy specimens, even for minute, minimal, or limited carcinomas. Gleason grading of a minimal or limited amount of carcinoma in needle biopsy [defined as less than 1 mm of carcinoma (34,35) or less than 5% (36) or 10% of needle core tissue involvement by carcinoma] can be just as accurate as for a large amount of tumor in needle biopsy (34, 35, 36 and 37). A small amount of carcinoma in needle biopsy tissue does not correlate with low-grade tumor on needle biopsy, and in fact, is usually of Gleason score 6 (35).

As noted above, if a tertiary, high-grade (pattern 4 or 5) component is found, then the predominant and highest grade should be summed to generate the Gleason score.

A separate Gleason grade should be assigned to separately submitted tissues (containers), designated by site (2). Additionally, it has been recommended that a composite or global score is rendered for needle biopsies with different Gleason grades in different, separately submitted needle cores (1,2) (Table 6-2). In a recent study, the composite Gleason score for six needle core tissue samples from different locations had the strongest association with radical prostatectomy extraprostatic extension by carcinoma and margin status compared with the highest Gleason score for any single core or weighted Gleason score (the average Gleason score weighted by tumor amount on all cores) (38). Confirmatory data are needed, but these data do support rendering a composite, overall, or global Gleason score for each case. Another recommendation is that each core should be given a Gleason grade (39), with the highest Gleason score used. Further research is needed to establish whether reporting a composite score and/or a highest score is the best approach. In the mean time, we recommend reporting both the composite Gleason score and the score of the core with the highest Gleason score.

REPORTING IN TRANSURETHRAL RESECTION AND PROSTATECTOMY CHIPS

Gleason grade reporting in TURP chips and enucleation specimens should follow the standard Gleason method of reporting the predominant grade as the primary grade and the second most common grade as the secondary grade.

REPORTING IN RADICAL PROSTATECTOMIES

Radical prostatectomy Gleason grade should be assigned in standard fashion, with the most common and the secondary Gleason grades in the whole gland used to determine the primary and secondary Gleason grades. Some published recommendations suggest only grading the "dominant nodule" (40) or reporting separate grades for separate tumors in the whole gland (1), but many cancerous prostate glands lack a dominant carcinoma nodule (41), and no data exist to support reporting separate tumors. The current recommendation for handling a tertiary high-grade (pattern 4 or 5) component is to keep the original Gleason score and note the presence of the tertiary high-grade component in a comment (14).
GRADING OF METASTATIC DEPOSITS

Grading in metastatic sites has been attempted using the Gleason system (42, 43, 44 and 45). The Gleason grading system is based on epithelial (carcinoma) stromal architectural relationships within the prostate; therefore, theoretically, Gleason grading should not be reported for prostatic carcinoma located outside the prostate or in metastatic sites. Nevertheless, several reports of Gleason grading have been found for carcinoma in pelvic lymph nodes (42, 43 and 44) and bone (45). Well-differentiated Gleason score 2 to 4 prostatic carcinoma in pelvic lymph nodes is nonexistent (42,43). Most Gleason scores assigned in metastatic deposits in lymph nodes were 7 to 10, with a minority of cases with scores of 5 or 6 (42, 43 and 44). In bone, most (78%) Gleason scores were 8 to 10, with 12% Gleason score 7, 7% Gleason score 6, and no cases of Gleason score 2 to 5 (45).

Comparison of Gleason histologic grade in lymph node metastasis with that of the Gleason grade of primary carcinoma in the prostate has demonstrated either a similar histologic pattern (42), or a trend toward a higher grade in the lymph node metastasis (43). This latter tendency has been termed “dedifferentiation,” which suggests reversion of a differentiated cell; clonal/genetic divergence, progression, and expansion are preferable descriptions for this process.

Overall, Gleason grade assignment of prostatic carcinoma metastatic deposits in lymph nodes and distant sites is not recommended.

GRADING AFTER RADIATION AND HORMONAL THERAPY

In general, the Gleason grading system should be applied only to prostatic carcinoma that shows no evidence of treatment effect (Table 6-4) (Figs. 6-1, 6-2, 6-3 and 6-4). This is because the Gleason system was originally devised based on untreated prostatic carcinomas and because both radiation and hormonal therapy can induce histologic alterations in prostatic carcinoma that simulate high-grade disease.

