Histopathology

Histopathology 2023 DOI: 10.1111/his.14867

Interobserver reproducibility of cribriform cancer in prostate needle biopsies and validation of International Society of Urological Pathology criteria

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Date of submission 16 November 2022
Accepted for publication 7 January 2023
Published online *Article Accepted* 16 January 2023

Egevad L, Delahunt B, Iczkowski K A, Leite T van der Kwast, Geert J L H van Leenders, K R M, Pan C-C, Samaratunga H, Tsuzuki T, Mulliqi N, Ji X, Olsson H, Valkonen M, Ruusuvuori P, Eklund M & Kartasalo K (2023) *Histopathology*. https://doi.org/10.1111/his.14867

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Aims: There is strong evidence that cribriform morphology indicates a worse prognosis of prostatic adenocarcinoma. Our aim was to investigate its interobserver reproducibility in prostate needle biopsies.

Methods and results: A panel of nine prostate pathology experts from five continents independently reviewed 304 digitised biopsies for cribriform cancer according to recent International Society of Urological Pathology criteria. The biopsies were collected from a series of 702 biopsies that were reviewed by one of the panellists for enrichment of high-grade cancer and potentially cribriform structures. A 2/3 consensus diagnosis of cribriform and noncribriform cancer was reached in 90% (272/304) of the biopsies with a mean kappa value of 0.56 (95% confidence interval 0.52–0.61). The prevalence of consensus cribriform cancers was estimated to 4%, 12%, 21%, and 20% of Gleason scores 7 (3 + 4), 7 (4 + 3), 8, and 9–10, respectively. More than two cribriform structures per level or a largest cribriform mass with ≥9 lumina or a diameter of ≥0.5 mm predicted a consensus diagnosis of cribriform cancer in 88% (70/80), 84% (87/103), and 90% (56/62), respectively, and noncribriform cancer in 3% (2/80), 5% (5/103), and 2% (1/62), respectively (all $P < 0.01$).

Conclusion: Cribriform prostate cancer was seen in a minority of needle biopsies with high-grade cancer. Stringent diagnostic criteria enabled the identification of cribriform patterns and the generation of a large set of consensus cases for standardisation.

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Keywords: cribriform, grading, needle biopsy, pathology, prostate cancer, reproducibility

Introduction

It has recently become apparent that cribriform morphology in acinar adenocarcinoma of the prostate predicts, a worse outcome than that of noncribriform cancer. Specifically, cribriform architecture is an independent predictor of disease-specific survival, both when found in pretreatment biopsies and in radical prostatectomy specimens.[1,2] Accordingly, the International Society of Urological Pathology (ISUP) and the European Association of Urology (EAU) recently issued recommendations that invasive cribriform cancer should be specifically reported when present in needle biopsies.[3,4]

Despite considerable efforts to standardize grading of prostate cancer, the lack of interobserver reproducibility remains problematic.[5–7] To date, few studies have addressed the reproducibility of cribriform morphology,[8–10] and to our knowledge no such investigations have been undertaken using whole-slide images of needle biopsy specimens. Recently, the ISUP proposed a consensus definition of cribriform architecture based on expert opinion.[11,12] The aim of the present study was to investigate the interobserver reproducibility of cribriform cancer, applying these new criteria to a large series of digitised needle biopsies derived from a recent population-based screening study.[13]

Materials and Methods

A series of 702 needle biopsy cores from 495 men with predominantly high-grade cancer were selected from biopsies from 2,295 men who were diagnosed with prostate cancer in the STHLM3 screening trial in 2012–2015.[13] All cancers had been diagnosed by a single pathologist (L.E.), who had assigned a Gleason score, both at the core and the case level. For the analyses in the present study, the core level scores were utilised. The cases were selected by one of the authors (K.K.), with a predominance of higher-grade tumours, to ensure a relatively high proportion of cribriform cancers. In men with Gleason score 7–10 cancers, one core was randomly selected for each ISUP grade present in the biopsy series. All cores with Gleason scores 7 (4 + 3) to 10 obtained in this manner, and a random selection of 86 of the remaining cores with Gleason scores 7 (3 + 4), were included. Our purpose was to enrich the dataset for cores with larger areas of Gleason pattern 4, while keeping the total number of cores down to a manageable number and also retaining some representation of Gleason score 3 + 4.

