

Grading of Invasive Cribriform Carcinoma on Prostate Needle Biopsy

An Interobserver Study among Experts in Genitourinary Pathology

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Abstract: The distinction between cribriform Gleason pattern 3 and 4 prostate cancer is controversial. Out of 3590 prostate cancers sent to one of the authors over 7 months, 30 needle biopsy cases were selected that possibly represented cribriform Gleason pattern 3 cancer. Thirty-six digital images were taken and sent to 10 experts in prostate pathology. Consensus was defined when at least 7/10 experts agreed on the grade. Sixty-seven percent (n = 24) of images reached consensus (23 pattern 4; 1 pattern 3). Of the 12 nonconsensus images, 7 were favor pattern 4 (6/10 experts agreed), 1 was favor pattern 3 (6/10 experts agreed), and 4 were equivocal (< 6 experts agreed). The most common criteria used to call pattern 4 in the 23 consensus pattern 4 images were in frequency: irregular contour, irregular distribution of lumens, slit-like lumens, large glands, number of glands, and small lumens. In the only consensus pattern 3 image, criteria used were regular contour, small glands, regular distribution of lumens, and uniform round lumens. Discrepancy between experts was qualified as primarily objective (different criteria present) in 38%, subjective (different interpretation of the same criteria) in 12%, and mixed (both objective and subjective) in 50%. The most frequent situation with different interpretations of the same criteria were regular versus irregular contour and small versus large glands, with the former more common. Even in this highly selected set of images thought to be the best candidates for cribriform pattern 3 from a busy consult

service, most experts interpreted the cribriform patterns as pattern 4. Moreover, most of the cribriform foci investigated (73%) were associated with more definitive pattern 4 elsewhere on the needle biopsy specimen. In conclusion, most of the small cribriform cancer foci seen on needle biopsy should be interpreted as Gleason pattern 4 and not pattern 3.

Key Words: cribriform, carcinoma of the prostate, prostate needle biopsy, Gleason grading

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According to the original drawing of D. F. Gleason, cribriform cancer was included in patterns 2, 3, 4, and 5.^{2,9,10} The original Gleason system did not describe the differences between the various cribriform patterns beyond the schematic diagram. Even with the revision of the Gleason system at an International Society of Urological Pathology (ISUP) consensus conference, the distinction between Gleason cribriform pattern 3 and 4 was still not resolved in terms of its practical application.^{7,8,12} It is currently unknown how most experts in prostate pathology would apply criteria to assign a grade on a relatively small focus of cribriform carcinoma on needle biopsy, which is not an obvious pattern 4.

MATERIALS AND METHODS

Out of 3590 prostate cancers sent to one of the authors (J.I.E.) in consultation over a period of 7 months (December 14, 2006 to July 2, 2007), 30 prostate needle biopsy cases were prospectively selected that possibly contained foci of cribriform Gleason pattern 3 cancer. The surrounding cancer grade on the same core and on other cores were noted by one of the authors (J.I.E.) for each biopsy according to the modified Gleason grading system.⁸ A digital file made of 36 static images taken from the selected needle biopsies was sent to a group of 10 experts in prostate pathology (M.B.A., A.B., L.E., D.J.G., P.A.H., V.E.R., W.A.S., J.R.S., T.M.W., and X.J.Y.) A questionnaire was attached to the digital file and respondents had to answer for each image which

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TABLE 1. Histologic Criteria Used by Experts to Separate Cribriform Gleason Pattern 3 From Gleason Pattern 4

Gleason Pattern 3	Gleason Pattern 4
Small glands	Large glands
Regular contour	Irregular contour/jagged edges
Regular distribution of lumens	Irregular distribution of lumens
Uniform round lumens	Variable slit-like lumens
	Number of glands

pattern they favor (Gleason pattern 3 or 4), and select from a list the criteria they used to make their choice (Table 1). Consensus was defined when at least 7/10 experts agreed on the grade. A pattern 3 or 4 was favored when 6/10 experts agreed on the grade. Equivocal answers were defined when 5/10 experts agreed/disagreed.

