Identification of Gleason Pattern 5 on Prostatic Needle Core Biopsy: Frequency of Underdiagnosis and Relation to Morphology

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Abstract: The presence of a Gleason pattern 5 prostatic adenocarcinoma is associated with a worse outcome. This study assesses the accuracy of grading a tumor as having Gleason pattern 5 and the potential factors contributing to its undergrading. From the consultation service of one of the authors, we identified 59 consecutive needle biopsy cases comprising 138 parts that, upon review, were graded as having Gleason pattern 5. All cases were reported as the final diagnosis by the outside pathologist. They were sent for a second opinion at the behest of clinicians or patients and not because the pathologist was seeking a second opinion. Considering the highest Gleason score in a given multicore specimen as the overall Gleason score, Gleason pattern 5 was missed in 34 of 59 (57.6%) cases by the outside pathologist. Compared with the outside pathologist's diagnosis, the Gleason score rendered at the second opinion was increased in 101 of 138 (73.2%) parts, was decreased in 5 of 138 (3.6%) parts, and remained unchanged in 32 of 138 (23.2%) parts. Gleason pattern 5 was not identified by the initiating pathologist in 67 of 138 (48.6%) of the evaluated parts. The architectural patterns of pattern 5 were as follows: single cells (n = 104, 75.3%); solid sheets (n = 69, 50%); cords (n = 62, 44.9%); and comedonecrosis (n = 3, 2.2%). Pattern 5 was missed more frequently when it was not the primary pattern. The most common Gleason pattern 5 architectural type was single cells and the least common was comedonecrosis. None of the architectural patterns appeared to be more correctly identified than the others; however, the most accurate grading was when the primary pattern was 5 and was composed mostly of solid sheets. Owing to the important prognostic and therapeutic implications of Gleason pattern 5, pathologists must be attuned to its varied patterns and to the fact that it may often represent a secondary or tertiary component of the carcinoma.

Key Words: prostate, needle biopsy, Gleason grade, Gleason score, radical prostatectomy

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The presence of Gleason pattern 5 prostatic adenocarcinoma is associated with a worse outcome.[6,10,11] Previous interobserver reproducibility studies have demonstrated that variability in identifying Gleason pattern 5 may lead to significant undergrading in needle core biopsies.[1,2,5] Thus, it is of interest to determine the frequency of underdiagnosis and the factors that may contribute to Gleason pattern 5 being missed on prostatic needle core biopsy.

MATERIALS AND METHODS

A total of 59 consecutive cases comprising 138 parts of prostatic needle core biopsies in which we identified Gleason pattern 5 were collected prospectively from the consultation service of one of the authors (J.I.E.). The cases were evaluated with regard to the following: whether pattern 5 was identified by the submitting pathologist, the Gleason score assigned by the initiating pathologist, the final Gleason score, the morphologic pattern of Gleason pattern 5, and its relationship to its underdiagnosis. In all cases in which there were discrepancies in grade, the slides from the original institution were original levels as opposed to recuts.

RESULTS

Amount of Core Involvement by Carcinoma and Gleason Pattern 5

The mean involvement of biopsy cores by prostatic carcinoma was 61.1% (range, 5% to 100%). On average, Gleason pattern 5 represented 53.3% of the carcinoma (range, 5% to 100%) and 32.1% (range, 1% to 100%) of the biopsy core length. Small foci of Gleason pattern 5 involving 5% of the carcinoma were only present in 2 of the 138 cases (1.4%). Gleason pattern 5 was present as a tertiary pattern in 20 of the 137 parts, and according to the modified Gleason system it was considered as the secondary pattern.[3]

Gleason Pattern 5 Subpatterns

Of the 138 cases studied, the architectural patterns of the Gleason 5 component were as follows: single cells (n = 104; 75.3%), solid sheets (n = 69; 50%), cords (n = 62; 44.9%), and comedonecrosis (n = 3; 2.2%). Examples of histologic architectural patterns are shown in Figures 1 and 2.