The assigned grading of each case was blinded for all participating pathologists. The series consisted of 86 (12%), 207 (29%), 263 (37%), and 146 (21%) biopsy cores that had been assigned a Gleason score of 7 (3 + 4), 7 (4 + 3), 8 and 9–10, respectively.

The biopsy cores from each case were embedded separately in paraffin blocks and sections were cut at 4 μm thickness. Haematoxylin and eosin-stained sections were scanned at 20× objective using either a Hamamatsu C9600-12 scanner running NDP.scan software v. 2.5.86 (Hamamatsu Photonics, Hamamatsu, Japan) or an Aperio ScanScope AT2 scanner running Aperio Image Library v. 12.0.15 software (Leica Biosystems, Wetzlar, Germany). Each scanned slide contained two levels of the biopsy. Immunohistochemical stains were not included and no attempt was made to distinguish between cribriform cancers with stromal invasion or intraductal growth of cribriform cancer.

For the study, all 702 cores were first reviewed by a single pathologist (L.E.) on a digital platform Cytomine[14] to determine if cribriform cancer was present. Epithelial masses with potentially cribriform morphology were outlined in 152 biopsies (Figure 1). The area and diameter of the largest focus in each case were then measured (L.E.). The total number of lumina and the number of rigid lumina (defined as rounded lumina with a punched-out contour) were counted. In addition to these cases, 152 tumours without a cribriform architecture were randomly selected from the series to give a total of 304 cores from 250 men. The distribution of cribriform cancer and the outlined areas of possible cribriform morphology were blinded for the other participating pathologists. The digital slides were then reviewed by a panel of nine experts in urological pathology who had published extensively on prostate pathology. Cytomine allows the digital slides to be displayed at a wide range of magnifications according to the preferences of the pathologists. A Medline search of the term *prostate* (May 2022) showed that the participants in the

study had 40–421 relevant publications (mean 170 publications). Each pathologist was asked to review the 304 biopsies and determine whether or not they contained cribriform patterns. The nine experts of the panel were from nine different countries in five continents (two from Europe, two from North America, one from South America, two from Asia, and two from Australasia). In line with previous ISUP studies on interobserver reproducibility and the recommendations from consensus conferences, two-thirds agreement was required to determine consensus.[6,7,15]

STATISTICAL ANALYSES

Multirater unweighted Cohen's kappa statistics were calculated for the nine observers. All confidence intervals were two-sided and calculated from 1000 bootstrap replicates. The Mann–Whitney *U* test was used for comparisons between groups. Pearson's chi-2 test was used for comparisons of proportions. A $P < 0.05$ was considered significant.

Results

The nine observers diagnosed a cribriform pattern in 56–175 (18%–58%) of images (mean 127, 42% and median 131, 43%) in the dataset of 304 slides. Consensus diagnoses of cribriform cancers and cancers in which no cribriform areas were present were reached in 112 (37%) and 160 (53%) biopsies, respectively, while there was no consensus in 32 biopsies (11%). The distribution of diagnoses across Gleason scores is shown in Table 1. The cribriform cancers reaching consensus were 4%, 12%, 21%, and 20% of cancers of Gleason scores 7 (3 + 4), 7 (4 + 3), 8 and 9–10, respectively, in the entire set of 702 biopsies. The mean kappa value of interobserver agreement was 0.56 (95% confidence interval 0.52–0.61) among the nine observers (Tables 2 and 3). Figures 2 and 3 show examples of tumours where there was a consensus diagnosis of cribriform cancer and biopsies with some features suggestive of cribriform morphology, but where no consensus was reached. More examples of tumours where there was a consensus diagnosis of cancer with or without cribriform morphology are shown in Suppl. Figures S1 and S2.