RESULTS

Diagnosis and Criteria

Out of 36 static images sent to the panel of experts, 67% (n = 24) reached consensus of which 23 were Gleason pattern 4 (Figs. 1–7) and 1 was Gleason pattern 3 (Fig. 8). Of the 12 nonconsensus images, 7 were favor Gleason pattern 4 (Figs. 9–13), 1 was favor Gleason pattern 3 (Fig. 14), and 4 were equivocal (Figs. 15, 16). Three pathologists more commonly diagnosed cribriform pattern 3 and were responsible for 66% (67 out of 101) of the Gleason pattern 3 diagnoses (Table 2). Overall, Gleason pattern 4 was diagnosed 259 times out of 360 possibilities (72%). Between 23 consensus Gleason

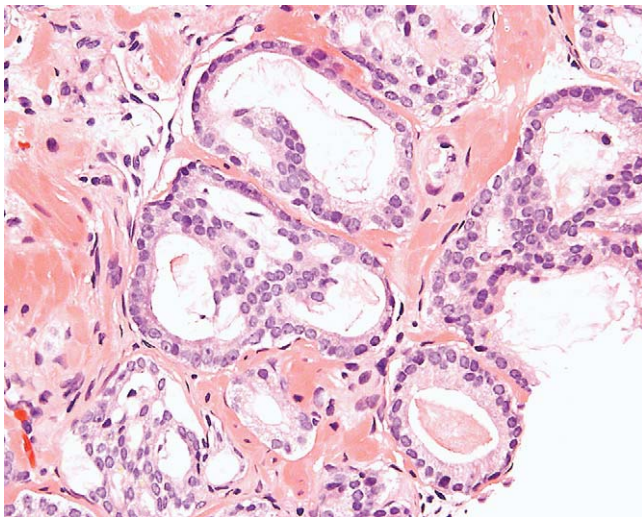


FIGURE 1. Consensus pattern 4 image (GP4:8, GP3:2). Irregular distribution of lumens (n=5), irregular contour/jagged edges (n=4), large glands (n=2), and number of glands (n=2) were selected by the experts who diagnosed pattern 4. Small glands (n=2), regular contour (n=2), and regular distribution of lumens (n=1) were selected by the experts who diagnosed pattern 3.

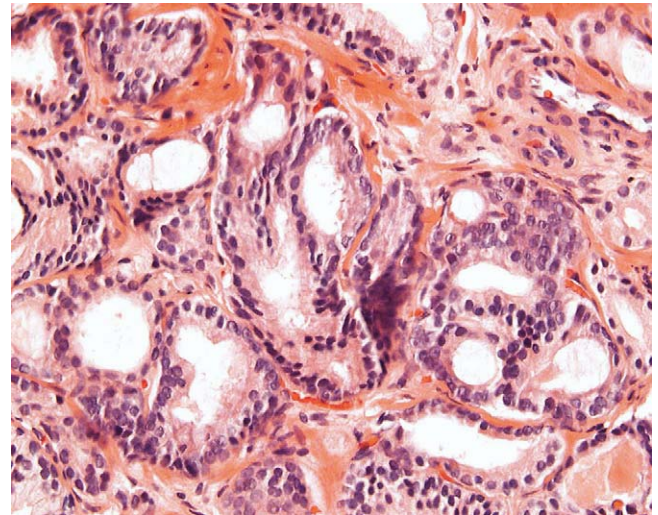


FIGURE 2. Consensus pattern 4 image (GP4:7, GP3:3). Irregular distribution of lumens (n=4), irregular contour/jagged edges (n=4), variable slit-like lumens (n=2), number of glands (n=2), and small lumens (n=1) were selected by the experts who diagnosed pattern 4. Small glands (n=2), regular contour (n=1), and regular distribution of lumens (n=1) were selected by the experts who diagnosed pattern 3.

pattern 4 images and 10 pathologists, there were a total of 190 Gleason pattern 4 diagnoses. Of these, the most common criteria used by the panel of experts to call pattern 4 were irregular contour (n = 122), irregular distribution of lumens (n = 92), slit-like lumens (n = 56), large glands (n = 51), number of glands (n = 45), and small lumens (n = 28). In the only consensus pattern 3 image, criteria were regular contour (n = 6), small glands

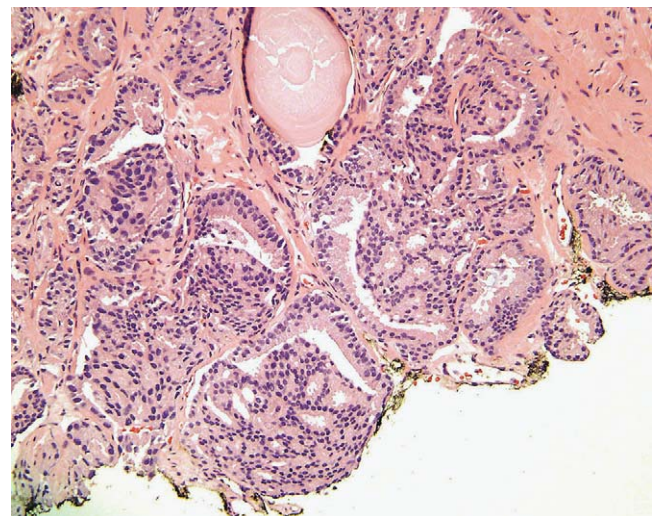


FIGURE 3. Consensus pattern 4 image (GP4:10, GP3:0). Irregular contour/jagged edges (n=8), large glands (n=4), irregular distribution of lumens (n=4), number of glands (n=3), variable slit-like lumens (n=2), and small lumens (n=1) were selected by the experts.