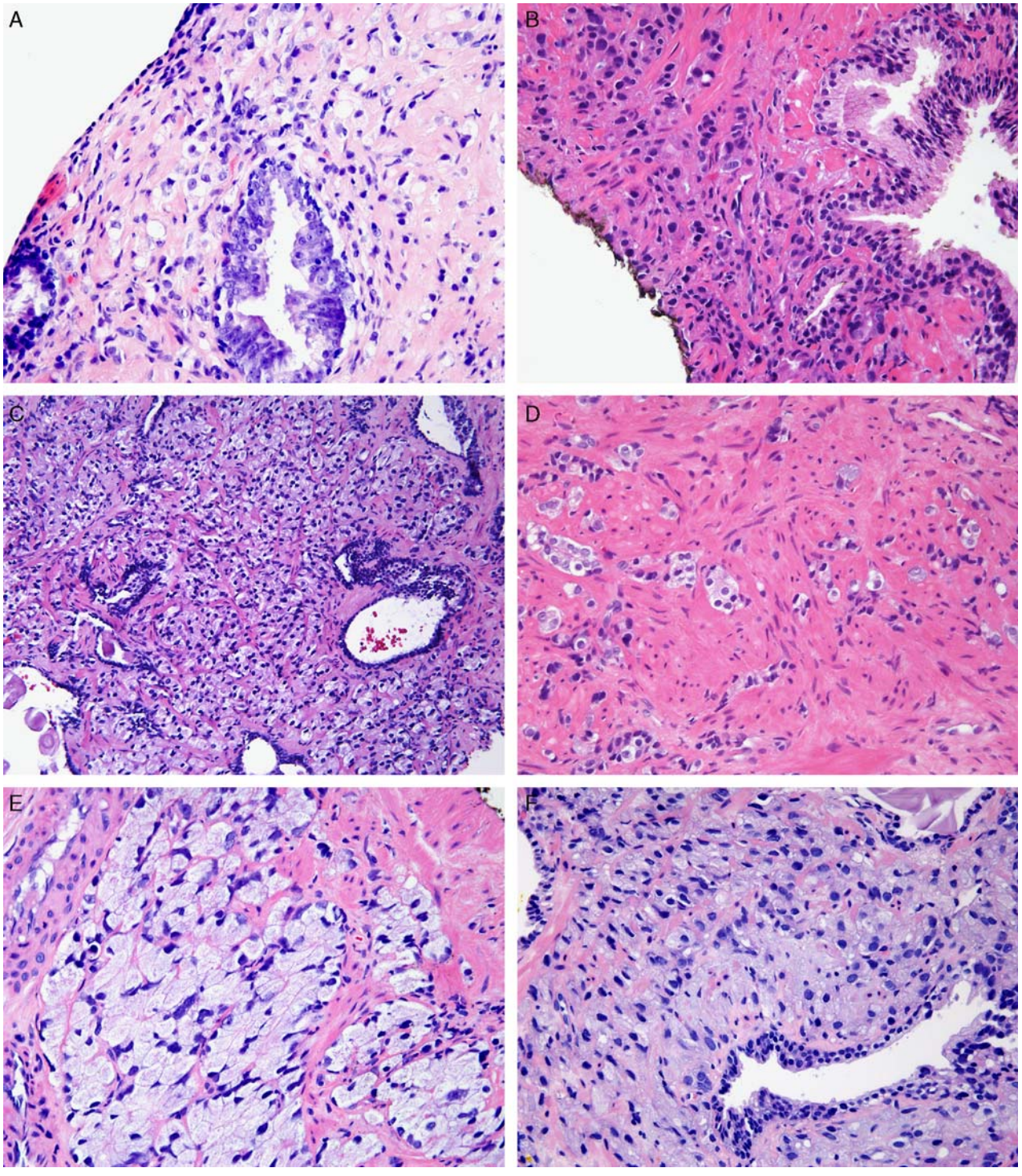

FIGURE 1. A to F, Single cells of Gleason pattern 5. In panels C and D, there are some solid small nests of cells that could be interpreted as poorly formed glands of Gleason pattern 4. However, there are numerous such nests without any luminal differentiation where tangential sections of poorly formed glands are not tenable, resulting in a diagnosis of Gleason pattern 5. In panel E, the cells have foamy features. full color online