In the 152 biopsies initially selected with cribriform cancer, the areas of cribriform architecture had been outlined before inclusion in the reproducibility study. The number of cribriform foci per slide with two levels was 1–44 (mean 7.2, median 5). Among biopsies with foci suggestive of cribriform cancer, 73% (111/152) reached consensus, while only one case lacking

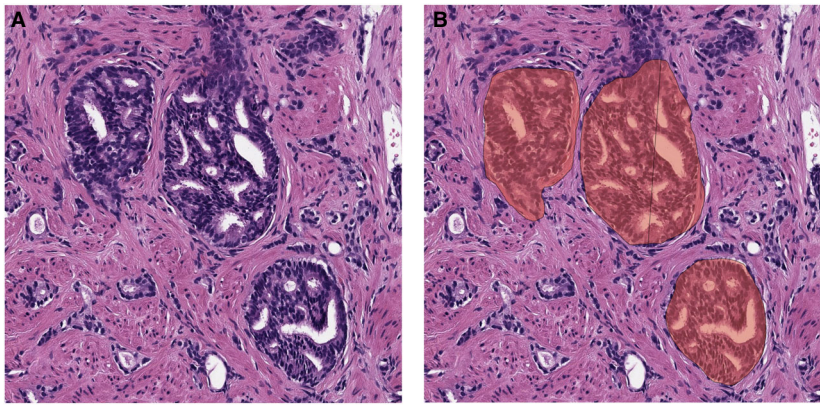

Figure 1. Case reaching consensus for cribriform morphology with nine votes for and none against. (A) Haematoxylin and eosin stains at 20× lens magnification. (B) Areas with cribriform features manually outlined in Cytomine.

Table 1. Distribution of all cases and cases with consensus for or against cribriform morphology and nonconsensus cases across Gleason scores

Gleason score	All cases	Selected cases	Consensus cribriform	Consensus not cribriform	No consensus
7 (3 + 4)	86 (12.3%)	27 (8.9%)	3	21	3
7 (4 + 3)	207 (29.5%)	91 (29.9%)	25	57	9
8	263 (37.5%)	118 (38.8%)	55	49	14
9–10	146 (20.8%)	68 (22.4%)	29	33	6
	702 (100%)	304 (100%)	112	160	32

Table 2. Reported cases with cribriform morphology, mean kappa values with confidence intervals (CI). Observer 1 did the review of all 702 cases but the kappa statistic was based on the final 304 (152 cribriform + 152 noncribriform) cases

Observer	Cribriform morphology (*n*)	Mean kappa	Kappa 95% CI
1	152	0.62	0.57–0.67
2	128	0.61	0.55–0.66
3	175	0.51	0.45–0.57
4	131	0.59	0.54–0.64
5	116	0.62	0.57–0.67
6	138	0.64	0.59–0.68
7	56	0.36	0.28–0.43
8	155	0.56	0.50–0.62
9	92	0.55	0.49–0.60
Mean	127.0	0.56	0.52–0.61

outlined areas of possible cribriform morphology reached consensus (with six of nine observers favouring cribriform cancer). Areas suggestive of cribriform morphology were outlined in this case and then analysed together with the other cribriform cancers. From the whole series of 304 biopsies, the nine trial pathologists' diagnosis of cribriform cancer ranged from 50–111 cases in those cases where a consensus of cribriform cancer had been achieved. Similarly the reported lack of cribriform morphology ranged from 118–159 biopsies in those cases where there was a consensus that no cribriform foci were present.

The number of outlined foci of possible cribriform morphology in biopsies with consensus for cribriform cancer, where there was no consensus and where the consensus was that no cribriform foci were present, ranged from 2–44 (mean 8.5, median 6), 1–21 (mean 4.3, median 4), and 2–8 (mean 3.2, median 3), respectively ($P < 0.001$ for consensus cribriform cancers versus the other groups combined or the latter group alone).