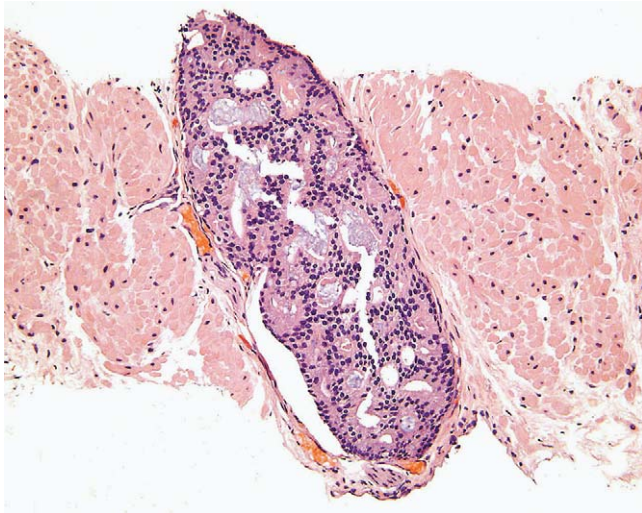


FIGURE 4. Consensus pattern 4 image (GP4:10, GP3:0). Large glands (n=6), irregular distribution of lumens (n=4), variable slit-like lumens (n=3), irregular contour/jagged edges (n=2), small lumens (n=1), and number of glands (n=1) were selected by the experts.

(n = 4), regular distribution of lumens (n = 3), and uniform round lumens (n = 2).

Gleason Grade in Surrounding and Distant Cancer

The highest grade in surrounding and distant cancer was noted for each 30 prostate needle biopsy cases selected for the study. Unequivocal Gleason pattern 4

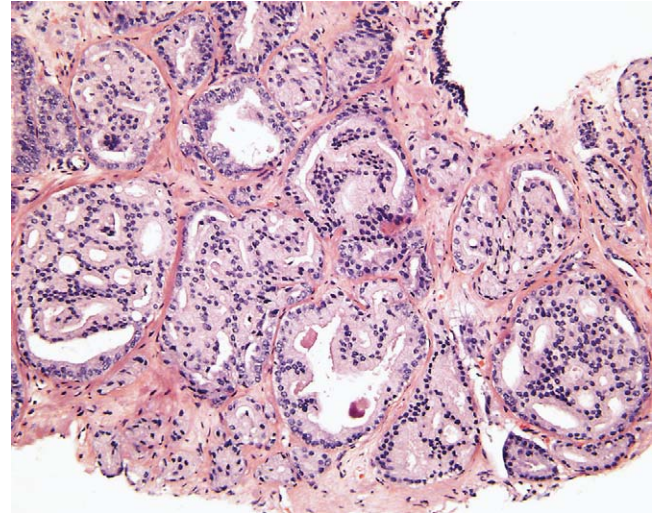


FIGURE 6. Consensus pattern 4 image (GP4:9, GP3:1). Irregular contour/jagged edges (n=8), number of glands (n=6), irregular distribution of lumens (n=4), variable slit-like lumens (n=4), large glands (n=3), and small lumens (n=1) were selected by the experts who diagnosed pattern 4. Small glands and regular contour were selected by the only expert who diagnosed pattern 3.

was seen in 73% (n = 22) of the cases. Of these, 3 cases showed one or more cores with Gleason score 8 and 19 cases showed 1 or more cores with Gleason score 7. In 8 needle biopsy cases, only Gleason pattern 3 was seen associated with the small cribriform foci in question. When submitted to the panel of experts, 3 of these cases with Gleason pattern 3 elsewhere ended up being

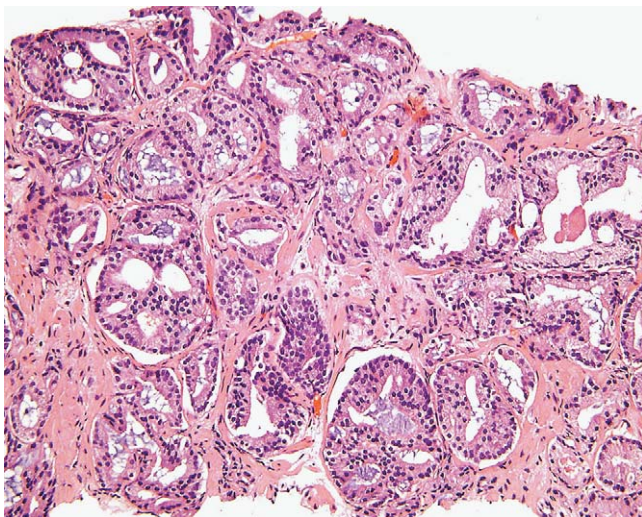


FIGURE 5. Consensus pattern 4 image (GP4:7, GP3:3). Number of glands (n=4), irregular contour/jagged edges (n=3), irregular distribution of lumens (n=2), variable slit-like lumens (n=2), and small lumens (n=1) were selected by the experts who diagnosed pattern 4. Regular contour (n=3), small glands (n=2), regular distribution of lumens (n=2), and uniform round lumens (n=1) were selected by the experts who diagnosed pattern 3.