Radiation therapy has variable effects on prostatic carcinoma, with individual cases demonstrating no effect, partial effect with admixed affected and unaffected areas, or complete effect (46). When no evidence or minimal evidence of therapy effect is found, Gleason grading may be used. In several studies, however, Gleason grading was performed in all cases of irradiated prostatic carcinoma (47, 48, 49, 50, 51, 52, 53, 54, 55, 56 and 57). The effect of radiation on Gleason grade is controversial, with some studies (49,51, 52 and 53) showing increased Gleason grade and others reporting no change (48,58) or even a trend toward lower Gleason scores (59). For patients with a higher grade after radiation therapy, grade progression or “dedifferentiation” related to radiation treatment has been suggested, but this is probably an artifact of treatment effect, resulting in patterns of high-grade carcinoma (46) (Figs. 6-1 and 6-2). As with untreated prostatic carcinoma, Gleason scores of irradiated prostatic carcinoma in needle biopsy tend to underestimate the Gleason score in the whole gland excised in a salvage radical prostatectomy procedure. Reporting of Gleason grade only for carcinomas with minimal to no evidence of radiation therapy effect is recommended.

Table 6.4. GLEASON GRADING AFTER RADIATION AND/OR HORMONAL THERAPY

| Should not be performed when evidence of treatment effect is found |
| Treatment effect can induce pattern alterations mimicking high-grade carcinoma |
| Effect of radiotherapy on Gleason grade is controversial, with most studies showing increase in grade after irradiation, which is likely an artifact |
| Similarly, hormonal therapy can cause changes simulating poorly differentiated carcinoma |
Hormonal therapy is similarly variable in effect and can cause pattern alterations resembling poorly differentiated carcinoma (46,60,61). In particular, in areas affected by androgen deprivation, a decrease in gland size, compressed or absent glandular lumina, single cell formation, and increased stromal separation of glands result in the appearance of a higher Gleason grade (Figs. 6-3 and 6-4). This upgrading has been observed after several different forms of androgen deprivation therapy, including estrogen (or diethylstilbestrol) administration, luteinizing hormone-releasing hormone (LH-RH) agonists (such as leuprolide acetate) with or without an antiandrogen (such as flutamide or bicultamide), and estramustine phosphate sodium. Androgen deprivation by surgical castration (orchiectomy) should produce a similar effect on grade, although androgen deprivation induced by the 5a-reductase inhibitor finasteride seems, in preliminary data, to show a minimal to modest effect on prostatic carcinoma (62, 63 and 64).

The apparent increase in histologic grade after hormonal therapy is most likely artifactual (as opposed to outgrowth of higher-grade, hormone-resistant tumor cells). Modified Gleason scoring with adjustment for small glands and increased stroma after hormonal therapy has been proposed (65) but has not been validated (60). Overall, the consensus view is to not report histologic grade after hormonal therapy (66).

**EXPERIMENTAL ASPECTS OF GLEASON GRADING**

As a measure of intrinsic biologic aggressiveness, Gleason grade may be enhanced in the future by both structural (morphologic and morphometric) and functional means (by using gene expression profiling, for example). One proposed morphologic approach is quantitation of the amount of high-grade (percentage Gleason grade 4/5) carcinoma (67, 68, 69, 70, 71, 72 and 73). In TURP chips, the percentage of score 4/5 was the most powerful predictor of death from prostate cancer (74). The percentage of a tumor that is Gleason grade 4/5 in the whole gland has been related to cancer volume, the presence of lymph node metastasis (69,70), and progression after radical prostatectomy (67,68). Indeed, in one study of peripheral zone cancer, percentage pattern 4/5 was a better predictor of biochemical (PSA) recurrence after surgery than pathologic stage or Gleason score (67); in a second study (75), the proportion of poorly differentiated cancer was the factor most strongly linked to the likelihood of biochemical failure. Thus, this factor may be used in the reporting of grade in radical prostatectomy specimens in the future, but validation at other institutions and the question of reliability of the estimate (interobserver agreement) must be addressed in different types of tissue samples. Furthermore, it is not clear how to quantitate percentage 4/5 cancer. In one study (67), 10% increments were used; a different, four-tiered categorization (less than 5%, 5% to 24%, 25% to 49%, greater than 50%) was applied in a second series (75). Reporting of percentage Gleason grade 4/5 in needle biopsy has been advocated (71), but only limited data have been published on the relationship of percentage Gleason pattern 4/5 in carcinoma in needle core tissue and pathologic and clinical end points. The percentage Gleason pattern 4/5 in needle cores is significantly related to percentage of that pattern in the whole gland (in radical prostatectomy specimens (71,72,76), but the correlation is variable (from a week r² = 0.32 to a strong r² of 0.8). Overall, use of the percentage 4/5 parameter in needle biopsy seems to be limited by a high false-negative rate (72). It does not appear to provide additional information beyond Gleason score in prediction of pathologic stage and cancer progression after radical prostatectomy (73). Therefore, the amount of carcinoma comprised of high-grade Gleason grade pattern 4/5 has potential for adding information to standard Gleason grade assignment in TURP chips and radical prostatectomy tissue, but use in needle core tissue is currently uncertain. Reporting of percentage Gleason grade 4/5 in TURP chips and radical prostatectomy tissues should be viewed as optional, and reporting of this parameter in other prostatic tissue samples should be categorized as experimental.
FIGURE 6-1. Gleason score 6 (3 + 3). A: Histology of adenocarcinoma of the prostate prior to external beam radiation therapy. B: Histology in posttreatment biopsy at 18 months. The adenocarcinoma appears “atrophic” and includes single cells with abundant vacuolated cytoplasm, mimicking a higher grade. This most likely represents artifactual grade inflation and, hence, should not be graded.