The morphometric measures and the number of lumina of the largest focus with cribriform features are presented in Table 4. In the 153 cases, the largest cribriform gland contained a mean of 16.3 lumina (range 4–134). The total number of lumina and the number of rigid lumina were greater in those where there was a consensus for cribriform cancer than in biopsies that failed to reach consensus for cribriform cancer. In 22% (25/112) of cribriform cases, there were fewer than 9 lumina and 23 of them did not have any rigid lumina. By contrast 71% (12/17) of biopsies where there was a consensus that no cribriform cancer was present had fewer than nine lumina in the largest area with possible cribriform features and rigid lumina were only seen in three of these cases. Rigid lumina were seen in 27% (30/112) of cribriform cancers and in 18% (3/17) of cases without cribriform cancer by consensus ($P = 0.36$). Both the diameter and the area of the largest epithelial mass with possible cribriform features were greater in cribriform cancer than in cases considered not to have cribriform foci by the panel, with a mean diameter of 0.55 versus 0.28 mm ($P < 0.001$) and area of 0.14 versus 0.04 mm^2 ($P < 0.001$), respectively. Comedonecrosis was found in 9% (6/68) of GS 9–10 cases. In four of them, there was comedonecrosis in

Table 3. Pairwise kappa values of the observers for diagnosis of cribriform cancer

Observer	1	2	3	4	5	6	7	8	9
1	—	0.70	0.61	0.68	0.70	0.72	0.32	0.66	0.54
2	0.70	—	0.54	0.68	0.69	0.68	0.34	0.64	0.59
3	0.62	0.54	—	0.56	0.54	0.62	0.25	0.54	0.44
4	0.68	0.68	0.56	—	0.65	0.69	0.37	0.57	0.53
5	0.70	0.69	0.54	0.65	—	0.74	0.41	0.63	0.64
6	0.72	0.68	0.62	0.69	0.74	—	0.37	0.65	0.62
7	0.32	0.34	0.25	0.37	0.41	0.37	—	0.29	0.51
8	0.66	0.64	0.54	0.57	0.63	0.65	0.29	—	0.50
9	0.54	0.59	0.44	0.53	0.64	0.62	0.51	0.50	—