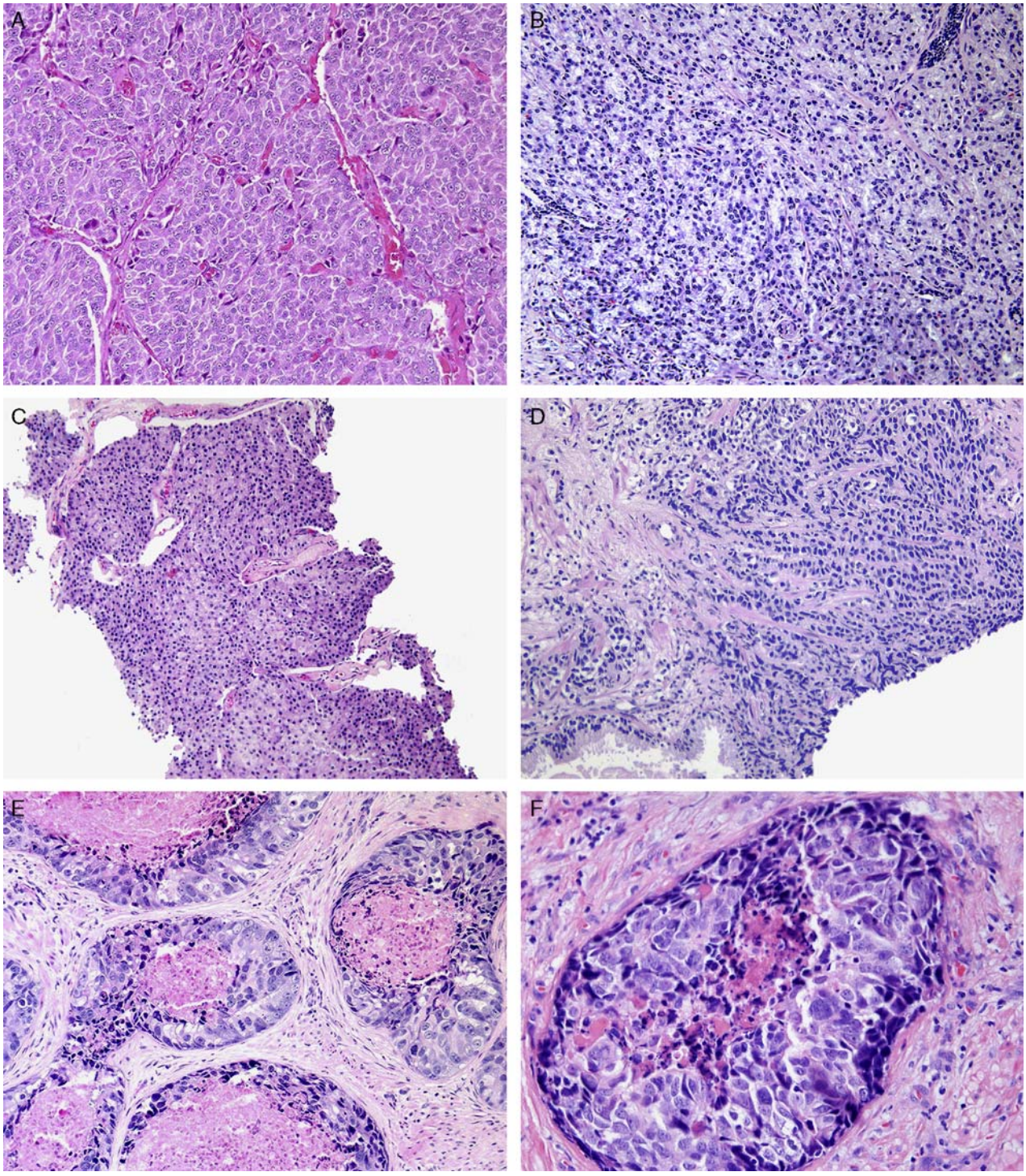

FIGURE 2. A to C, Gleason pattern 5 composed of solid sheets. Despite a very vague attempt of luminal formation in Figure 1C, the lesion lacks cribriform architecture, is very poorly differentiated, and essentially consists of sheets of cells. D, Cords of Gleason pattern 5. E to F, Comedonecrosis Gleason pattern 5 with more obvious (E) and more focal examples (F).

Identification of Gleason Pattern 5 by the Outside Pathologist

Considering the highest Gleason score in a given multicore specimen as the overall Gleason score, Gleason pattern 5 was missed in 34 of 59 (57.6%) cases (Table 1). Gleason pattern 5 was not identified by the initiating pathologist in 67 of 138 (48.6%) of the evaluated parts (Table 2).