FIGURE 6-2. Gleason score 6 (3 + 3). A: Discrete, small glands infiltrate prostate stroma and between benign glands. B: After combined radiation and hormonal therapy, the posttherapy biopsy shows marked atrophy, and the cytoplasm of the carcinoma is cleared. The carcinoma should not be graded in the posttreatment setting due to the potential for artifactual grade increase.
FIGURE 6-3. A: Adenocarcinoma of the prostate after total androgen blockade. B: After hormonal therapy, the tumor appears as small, shrunken glands and single cells. The carcinoma should not be graded in the posttreatment setting due to the potential for artifactual grade increase.

FIGURE 6-3. B: (continued)

FIGURE 6-4. A, B: Adenocarcinoma of the prostate with treatment effects. Assigning a Gleason score in this radical prostatectomy specimen after neoadjuvant total androgen blockade may result in assignment of a high Gleason score with a resultant higher expectation of the risk for recurrence and metastasis. In this setting, the latter estimates should be based on the biopsy Gleason score.

FIGURE 6-4. B: (continued)

REFERENCES


of survival for prostate carcinoma patients


60. Reuter VE. Pathological changes in benign and malignant prostatic tissue following androgen deprivation therapy. Urology 1997;49[Suppl]:1-22.


71. Stamey TA. Making the most out of six systematic sextant biopsies. Urology 1995;45:2-12.


Subject Index

Page numbers ending in "f" refer to figures. Page numbers ending in "t" refer to tables.

A
adenoid cystic carcinoma, 61t, 62, 63, 70f
adenosquamous and squamous cell carcinoma, 61t, 62, 70f
androgen deprivation therapy, 106
apoptotic cells, 49f
atrophic carcinoma, 60, 61t, 64, 73f

B
basaloid carcinoma, 23, 61t, 62, 63, 70f
benign prostatic hyperplasia (BPH), 2, 3, 17, 56, 71, 73 See also Pseudohyperplastic carcinoma
Böcking grading method, 83, 87
borderline patterns, and reproducibility, 86, 87, 87t
borders, tumor, in Gleason grading system, 5
See also Circumscription
brachtherapy
predicting outcome after, 96, 97t
role of Gleason score in, 98t
Broders grading system, 1, 2, 87

C
carcinoid-like carcinoma, 64, 75f
carcinoma. See Adenocarcinoma, prostatic carcinosarcoma, 61, 62, 70 See also Sarcomatoid carcinomas
circumscription, 15f, 16, 17, 18f, 19f, 20f, 21f, 25f, 50f, 51f, 52f
collagenous micronodules, 60, 65, 79f
colloid carcinoma, 34, 41f, 60, 61, 61t, 68f, 79f
comedonecrosis, 44, 44f, 45f, 46f, 61, 66f, 67f
compression artifact, 33f
cribriform architecture
with comedonecrosis, 44, 44f, 45f, 46f
in Gleason grade 3, 22, 23, 25f, 31f, 32f, 54f, 55f, 72f
in Gleason grade 4, 34, 37f, 39f, 40f, 41f, 55f, 77f
morphology of, 39f
in prostatic ductal adenocarcinoma, 60
cribriform proliferations, in reproducibility, 86, 87, 87t, 89f, 90f
cytoplasm, 3t, 21f, 27f, 28f, 30f, 33, 35f, 36f, 37f, 46f
granular eosinophilic, 64, 76f
vacuolated, 33f, 64, 69f, 107f