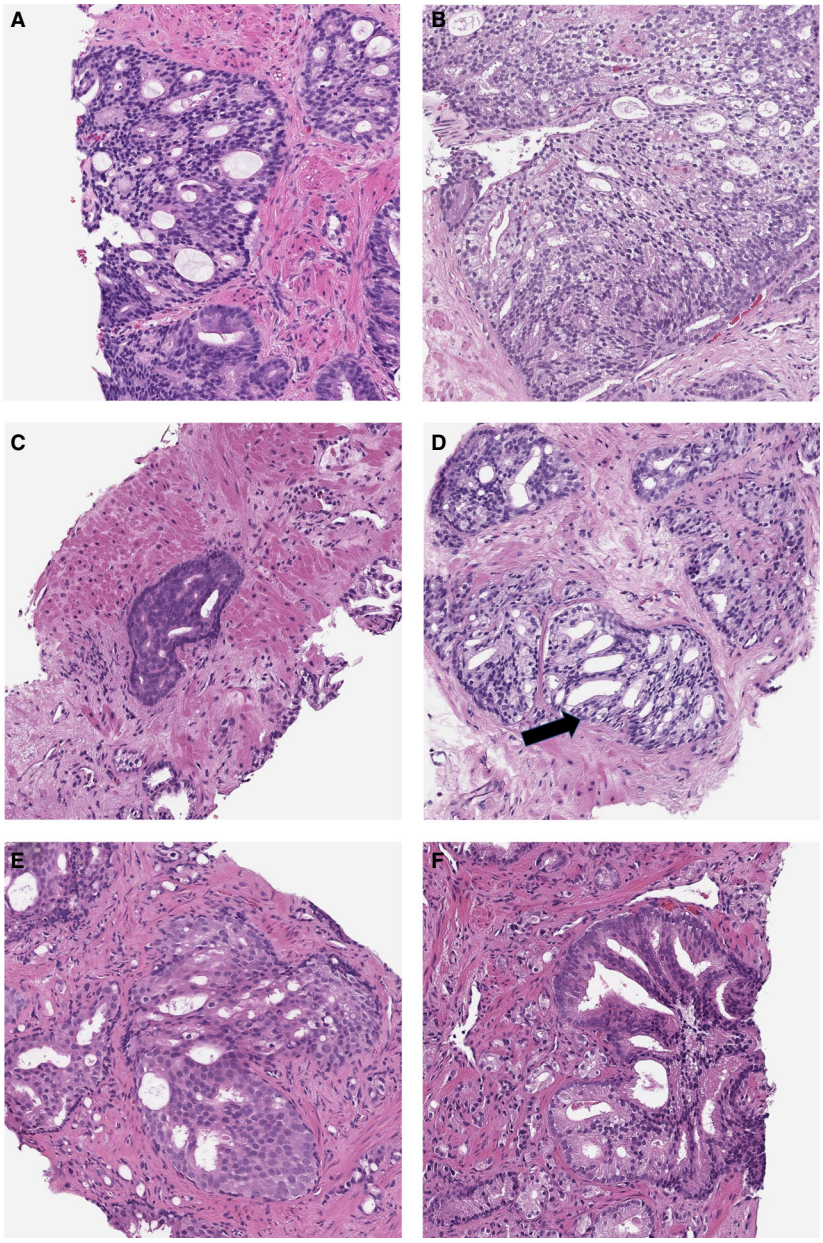

Figure 2. Cases reaching consensus for cribriform morphology with nine votes for and none against. (A) Rounded, large glands with a largest diameter 0.40 mm. Numerous lumina, some with a rigid outline. (B) Large cribriform sheet (0.70 mm in diameter). Occasional capillary vessels in the upper part of the field, but also large cohesive areas. (C) Intraductal cribriform cancer, which is small (0.24 mm in diameter) but contains several distinct lumina. (D) Some glands merge into a fusion pattern (upper right and lower left) but also a well-circumscribed cribriform gland (arrow). (E) Branching intraductal cancer with both cribriform areas and some solid parts. (F) Branching, large cribriform gland with a diameter of 0.41 mm. All microphotographs show haematoxylin and eosin stains at 20× lens magnification.

cribriform glands. All of them reached consensus for cribriform cancer.

At least nine lumina in the largest cribriform gland predicted a consensus diagnosis of cribriform cancer in 84% (87/103) and absence of cribriform cancer in 5% (5/103) of cases ($P < 0.001$). The largest epithelial mass with cribriform features with a diameter of 0.5 mm or more predicted a consensus diagnosis of cribriform cancer in 90% (56/62) and a consensus diagnosis that cribriform carcinoma was not present in 2% (1/62), ($P < 0.01$). More than two outlined cribriform structures per level (a total count of five or more per two levels) predicted a consensus diagnosis of cribriform cancer in 88% (70/80) of cases and a consensus diagnosis that cribriform cancer was not present in 3% (2/80) of cases ($P < 0.001$).

