21st Century Publisher

21ST CENTURY PATHOLOGY

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Retrospective Commentary

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# Cribriform Pattern of Prostate Cancer: Its Diagnostic Importance

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**Received:** 06 March 2022; **Accepted:** 19 March 2022; **Published:** 25 March 2022



## *Abstract*

*This retrospective commentary discusses how the cribriform pattern of prostate cancer has evolved to attain extensive recognition by surgical and urologic pathologists. Cribriform pattern of high-grade cancer confers a much worse prognosis than non-cribriform high-grade cancer and should be reported in pathology reports when high-grade (Gleason grades 4-5) cancer is present. The definition of what qualifies as cribriform has been studied recently and has been more precisely defined.*

***Keywords:*** *Prostate; Cancer; Carcinoma; Pattern; Cribriform; Intraductal; ISUP*

## Introduction

The original 5-tiered formulation for prostate cancer histologic grading of Dr. Donald F. Gleason based on his study of cases at the Minneapolis Veterans Administration Hospital in 1966 [1], has undergone several modifications since then. One major change had to do with the collapsing of Gleason grades 1-3 into Gleason grade 3 since the patterns of all 3 were associated with similar outcomes. A second major change revolved around expansion of the continuum of Gleason 4 lesions to include fused, poorly formed, and cribriform acini. The latter is the topic of the rest of this essay.

## I. Historical tendencies in grading cribriform cancer

Large cribriform acini, among all possible cancer patterns, had been encompassed in Gleason's original pattern 3, and a generation of pathologists had learned to regard any cribriform pattern as Gleason 3. However, by 2005, the majority of urologic pathologists came to believe that most (but not all) cribriform cancer should be Gleason 4 since, in their experience, it was often associated with other high-grade patterns such as fused acini and single cells, large tumor volume, and higher stages. If that were true, then, over the decades, many men's aggressive cancers had been relatively undegraded. When the International Society of Urological Pathology (ISUP) held its first consensus conference on Gleason grading of prostatic carcinoma in 2005, some cribriform cancer was still acknowledged as Gleason 3, but "The criteria used to diagnose cribriform pattern 3 were rounded, well-circumscribed glands of the same size of normal glands" [2].

Of course, the original cribriform pattern was conceived of before the immunohistochemistry era, so some of it may also have been cribriform high-grade prostatic intraepithelial neoplasia (HGPIN). By 2007, with the help of immunostains, only 8-15% of cribriform tumor glands in a series of specimens were considered to qualify as Gleason 3 [3], and even those glands were considered probably to belong to Gleason 4 because of their close spatial association with large cribriform glands.

## II. Hard evidence to support the theory about cribriform cancer

This controversy could be settled only through a study of all prostate cancer patterns present in a substantial case series, with patient follow-up. The needed evidence was lacking until 2011, when we published the results of a large and laborious digital annotation study of prostatectomy slide sets from 3 institutions, with patient follow-up, that definitively demonstrated that both large and small cribriform cancer was not only at least compatible with Gleason 4 but that their presence and amount conferred a distinctly worse prognosis than non-cribriform Gleason 4 cancer [4]. To wit, a cribriform pattern was present in 61% (46/76) of failures but 16% (12/77) of nonfailures ($P < .0001$). Cribriform pattern presence carried the highest odds ratio for PSA failure, 5.89 compared to the absence of cribriform, by multivariate analysis (95% confidence interval, 2.53-13.70; $P < .0001$). Also,

both small and large cribriform patterns were significantly linked to failure, putting to rest the notion that small cribriform cancer could remain in Gleason grade 3.

The 2011 study assessed only biochemical failure as a significant endpoint since there were too few deaths from prostate cancer to make survival a significant endpoint. Kweldam CF, et al. (2015) showed in 2015 that cancer-specific death was also predicted by the cribriform pattern [5]. We then showed that 3+5=8 versus 4+4=8 cancer did not matter for the outcome as much as did the presence of cribriform morphology [6]. Moreover, the presence of cribriform cancer on needle biopsy appeared more important than the percentage of Gleason 4 cancer for predicting outcome [7]. There followed dozens of studies on cribriform cancer, which we reviewed in 2018 [8], all reinforcing the finding that cribriform cancer (some studies included intraductal cancer, which is also cribriform but whose only difference is the retention of basal cells) possessed independent predictive value for prostatectomy stage, relapse, and survival versus non-cribriform Gleason 4 cancer. Therefore, when the ISUP met again in 2019 to update its grading recommendations, a key resolution was to endorse mentioning whether or not cribriform cancer was present, in all prostate biopsy and prostatectomy specimens that contained a component of Gleason 4 cancer [9]. Recently, the synoptic prostatectomy template endorsed by the College of American Pathologists has been updated to include a mention of cribriform cancer status.

## III. A firmer definition of criteria for cribriform cancer

In the aftermath of the ISUP's 2019 meeting, it was realized that since reporting of cribriform cancer was becoming standard, there needed to be a more precise definition of what cribriform is; thus studies of agreement on a cribriform diagnosis needed to be carried out. Notably, for intraductal carcinoma (which differs only by having basal cells) a survey had shown only modest agreement among urologic pathologists [10]. Several prostatic pathology experts of the ISUP published in 2021, practical consensus criteria [11], namely: "A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification ×10). There should be no intervening stroma or mucin separating individual or fused glandular structures." This was published with explanatory notes and should facilitate reporting of this important pattern (Figure 1).