TABLE 1. Correlation of Outside and JHH Gleason Score by Case

Initial Diagnosis	Final Diagnosis
Benign (n = 1)	4+5 = 9 (n = 1)
3+3 = 6 (n = 1)	3+5 = 8 (n = 1)
3+4 = 7 (n = 3)	3+5 = 8 (n = 2)
	4+5 = 9 (n = 1)
4+3 = 7 (n = 12)	3+5 = 8 (n = 3)
	4+5 = 9 (n = 7)
	5+4 = 9 (n = 2)
4+4 = 8 (n = 17)	3+5 = 8 (n = 1)
	5+3 = 8 (n = 1)
	4+5 = 9 (n = 9)
	5+4 = 9 (n = 5)
	5+5 = 10 (n = 1)
3+5 = 8 (n = 2)	3+5 = 8 (n = 1)
	5+4 = 9 (n = 1)
5+3 = 8 (n = 2)	5+3 = 8 (n = 2)
4+5 = 9 (n = 11)	3+5 = 8 (n = 1)
	4+5 = 9 (n = 4)
	5+4 = 9 (n = 5)
	5+5 = 10 (n = 1)
5+4 = 9 (n = 8)	3+5 = 8 (n = 2)
	4+5 = 9 (n = 1)
	5+4 = 9 (n = 3)
	5+5 = 10 (n = 2)
5+5 = 10 (n = 2)	5+5 = 10 (n = 2)

Difference Between Final and Initial Gleason Score

The final Gleason score was increased in 101 (73.2%) parts, was unchanged in 32 (23.2%) parts, and was decreased in 5 (3.6%) of the 138 parts. In the 67 parts in which the initiating pathologist did not identify a Gleason pattern 5, 65 parts resulted in a greater final Gleason score (the 2 remaining cases were initially diagnosed as 4+4 = 8 and the final diagnoses were 3+5 = 8 and 5+3 = 8). In 2 parts, the original diagnosis was "benign prostatic tissue," and the final diagnosis was a small foci of Gleason score 4+5 = 9 in one part and 5+5 = 10 in the other. In both cases the carcinoma involved 5% of the core. The parts came from different cases, with the 5+5 = 10 part representing the only cancer present in the case. Another case had an initial diagnosis of Gleason score 3+3 = 6, and the final Gleason score was 3+5 = 8. In this case, pattern 5 represented < 10% of the total volume of the carcinoma on the needle core. The results for the other comparisons are summarized in Table 2.

In 34 of 138 parts (24.6%) and 17 of 59 (28.8%) cases, the outside assigned Gleason score was < 7 without pattern 5 compared with 8 to 10 with pattern 5 as diagnosed at our institution. In 33 of 138 parts (23.9%) and 17 of 59 (28.8%) cases, the outside assigned Gleason score was 8 without pattern 5 compared with 9 to 10 as diagnosed at our institution.

TABLE 2. Correlation of Outside and JHH Gleason Score by Part

Initial Diagnosis	Final Diagnosis
Benign (n = 2)	4+5 = 9 (n = 1)
	5+5 = 10 (n = 1)
3+3 = 6 (n = 1)	3+5 = 8 (n = 1)
3+4 = 7 (n = 5)	3+5 = 8 (n = 2)
	4+5 = 9 (n = 3)
4+3 = 7 (n = 26)	3+5 = 8 (n = 4)
	4+5 = 9 (n = 17)
	5+4 = 9 (n = 5)
4+4 = 8 (n = 33)	3+5 = 8 (n = 1)
	5+3 = 8 (n = 1)
	4+5 = 9 (n = 23)
	5+4 = 9 (n = 7)
	5+5 = 10 (n = 1)
3+5 = 8 (n = 2)	3+5 = 8 (n = 1)
	5+4 = 9 (n = 1)
5+3 = 8 (n = 4)	5+3 = 8 (n = 4)
4+5 = 9 (n = 29)	3+5 = 8 (n = 2)
	4+5 = 9 (n = 11)
	5+4 = 9 (n = 15)
	5+5 = 10 (n = 1)
5+4 = 9 (n = 29)	4+4 = 8 (n = 1)
	3+5 = 8 (n = 1)
	4+5 = 9 (n = 1)
	5+4 = 9 (n = 9)
	5+5 = 10 (n = 15)
5+5 = 10 (n = 17)	5+5 = 10 (n = 7)

Underdiagnosis by Primary Gleason Pattern and Architectural Pattern

Depending on whether the primary Gleason pattern was 3, 4, or 5, Gleason pattern 5 was underdiagnosed in 8 of 10 (80%), 43 of 56 (76.8%), or 15 of 72 (20.8%) cases, respectively. Gleason pattern 5 was underdiagnosed in 27 of 53 (50.9%), 20 of 31 (39.2%), 17 of 31 (54.8%), and 2 of 2 (100%) cases when the predominant pattern comprised single cells, solids, cords, and comedonecrosis, respectively. Breakdowns of the identification of Gleason pattern 5 stratified by primary Gleason pattern are depicted in Tables 3 to 5.