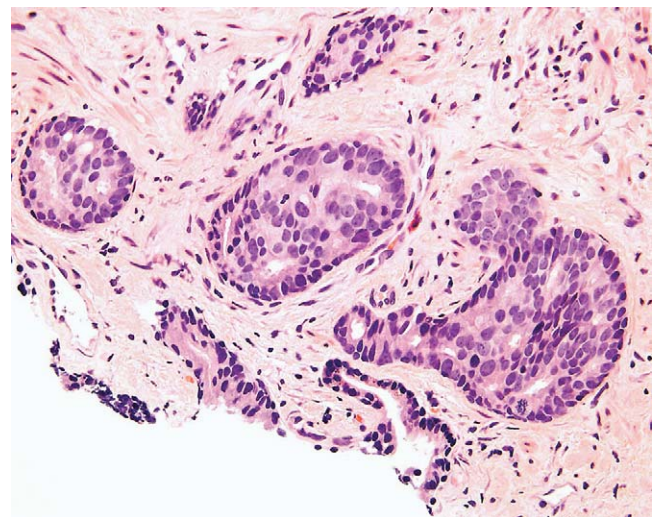


FIGURE 7. Consensus pattern 4 image (GP4:7, GP3:3). Irregular contour/jagged edges (n=5), irregular distribution of lumens (n=4), variable slit-like lumens (n=2), number of glands (n=1), and small lumens (n=1) were selected by the experts who diagnosed pattern 4. Small glands (n=3) and regular contour (n=2) were selected by the experts who diagnosed pattern 3.

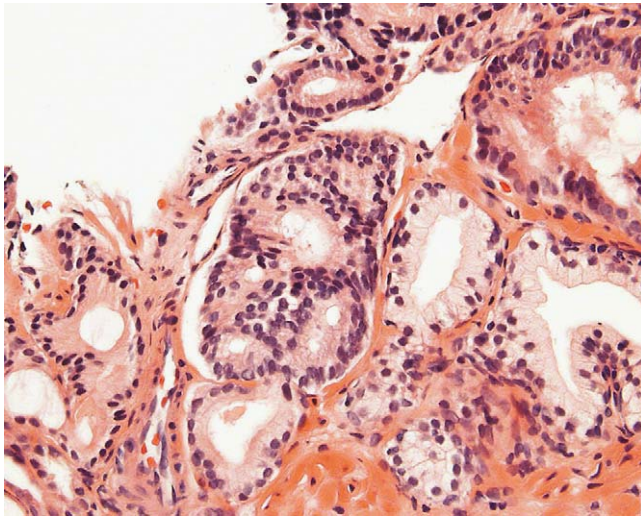


FIGURE 8. Consensus pattern 3 image (GP4:3, GP3:7). Regular contour (n=6), small glands (n=4), regular distribution of lumens (n=3), and uniform round lumens (n=2) were selected by the experts who diagnosed pattern 3. Irregular distribution of lumens (n=1), number of glands (n=1), and irregular contour/jagged edges (n=1) were selected by the experts who diagnosed pattern 4.

consensus Gleason pattern 4 (Figs. 1, 2), 3 ended up to be favor Gleason pattern 4 (Figs. 9–11), and 2 ended up to be equivocal (Figs. 15, 16). The only consensus Gleason pattern 3 image (Fig. 8) came from a needle biopsy case in which 2 other images were taken and interpreted as consensus Gleason pattern 4 (Fig. 2) and favor Gleason pattern 4. The only favor Gleason pattern 3