decision-making, clinical
and Gleason score, 98, 98t
therapeutic, 93
dedifferentiation, 10, 50, 105
desmoplasia, 22
ductal adenocarcinoma, prostatic, 60, 61, 61t, 65f, 66f, 67f, 68f

e
endometrioid carcinoma, 60, 61, 61t, 65f, 66f, 67f, 68f
eosinophilic secretions, 49f
external beam radiation therapy, 96, 97, 96t, 97t

F
fine needle aspiration biopsy, Gleason grade reporting for, 104
foamy gland pattern, 42f, 57f, 61t, 64, 74f, 75f
fusion, gland
in Gleason grade 4, 33, 34, 35f, 36f, 37f, 38f, 39f, 40f, 41f, 42f, 44f, 52f, 53f, 54f, 55f, 56f, 57f, 58f, 69f, 70f, 74f
and Gleason score 7, 7, 52f, 53f, 54f, 55f, 56f and Gleason score 8, 21f, 36f, 37f, 38f, 39f, 40f, 41f
and Gleason score 9, 44f, 46f, 57f
with perineural involvement, 79f, 80f

gland size, in Gleason grading system, 5
Gleason grade 1, 15f, 16f, 50f
application in needle biopsy specimens, 13, 14f
application in transurethral resection and prostatectomy specimens, 13, 14, 15f
original Gleason criteria, 13, 14f
pitfalls in grading, 14, 16f
Gleason grade 2, 15f, 18f, 19f, 20f, 21f, 50f, 51f, 52f, 57f
application in needle biopsy specimens, 9f, 14f, 16, 17, 18f, 19f, 20f
application in transurethral resection and prostatectomy specimens, 17, 18f, 20f
atrophic carcinoma as, 61t, 64
original Gleason criteria, 14f, 16, 18f
pitfalls in grading, 9f, 16f, 17, 20f, 21f
pseudohyperplastic carcinoma as, 61t, 64, 71f, 72f
reproducibility study, 88f, 89f
Gleason grade 3, 16f, 19f, 20f, 21f, 24f, 25f, 26f, 27f, 28f, 29f, 30f, 31f, 32f, 33f, 37f, 38f, 39f, 42f, 43f, 49f, 51f, 52f, 53f, 54f, 55f, 56f, 57f, 58f
application in needle biopsy specimens, 9f, 22, 23, 24f, 25f, 26f, 29f, 30f, 31f, 32f, 33f
application in transurethral resection and prostatectomy specimens, 23
atrophic carcinoma as, 61t, 64, 73f
carcinoid-like (organoid) pattern as, 64
collagenous micronodules as, 65, 79f
glomerulations as, 78f
morphologic variations in, 22, 24f, 25f, 26f, 28f, 31f, 32f, 37f, 43f
original Gleason criteria, 14f, 22, 24f
in Paneth cell-like pattern, 76f
for perineural invasion, 65, 80f
pitfalls in grading, 16f, 23, 24f, 27f, 28f, 30f, 32f, 33f, 43f, 77f
prevalence of, 8, 8t
prostatic ductal adenocarcinoma as, 61, 61t, 68f
pseudohyperplastic carcinoma as, 61t, 64, 71f, 72f
and radiation therapy, 107f
reproducibility study, 88f, 89f, 90f, 91f
sclerosing adenosis-like pattern as, 65, 77f
xanthomatous (foamy gland) pattern as, 61t, 74f, 75f
Gleason grading system for prostatic ductal adenocarcinoma as, 61, 61t, 65f, 66f, 67f
mucinous (colloid) carcinoma as, 61, 75f
collagenous micronodules as, 65, 79f
glomerulations as, 65, 78f
morpologic variations in, 33, 37f, 39f
mucinous (colloid) carcinoma as, 61, 61t, 68f
original Gleason criteria, 14f, 33, 35f
Paneth cell-like pattern as, 76f, 77f
for perineural invasion, 65, 79f, 80f
pitfalls in grading, 21f, 34, 41f, 42f, 43f as predictor of outcome, 106
prostatic ductal adenocarcinoma as, 61, 61t, 65f, 66f, 67f
adenofoamy-like pattern as, 61t, 74f
Gleason grade 5, 21f, 39f, 45f, 46f, 47f, 48f, 56f, 57f, 58f, 61
application in needle biopsy specimens, 44, 44f