Discussion

The understanding that cribriform morphology is a marker of potentially aggressive cancer is one of the most important recent insights in prostate pathology. The overwhelming evidence of the clinical importance of cribriform cancer in pretreatment biopsies has evoked an interest in the diagnostic accuracy of reporting pathologists.[2,16,17] The presence of

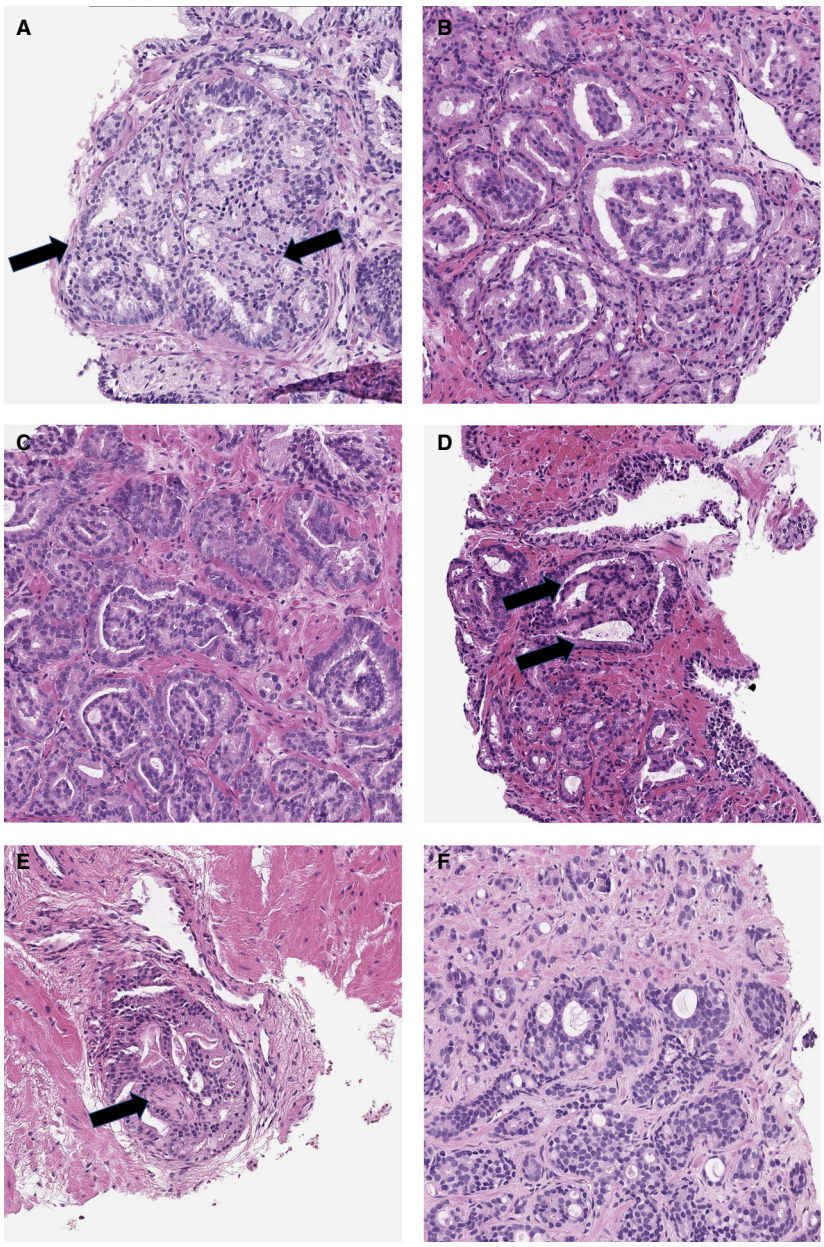

Figure 3. Cases with structures showing some cribriform features but with a consensus against cribriform morphology with six votes against cribriform cancer and three votes for (A–C) or seven votes against and two votes for (D–F). (A) Large epithelial masses with some scalloping of the borders (arrows) and strips of stroma favouring glandular fusion. (B,C) Glandular fusion bordering on cribriform or glomeruloid patterns. (D) Large gland with some elongated spaces (arrows). (E) Perineural invasion of cancer. Chain of glandular structures with multiple lumina surrounding nerve (arrow), a feature that is not part of the definition of cribriform cancer. (F) Small glandular structures with some lumina and some rosette-like spaces and a largest diameter of 0.17 mm. All microphotographs show haematoxylin and eosin stains at 20× lens magnification.

cribriform cancer has consequences for patient care, as it has been recommended that such patients may not be candidates for active surveillance.[4] It is thus of clinical importance that the reporting of cribriform morphology be consistent. The current study is, to our knowledge, the first to investigate the interobserver reproducibility of diagnosing cribriform cancer in needle biopsy specimens.