DISCUSSION

When a man is diagnosed with prostate cancer on needle biopsy, the available information includes clinical stage, serum prostate-specific antigen (PSA) level, prostate size estimated by ultrasound, biopsy Gleason score, and extent of cancer on needle biopsy. Among these variables, Gleason score is the most powerful predictor of prostate cancer prognosis and in determining therapy. Much work has been carried out to predict the risk of upgrading of prostate cancer on needle biopsy, especially from Gleason score 6 to 7 or higher. The most common

TABLE 3. Identification of Gleason Pattern 5 When Gleason Pattern 3 is the Primary Pattern

Architectural Pattern	Pattern 5 Not Identified by Outside Pathologist (n = 8)	Pattern 5 Diagnosed by Outside Pathologist (n = 2)	Total
Single cells	3 (75%)	1 (25%)	4 (100%)
Solid sheets	2 (66.7%)	1 (33.3%)	3 (100%)
Cords	3 (100%)	0 (0%)	3 (100%)
Comedonecrosis	—	—	

TABLE 4. Identification of Gleason Pattern 5 When Gleason Pattern 4 is the Primary Pattern

Architectural Pattern	Pattern 5 Not Identified by Outside Pathologist (n = 43)	Pattern 5 Diagnosed by Outside Pathologist (n = 13)	Total
Single cells	15 (78.9%)	4 (21.1%)	19 (100%)
Solid sheets	16 (72.7%)	6 (27.3%)	22 (100%)
Cords	10 (76.9%)	3 (23.1%)	13 (100%)
Comedonecrosis	2 (100%)	0 (0%)	2 (100%)

variables associated with an increased risk of upgrading from needle biopsy to radical prostatectomy are: (1) suboptimal needle biopsy sampling; (2) increased serum PSA levels; (3) increased extent of cancer on biopsy; (4) increased clinical stage; (5) lower prostate size; and (6) in some studies increased age.[4] Almost none of the studies have reported discrepancies between Gleason score 8 versus 9 to 10, as high-grade cancer is often lumped together as Gleason score 8 to 10. However, we have shown that men with Gleason score 9 to 10 on biopsy or radical prostatectomy have a significantly worse prognosis than men with Gleason score 8 in terms of biochemical recurrence. Consequently, it is important to accurately diagnose Gleason score 9 to 10 tumor, as opposed to lower-grade cancer. Men with Gleason score 8 tumors at needle biopsy and radical prostatectomy have a 63% to 64% estimated risk of being biochemically free of recurrence at 5 years. There is a precipitous drop in predicted cure for men with Gleason score 9 to 10 cancer at biopsy or radical prostatectomy, where only 34% are predicted to be biochemically free of disease at 5 years.[8]

There are several reasons for discrepancies between needle biopsy and radical prostatectomy grades. These include (1) sampling error, (2) borderline grades, and (3) pathology error. It has been demonstrated that there is increased upgrading from needle biopsy to radical prostatectomy with sextant, as opposed to extended biopsy.[4] However, even in the setting of extended biopsy sampling, which is the current standard of practice, sampling error is prevalent. If it is assumed that pathology error is at a relative minimum at our institution as a result of the presence of specialized expertise in genitourinary pathology, a recent study from our institution still found 25% upgrading due to sampling error from Gleason score 8 on biopsy to Gleason score 9 to 10 on radical prostatectomy.[4] Sampling error and borderline grades resulting in the undergrading of Gleason pattern 5 cannot be circumvented, whereas pathology error can be minimized. Although some of the cases in this study represent misdiagnoses, others may represent a difference in diagnostic thresholds for Gleason pattern 5. A limitation of this study is that the slides were returned to their respective institutions; hence, a case review by several expert genitourinary pathologists to establish interobserver reproducibility in the subset of carcinoma patterns present in this study was not possible. We have illustrated the range of morphology within Gleason pattern 5 to try to depict our threshold. As a general rule, we try to have a high threshold before diagnosing Gleason pattern 5 and would not do so based on a few individual cells or solid nests that could represent tangential sectioning off of poorly formed Gleason pattern 4 glands.