application in transurethral resection and prostatectomy specimens, 44, 44f, 45f, 46f, 47f, 48f
application in transurethral resection and prostatectomy specimens, 44, 44f, 45f, 46f, 47f, 48f
original Gleason criteria, 14f, 44, 44f
pitfalls in grading, 44, 49f as predictor of outcome, 106
prostatic ductal adenocarcinoma as, 61, 61t, 66f, 67f
reporting, 102, 106
reproducibility study, 89f, 90f
sclerosing adenosis-like pattern as, 65
Gleason grading system, 14f, 44, 44f
Gleason grading patterns
original, 4, 4f, 6f
use of term, 5
Gleason grading system
adenosquamous and squamous cell, 61t, 62, 70f
advantages of, 6
atrophic, 60, 61t, 64, 73f
basaloid and adenoid cystic, 23, 61, 62, 63, 70f
carcinoid-like (organoid) as, 64, 75f
collagenous micronodules, 60, 65, 79f
correlation of grades, 8, 8t
ductal, 60, 61, 61t, 65f, 66f, 67f, 68f
educational programs for, 86, 87f
endorsement of, 2
experimental aspects of, 106
Gleason grade 1, 15f, 66f
Gleason grade 2, 15f, 18f, 19t, 20f, 21f, 50f, 51f, 52f, 57f
Gleason grade 3, 16f, 19f, 20f, 21f, 24f, 25f, 26f, 27f, 28f, 29f, 30f, 31f, 32f, 33f, 37f, 38f, 39f, 42f, 43f, 49f, 51f, 52f, 53f, 54f, 55f, 56f, 57f, 58f
Gleason grade 4, 21f, 31f, 32f, 35f, 36f, 37f, 38f, 39f, 40f, 41f, 42f, 44f, 46f, 49f, 52f, 53f, 54f, 55f, 56f, 57f, 58f
Gleason grade 5, 21f, 39f, 45f, 46f, 47f, 48f, 56f, 57f, 58f, 61
glomerulations, 60, 65, 78f
grade progression in, 10
grading schemes for, 2, 3
historical perspectives of, 1, 2, 3
after hormonal therapy, 105, 106, 105t, 108f
lymphoepithelioma-like, 61t, 63
in metastatic deposits, 102f, 105
mucinous (colloid), 34, 41f, 60, 61t, 61t, 68f
Paneth cell-like and oncocytic change, 64, 76f, 77f, 80f
patterns of, 4, 4f, 5f, 6f, 14f
perineural invasion, 65, 77f, 79f, 80f
potential grading errors in, 9, 10, 9f, 14, 17, 23, 34, 44, 86, 87t
principles of, 3, 4, 5, 6, 7
pseudoepithelial, 56f, 60, 61t, 63, 64, 71f, 72f
after radiation therapy, 105, 105t, 107f
reporting in, 101, 102, 103, 104, 105, 106, 102t, 103f
reproducibility of, 83, 84f, 85t, 87
sarcomatoid (carcinosarcoma), 61, 67, 70f
sarcomatoid-like pattern as, 65, 77f
signet ring cell, 23, 48f, 56f, 60, 61t, 62, 69f
small cell (neuroendocrine), 50f, 61t, 63f, 71f
tertiary patterns in, 6, 6f, 9, 50f, 51f, 52f, 53f, 54f, 55f, 56f, 57f, 58f
in needle biopsy, 9, 10
nomograms using, 93, 94, 94t, 95t, 96t
and pathologic stage, 93, 94t
for predicting outcome, 93, 94t, 95t, 96t, 97, 98, 97t
after radiation and hormonal therapy, 105, 106, 105t, 107t, 108f
and radical prostatectomy, 9, 10
reporting of, 101, 102, 102t, 103f
Gleason score
Gleason score 2, 14f, 15f, 16f
Gleason score 3, 15f, 50f
Gleason score 4, 18f, 19f, 20f
Gleason score 5, 19f, 20f, 21f, 51f, 52f
in prostatic ductal adenocarcinoma, 60
for pseudoepithelial carcinoma, 71f, 72f
reproducibility study, 88f
Gleason score 6, 16f, 20f, 24f, 25f, 26f, 27f, 28f, 29f, 30f, 31f, 32f, 33f, 37f, 38f, 39f, 42f, 43f, 49f, 51f, 52f, 53f, 54f, 55f, 56f, 57f, 58f
Gleason score 7, 31f, 37f, 38f, 42f, 49f, 52f, 53f, 54f, 55f, 56f, 57f
for atrophic carcinoma, 73f
for Paneth cell-like change, 76f
for perineural invasion, 80f
in prostatic ductal adenocarcinoma, 60, 68f