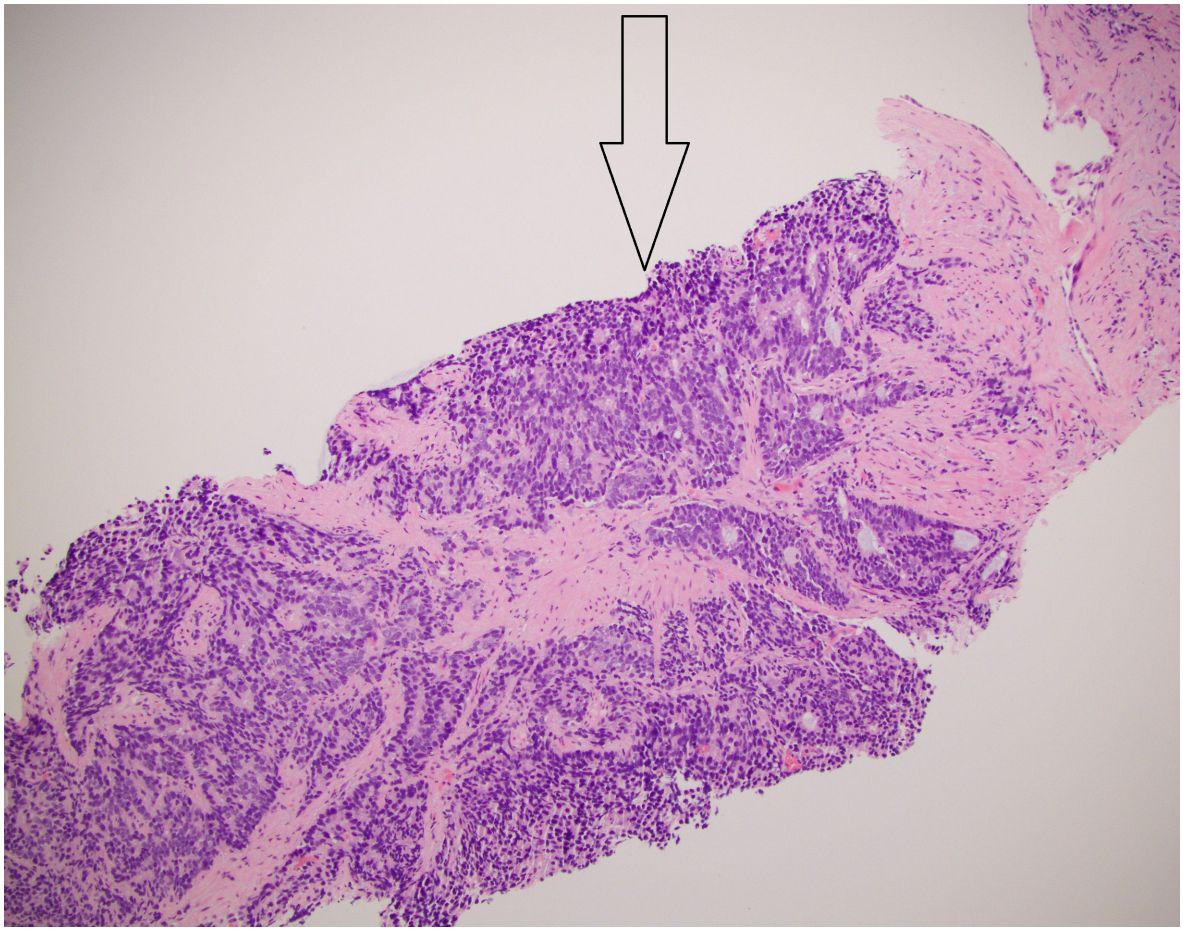

**Figure 1:** Threshold for diagnosis of cribriform cancer on biopsy. This tumor is obviously high grade, Gleason 4. Arrow indicates the portion that qualifies as cribriform, possessing multiple pinpoint lumina without intervening stroma. The tumor toward the bottom and left, would be termed by urologic pathologists as mostly a "complex fused" pattern but it does not qualify as cribriform owing to intervening stroma.

Analysis of the study set used to arrive at this definition revealed that final consensus was achieved in 21 of 32 cases, defined as 9 of 12 panelists agreeing or disagreeing with one or fewer strongly supporting an opposing choice [12]. The presence of intervening stroma precluded calling cribriform cancer (p = 0.006). Mucin presence detracted (p = 0.003) from the willingness to call cribriform cancer (only 3 cases had mucin). Lumen number was associated with cribriform consensus (p = 0.0006), and all consensus cases had ≥9 lumens. Predominant papillary pattern or an irregular outer boundary also detracted from calling cribriform (p = NS).

## Conclusion

The above mutually reinforcing studies should facilitate the assignment of prostate cancer according to the correct grouping of Gleason scores system, 3+3 | 3+4 | 4+3 | 4+4 | and 9-10, based on correctly-assessed proportions of Gleason 3 and 4 present in specimens. Current efforts are underway to augment the practical value for clinicians of cribriform cancer presence.

We are assessing how the presence of cribriform cancer affects the Cancer of the Prostate Risk Assessment (CAPRA) [13] and National Comprehensive Cancer Network (NCCN) [14] systems that are now clinically used to stratify patient risk. As we can see from the above discussion, in the past decade, the importance of cribriform prostate cancer has evolved from a concept understood only by pathologists to a matter of practical interest to urologists, oncologists, and patients (who now instantly read their pathology reports online) for management decisions.

## Conflict of Interest

The author have no conflict of interest.

## Overlapping Publication

This article have not been submitted to any other journal for publication.

## Funding

Author have not received any funding from any private and government organization.

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