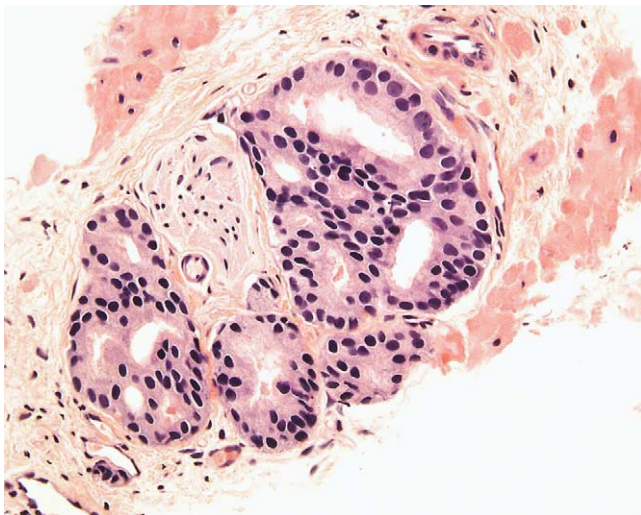


FIGURE 9. Favor pattern 4 image (GP4:6, GP3:4). Irregular contour/jagged edges (n=3), irregular distribution of lumens (n=2), variable slit-like lumens (n=1), and number of glands (n=1) were selected by the experts who diagnosed pattern 4. Regular contour (n=3), small glands (n=2), and regular distribution of lumens (n=2) were selected by the experts who diagnosed pattern 3.

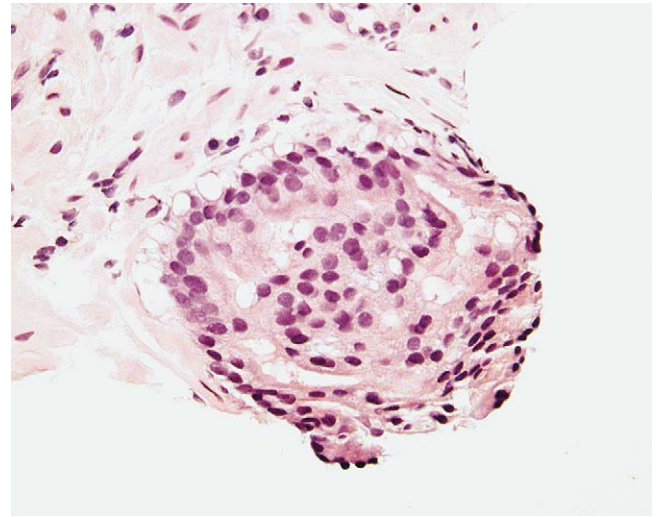


FIGURE 10. Favor pattern 4 image (GP4:6, GP3:4). Variable slit-like lumens (n=4), irregular distribution of lumens (n=3), irregular contour/jagged edges (n=1), and small lumens (n=1) were selected by the experts who diagnosed pattern 4. Regular contour (n=3) and small glands (n=2) were selected by the experts who diagnosed pattern 3.

image (Fig. 14) came from a needle biopsy case that showed obvious Gleason pattern 4 elsewhere in the biopsy.

Discrepancy Between Experts

Out of 36 images of cribriform cancer sent, 26 ended up having at least 2 or more experts in disagreement with

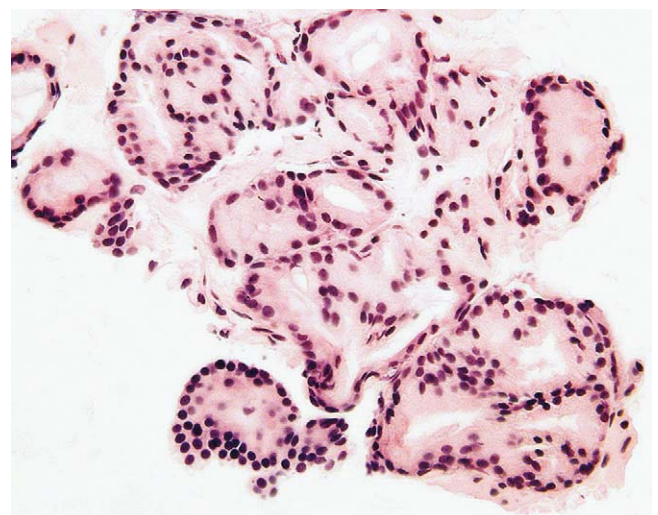


FIGURE 11. Favor pattern 4 image (GP4:6, GP3:4). Irregular contour/jagged edges (n=4), variable slit-like lumens (n=2), number of glands (n=2), and irregular distribution of lumens (n=1) were selected by the experts who diagnosed pattern 4. Small glands (n=3), regular contour (n=2), and regular distribution of lumens (n=2) were selected by the experts who diagnosed pattern 3.