for pseudoepithelial carcinoma, 72f, 73f
and radiation therapy, 107f
reproducibility study, 88f
for sclerosing adenosis-like pattern, 77f
for xanthomatous pattern, 74f, 75f
Gleason score 7, 31f, 37f, 38f, 42f, 49f, 52f, 53f, 54f, 55f, 56f, 57f, 58f
for atrophic carcinoma, 73f
for collagenous micronodules, 79f
for glomerulations, 78f
for mucinous carcinoma, 68f
for Paneth cell-like change, 76f
for perineural invasion, 80f
prevalence of, 7, 8t, 7t
in prostatic ductal adenocarcinoma, 60
reproducibility study, 89f, 90f
in xanthomatous pattern, 74f
Gleason score 8, 21f, 32f, 35f, 36f, 37f, 38f, 39f, 40f, 41f, 56f, 57f, 58f
for carcinoid-like pattern, 75f
for glomerulations, 78f
for mucinous carcinoma, 68f
for Paneth cell-like change, 77f
for perineural invasion, 79f
for prostatic ductal adenocarcinoma, 60, 61, 65f, 66f, 67f
radiation therapy
Gleason grading after, 102f, 105, 105f, 107f
and Gleason score distribution, 7, 8, 7f
with hormonal therapy, 107f
predicting outcome after, 96, 97, 96f, 97f
role of Gleason score in, 98f
radical prostatectomy
correlation with needle biopsy, 9, 10
and Gleason score distribution, 7, 7f
predicting outcome after, 94, 94f, 95f, 96f
predicting pathologic stage at, 93, 94f
progression-free survival after, 94, 94f, 95f
rate of death after, 95f
reporting in, 102f, 104
role of Gleason score in, 98f
radical prostatectomy specimens
grade heterogeneity in, 101
predicting outcome in, 106
reporting
elements for, 103f
of fine needle aspirates, 104
Gleason grade 3 subgrades, 22, 23
Gleason grades 4/5, 102, 106
lumping in, 102, 103f
in needle core biopsy, 104
after radiation and hormonal therapy, 105, 106
in radical prostatectomy, 104
recommendations for, 101, 102f
of tertiary grades, 6, 101, 102f
in transurethral resection and prostatectomy
chips, 104
reproducibility. See also Grading errors
defined, 83
problem areas with, 86, 87, 87f
web-based tutorials in, 86, 87f
reproducibility studies
effect of education on, 83
of Gleason grading system, 83, 84f, 85f, 86
Interobserver, 83, 84f, 85f, 86f, 87
Intraobserver, 83, 84f, 85f, 86f, 87
retraction artifact, 30f
sampling, and grading errors, 9, 10
sampling techniques, 3
sarcomatoid carcinoma, 61f, 62, 70f
sclerosing adenosis-like carcinoma, 64, 65, 77f
score, use of term, 5, See also Gleason score
sepal vesicle, invasion of, 55f, 93
shape, tumor, in Gleason grading system, 5f
signet-ring cell carcinoma, 48f, 56f, 60, 61, 62, 61f, 69f
signet ring cells, 23, 33, 34
signet ring-like cells, 42f
small cell (neuroendocrine) carcinoma, 50f, 61f, 63, 71f
squamous cell carcinoma, adenosquamous and, 61f, 62, 70f
staging systems. See Gleason grading system;
Grading systems
stromal invasion, 5, 16, 19, 24, 26, 27, 28. See also Infiltration
transitional cell carcinoma, 61f, 63
transurethral resection (TURP) chips/specimens
Gleason grade 1, 13, 14, 15f
Gleason grade 2, 17, 18f, 20f
Gleason grade 3, 23
Gleason grade 4, 34
Gleason grade 5, 44, 45f, 46f, 47f, 48f
Gleason grade reporting in, 104
grade heterogeneity in, 101
grades 4/5 as predictor of outcome in, 106
TURP. See Transurethral resection