An international panel of experts in prostate pathology independently assessed a series of prostate needle biopsies for the presence of cribriform morphology using recently published ISUP criteria.[12] Consensus for or against the presence of cribriform cancer was reached in 90% of biopsies, with a mean kappa value of 0.56. Despite a spread between some observers from different continents, the overall results are in line with previous reproducibility studies on Gleason grading.[5,7,18,19]

Van der Kwast *et al.* recently used the Delphi method[20] for the development of criteria for cribriform prostate cancer.[12] An ISUP panel reviewed a set of microphotographs for the assessment of cribriform morphology and agreed on the following definition: "A confluent sheet of contiguous malignant epithelial

Table 4. Morphometric data of the largest outlined epithelial mass with cribriform features in cases that reached consensus for or against cribriform morphology and nonconsensus cases. Mean and range. The *P*-values were <0.001 for cribriform versus not cribriform measures, except for rigid lumina ($P = 0.36$)

Consensus	Lumina (*n*)	Rigid lumina (*n*)	Diameter (mm)	Area (mm^2)
Cribriform	19.0 (4–134)	1.2 (0–10)	0.55 (0.19–1.63)	0.14 (0.02–1.15)
No consensus	10.1 (4–24)	0.4 (0–2)	0.40 (0.22–0.97)	0.07 (0.02–0.21)
Not cribriform	7.6 (5–14)	0.3 (0–2)	0.28 (0.17–0.55)	0.04 (0.01–0.08)
All	16.3 (4–134)	1.0 (0–10)	0.50 (0.17–1.63)	0.12 (0.01–1.15)

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." Iczkowski *et al.* then analysed morphological features of the 14 cases with a consensus diagnosis of cribriform cancer given by this panel and found an association between the presence of at least nine lumina and consensus for cribriform cancer.[11] In the present study, we confirm that structures acknowledged by experts as cribriform have a greater mean number of lumina than structures with cribriform features that failed to reach consensus for cribriform cancer. The majority of cribriform consensus cases had more than nine lumina in the largest gland, but 22% had fewer than that. The cutoff of nine lumina does not appear to be an absolute criterion for the diagnosis of cribriform cancer. The prevalence of rigid lumina did not differ significantly between cribriform and noncribriform cancer. No such lumina were seen in as many as 74% of cribriform cancers, indicating a lack of diagnostic utility. Although we cannot be certain as to why some of the cases did not reach consensus for cribriform cancer, it appears from Figure 3 and Suppl Figure S2 that the reasons may include the presence of scalloped borders or the small size of the epithelial masses, features that could be consistent with, e.g. glandular fusion.

The extent of cribriform glands within the biopsy was of diagnostic value. Consensus cases of cribriform cancer had a greater number of outlined areas of cribriform morphology than cases that did not reach consensus for this diagnosis. Thus, the greater number of foci with cribriform features, the higher is the likelihood that the findings will be sufficient for a diagnosis of cribriform cancer. With more than two foci per level, the probability of a consensus diagnosis of cribriform cancer was 88%, while only 3% of biopsies with this extent reached consensus that cribriform cancer was not present. The size of the glands was also found to be diagnostically useful. A diameter of 0.5 mm or more was diagnostic for cribriform cancer in more than 90%, while 2% of tumours with glandular structures of this size were not recognised as cribriform. Thus, the more extensive the epithelial masses, then the greater is the likelihood that they represent cribriform carcinoma. Based on these results, it is suggested that a diagnosis of cribriform cancer be favoured by the presence of large sised and multifocal cribriform structures, together with a large number of lumina.