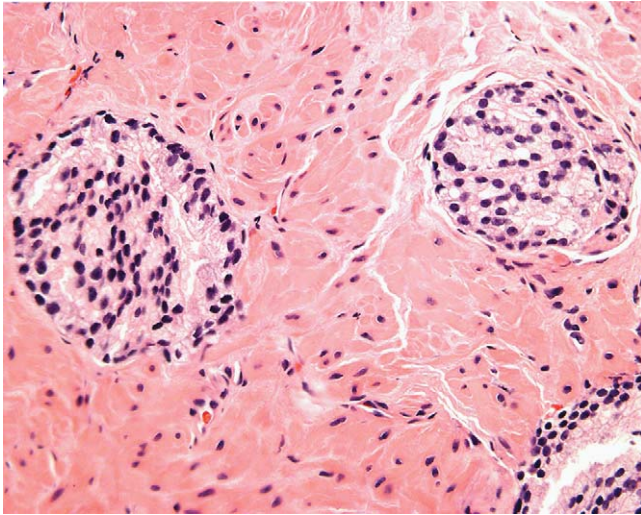


FIGURE 12. Favor pattern 4 image (GP4:6, GP3:4). Irregular distribution of lumens (n=4), variable slit-like lumens (n=4), small lumens (n=1), and number of glands (n=1) were selected by the experts who diagnosed pattern 4. Small glands (n=4) and regular contour (n=4) were selected by the experts who diagnosed pattern 3.

the rest of the panel regarding the grade. Discrepancy between pathologists was qualified as primarily objective when different criteria were used by them (eg, regular contour vs irregular distribution of lumens seen with Figs. 12 and 16), subjective when there was a different interpretation of the same criteria (eg, regular contour vs irregular contour seen with Fig. 7), and mixed when it was

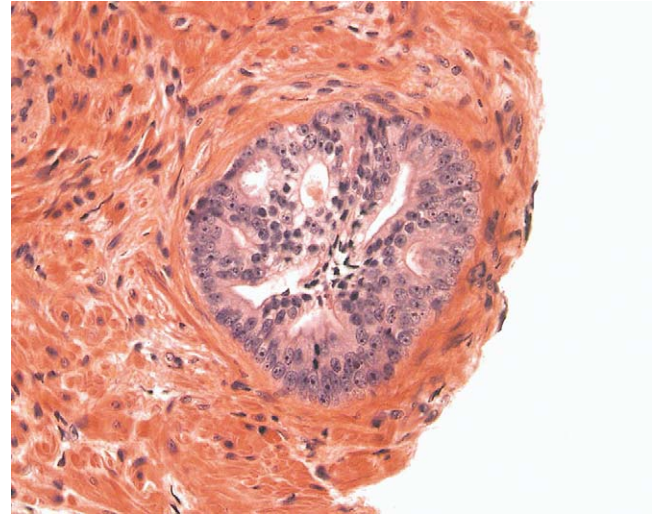


FIGURE 14. Favor pattern 3 image (GP4:4, GP3:6). Regular contour (n=5), small glands (n=3) and regular distribution of lumens (n=1) were selected by the experts who diagnosed pattern 3. Variable slit-like lumens (n=4) and irregular distribution of lumens (n=2) were selected by the experts who diagnosed pattern 4.

both objective and subjective (seen with Figs. 5, 9, 11). Discrepancy between experts was objective in 38% (n = 10), subjective in 12% (n = 3), and mixed in 50% (n = 13). The most frequent criteria with objective discrepancy were small glands, regular contour, irregular distribution of lumens, and variable slit-like lumens. The most conflicting criteria observed in subjective and mixed

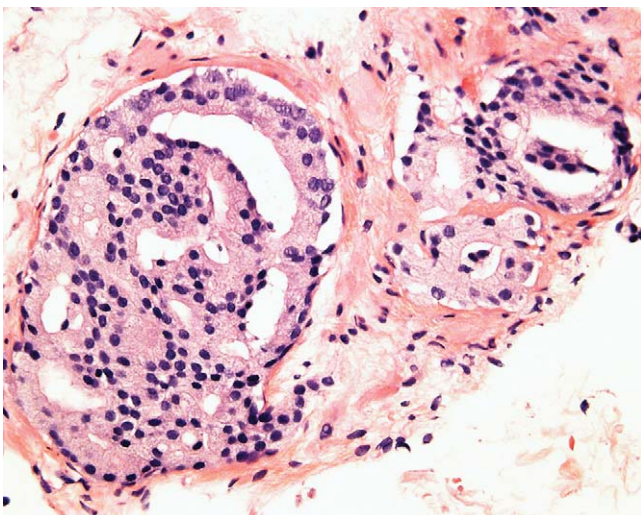


FIGURE 13. Favor pattern 4 image (GP4:6, GP3:4). Irregular distribution of lumens (n=3), large glands (n=2), variable slit-like lumens (n=2), small lumens (n=1), and irregular contour/jagged edges (n=1) were selected by the experts who diagnosed pattern 4. Regular contour (n=4), small gland (n=1), regular distribution of lumens (n=1), and uniform round lumens (n=1) were selected by the experts who diagnosed pattern 3.