TABLE 5. Identification of Gleason Pattern 5 When Gleason Pattern 5 is the Primary Pattern

Architectural Pattern	Pattern 5 Not Identified by Outside Pathologist (n = 15)	Pattern 5 Diagnosed by Outside Pathologist (n = 57)	Total
Single cells	9 (30.0%)	21 (70%)	30 (100%)
Solid sheets	2 (7.4%)	25 (92.6%)	27 (100%)
Cords	4 (26.7%)	11 (73.3%)	15 (100%)
Comedonecrosis	—	—	

The first step to improving the diagnosis of Gleason pattern 5 on needle biopsy is the recognition that this is a problem. It had been our anecdotal experience borne out by this study that pathologists underdiagnose Gleason pattern 5 prostate cancer, possibly because of hesitance to assign a grade that has such adverse prognostic implications. This study demonstrates that there is a marked tendency for pathologists to undergrade Gleason pattern 5. Pattern 5 was missed in almost 50% of the prostate needle core biopsies examined, most frequently when it was not the primary pattern. None of the architectural patterns appeared to be more clearly identified than the others; however, the most accurate grading was when the primary pattern was 5 and composed mostly of solid sheets. The least common pattern was comedonecrosis, which was overlooked in all 3 cases in which it was present.

In a minority of cases, the discrepancy in Gleason scores between the outside pathologist and the second opinion review may have been attributed to the definition of Gleason score on needle biopsy when there are 3 grade patterns on a single core. In the modified Gleason grading system, if there are 3 grade patterns present, the Gleason score is derived by adding the most common and the highest pattern.[3] For example, if on a core there is predominantly Gleason pattern 4, less pattern 3, and least pattern 5, the Gleason score would be Gleason score $4+5=9$ as opposed to Gleason score $4+3=7$ with tertiary pattern 5. As seen in Table 2, in 17 of 138 parts, this situation could have resulted in the grade discrepancy. Similarly, if the primary pattern was 3 with less pattern 4 and least pattern 5, the modified Gleason score would be $3+5=8$ instead of Gleason score $3+4=7$ with tertiary pattern 5. Five of 138 parts had this potential scenario (Table 2). Even if we assume that in all of these 22 parts the grade discrepancy resulted from differences in the application of Gleason scoring, there still remains 45 of 138 (32.6%) parts where the undergrading could only be accounted for by missing pattern 5. In terms of the number of cases in which this situation

could have been in effect, there were 2 with an outside diagnosis of 3 + 4 = 7 (JHH diagnosis of 3 + 5 = 8) and 7 with an outside diagnosis of 4 + 3 = 7 (John Hopkins Hospital diagnosis of 4 + 5 = 9) (Table 1).

What is the impact of underrecognition of Gleason pattern 5? Men with a Gleason score 7 tumor are typically not worked up with bone scan and computed tomography of the abdomen and pelvis, whereas this is routine in men with Gleason score 8 to 10 cancer (personal communication Dr Theodore DeWeese, Director Radiation Oncology, JHH). When a biopsy is graded as Gleason score 8, when in fact it is Gleason score 9 to 10, there are more subtle differences in choices relating to surgery; however, it has no impact on radiotherapy. Many urologists will perform radical prostatectomy on men with Gleason score 8 disease, especially if it is limited on biopsy and preoperative serum PSA is not markedly elevated. Men with Gleason score 9 to 10 tumors are less likely to be treated surgically as these men typically have very advanced disease that does not benefit from surgery.[11,12] These are the men who are at significant risk for pelvic lymph node metastases, seminal vesicle invasion, and extensive positive margins. Previous studies have demonstrated that even small volumes of high-grade prostate cancer on needle core biopsies may be associated with more extensive high-grade disease in the corresponding radical prostatectomy.[7,9] Many urologists would want to know if there is Gleason pattern 5 on biopsy, as that could deter them from taking the patient to surgery. In summary, because of the important prognostic and therapeutic implications of Gleason pattern 5, pathologists must be attuned to its varied architectural patterns and to the fact that it may often represent a minor component of prostatic carcinoma.

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