For the identification of cribriform morphology to have clinical utility, it is critical that the assessment of this feature is sufficiently reproducible. In a study on the prognostic impact of variants of Gleason pattern 4 in radical prostatectomy specimens, Dong *et al.* found that the cribriform variant of Gleason pattern 4 had a greater reproducibility than poorly formed or fused glands.[8] This is expected, as cribriform glands have a more complex morphology that is less likely to be mimicked by tangential cutting. In a study based on microphotographs of prostate cancers, Kweldam *et al.* investigated the interobserver reproducibility of Gleason pattern 4 among 23 experts in urological pathology.[9] The panellists were asked to determine the dominant Gleason pattern to 60 images and for cases of Gleason pattern 4, the morphological subtype of this grade. An agreement on Gleason pattern was reached among 80% of the pathologists in 78% of the cases. In nonconsensus cases, poorly formed or fused glands were more often seen than cribriform glands.

To our knowledge, the only previous study that specifically addressed the reproducibility of cribriform cancer was conducted by Shah *et al.*[10] In that study 27 predominantly North American pathologists with an experience of uropathology ranging from 2 to 40 years assessed the presence of cribriform cancer in microphotographs from 44 radical prostatectomy specimens. The kappa statistic of interobserver reproducibility was only 0.40.

In the current study we applied the recent ISUP definition of cribriform cancer. By using these

stringent criteria we obtained a higher kappa value than previously published (0.56 versus 0.40).[10] Although no single morphological feature was pathognomonic, we found several indicators of cribriform morphology, i.e. the number of lumina, the extent of the lesion, and glandular size. Earlier studies on the prognostic impact of cribriform morphology were undertaken prior to the publication of the ISUP definition of cribriform cancer and it remains to be investigated if the consensus results presented here have the same predictive value. A sufficiently powered prognostic study would require numbers beyond what is reasonable in a reproducibility study. Another point of interest is the ability of needle biopsies to predict cribriform cancer in surgical specimens. Both sampling errors and the problems with interpretation of morphological patterns in limited biopsy samples may lead to under-, as well as overreporting of cribriform cancer in preoperative biopsies.

The strengths of this study include the well-documented prostate pathology expertise of all panellists, the wide international inclusion of participants from five continents, and the population-based cohort of prostate cancers. We believe that this set of consensus criteria may serve as a guide for pathologists to facilitate the diagnosis of cribriform prostate cancer in needle biopsies.

Conflict of Interest

None of the authors have any conflicts of interest to declare.

Funding Information

The study received funding from the Swedish Cancer Foundation (20 1358), the Stockholm Cancer Society (204043), David and Astrid Hägelén Foundation, Orion Research Foundation, and Oskar Huttunen Foundation.

Author Contributions

L.E. was responsible for the study concept and design, provided acquisition, analysis and interpretation of data, and prepared the initial draft of the article; B.D., K.A.I., T.K., G.L., K.L., C.C.P., H.S., and T.T. provided acquisition of data and editing of the article; K.K. and M.E. contributed to the study concept and design, provided analysis and interpretation of data, statistical analysis, and editing of the article; N.M., X.J., and H.O. provided technical support and editing of the article, K.K., M.V., and P.R. set up and maintained the digital database and provided technical support. All authors read and approved the final paper.

Ethics Approval

The study was approved by the Regional Ethic ReviewBoard, Stockholm (2012/572-31/1, 2018/845-32).

Data Availability Statement

The research data will not be made fully publicly available for the privacy of the individuals that participated in the STHLM3 screening trial.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. A–F. Cases reaching consensus for cribriform morphology with 9 votes for and none against. All microphotographs show haematoxylin and eosin stains at 20× lens magnification.

Figure S2. A–F. Cases with structures showing some cribriform features but with a consensus against cribriform morphology with 6 votes against cribriform cancer and 3 votes for (A–C) or 7 votes against and 2 votes for (D–F). All microphotographs show haematoxylin and eosin stains at 20× lens magnification.