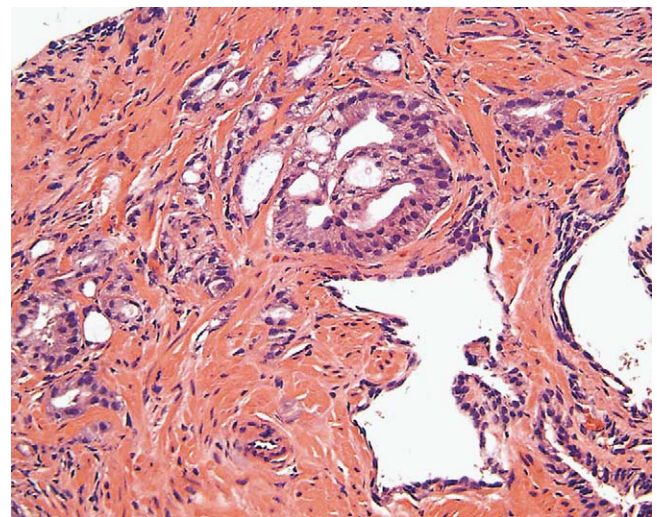


FIGURE 15. Equivocal image (GP4:5, GP3:5). Regular contour (n=3), small glands (n=2), uniform round lumens (n=1), and large lumens (n=1) were selected by the experts who diagnosed pattern 3. Irregular distribution of lumens (n=3), variable slit-like lumens (n=2), small lumens (n=1), and irregular contour/jagged edges (n=1) were selected by the experts who diagnosed pattern 4.

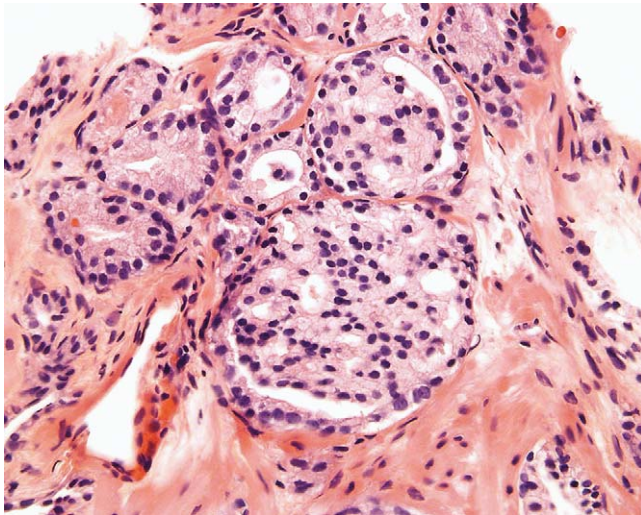


FIGURE 16. Equivocal image (GP4:5, GP3:5). Small glands (n=4), regular contour (n=4), and regular distribution of lumens (n=1) were selected by the experts who diagnosed pattern 3. Irregular distribution of lumens (n=4), variable slit-like lumens (n=3), small lumens (n=1), and number of glands (n=1) were selected by the experts who diagnosed pattern 4.

discrepancy (n = 16) were regular versus irregular contour in 88% (n = 14) and small versus large glands in 31% (n = 5).

DISCUSSION

The diagnosis and grading of cribriform carcinoma of the prostate have been controversial since the introduction of the Gleason grading system in 1966.⁹ According to the original drawing of D. F. Gleason, cribriform cancer was included in patterns 2, 3, 4, and 5, the latter being defined exclusively by the presence of comedonecrosis.^{2,9,10} Current basal cell immunohistochemistry has introduced further complexity in the classification of cribriform lesions by highlighting new challenging entities like cribriform high-grade prostatic intraepithelial neoplasia and intraductal carcinoma of the prostate that would have fulfilled morphologic description of cribriform cancer.^{1,3-5,11,15,18,19} In 2005, the Gleason grading system underwent its first major revision at an ISUP consensus conference.^{6,8,12} One of the most important inputs from the consensus was the modification of the Gleason pattern 4 that now includes most cribriform patterns because there is an increased understanding that invasive cribriform carcinoma is a relatively aggressive disease.¹⁷ More stringent criteria have been proposed to help pathologists separate the new cribriform Gleason pattern 3 from pattern 4, a distinction that would significantly impact on further therapeutic options and prognosis.^{6,8} Cribriform Gleason pattern 3 is depicted as individual small round glands with regular contour and large round evenly spaced lumens opposed to Gleason pattern 4, which is characterized by larger glandular formations with irregular contour or jagged edges and/or

TABLE 2. Frequency (%) of Gleason Patterns 3 and 4 Assigned by 10 Experts in Prostate Pathology to 36 Static Images of Small Foci of Cribriform Cancer Taken From 30 Prostate Needle Biopsy Cases

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10
Gleason pattern 4	78% (n = 28)	36% (n = 13)	33% (n = 12)	75% (n = 27)	92% (n = 33)	94% (n = 34)	89% (n = 32)	100% (n = 36)	44% (n = 16)	78% (n = 28)
Gleason pattern 3	22% (n = 8)	64% (n = 23)	67% (n = 24)	25% (n = 9)	8% (n = 3)	6% (n = 2)	11% (n = 4)	0% (n = 0)	56% (n = 20)	22% (n = 8)

smaller irregularly distributed lumens or slit-like lumens thought to be formed by the fusion of glands. The number of cribriform glands also seems to be a factor. Whereas, a single cribriform gland that fits the criteria for Gleason pattern 3 might be graded as pattern 3, some experts in the current study would diagnose pattern 4 in the setting of numerous such glands.

Our results demonstrate a definite trend among experts in prostate pathology toward interpreting infiltrating cribriform carcinoma as Gleason pattern 4. In fact, most of the cribriform glands initially considered by Gleason to be pattern 3 before the new 2005 ISUP consensus classification are now reconsidered as pattern 4 or cribriform high-grade intraepithelial neoplasia by many authors.^{8,13} These modifications with the others proposed in the modified Gleason grading system have been recently validated in different studies by showing a better correlation between needle biopsy grading and radical prostatectomy findings, and improved predictive accuracy in predicting biochemical disease-free survival after radical prostatectomy.^{12,16}

Even in our highly selected set of images thought to be the best morphologic candidates for cribriform pattern 3 cancer from a busy consult service, Gleason pattern 4 was either the consensus or favored diagnosis by a panel of experts in 30 images out of 36. Although cribriform Gleason pattern 3 was individually diagnosed by each expert, because of subjective and objective major discrepancies between them and the use of stringent criteria, a clear histomorphologic definition of what should be called cribriform pattern 3 was not achieved. Interestingly, the only image that was consensus cribriform Gleason pattern 3 originated from a case in which 2 other images were interpreted as consensus pattern 4 and favor pattern 4, which made the distinction between pattern 3 and 4 irrelevant in this situation. Moreover, the presence of coexistent obvious Gleason pattern 4 in the surrounding or distant cancer in up to 73% of our cases questions the biologic relevance and true existence of cribriform Gleason pattern 3. Martinez-Rodriguez et al¹⁴ came to the same conclusions in a study of 32 cases of prostate cancer (65.6% on needle biopsy; 34.4% on radical prostatectomy), which had candidate cribriform Gleason pattern 3 cancer seen from 1/99 to 10/2005. With the original Gleason grading system, cribriform pattern 3 cancer was confirmed using immunohistochemistry in 22/32 cases. With the more strict 2005 ISUP classification system, only 6 cases were classified as cribriform Gleason pattern 3 cancer. All together, cribriform pattern 3 ranged between 8% and 15% of the total amount of the cribriform tumor glands, with the remaining being Gleason pattern 4. Glands with the appearance of cribriform pattern 3 on cut downs for immunohistochemistry were spatially in close proximity to cribriform pattern 4 and in some cases on serial sections “cribriform pattern 3” glands started to show angulated contours of cribriform pattern 4. The authors concluded that cribriform pattern 3 was closely related to cribriform pattern 4 and that cribriform pattern 3 should be considered cribriform pattern 4.

An analogous situation with cribriform Gleason pattern 3 is the grading of Gleason patterns 2 to 4 on needle biopsy. The recommendation of the Gleason consensus panel was “The diagnosis of Gleason score 2 to 4 should rarely, if ever be made on needle biopsy.” It does allow for the exceedingly rare case where low grade cancer has been sampled on needle biopsy.⁸ With all the above caveats, for practical purposes, Gleason score 2 to 4 is not diagnosed on needle biopsy. Just as one requires the perfect yet unattainable low grade cancer to render a diagnosis of Gleason score 2 to 4 on biopsy, similarly the criteria for cribriform Gleason pattern 3 on biopsy is so stringent that for all intents and purposes, it is a diagnosis that will “rarely, if ever be made.” Of 3590 cases sent for consultation that formed the denominator in the current study (the vast majority Gleason score 6), the only 2 cases with either a consensus or favor Gleason pattern 3 came from needle biopsy cases in which there was obvious Gleason pattern 4 elsewhere in the biopsy. In conclusion, small cribriform cancer foci seen on needle biopsy should, with exceedingly rare exception, be interpreted as Gleason pattern 4 and not pattern 3.

It has been difficult to characterize the clinical behavior of carcinomas with the cribriform patterns illustrated in this study because they are rarely found in a pure form. Future research that may address this issue would be to follow patients with this type of cribriform carcinoma and admixed noncribriform Gleason pattern 3 on biopsy to determine whether radical prostatectomy findings are more like a score of 6 or 7. However, the low numbers of these needle biopsy cases would require a multi-institutional study.

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