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Molecular risk classifier score and biochemical recurrence risk are associated with cribriform pattern type in Gleason 3+4=7 prostate cancer

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Purpose: Among Gleason pattern 4 types, cribriform pattern is associated with the worst outcomes. We hypothesized that larger cribriform patterns would be associated with increased Decipher scores and higher biochemical recurrence (BCR) risk in Gleason 3+4=7 prostatectomy patients.

Materials and Methods: The slide from patients who underwent prostatectomy from January 2016 to March 2020 on which Decipher was performed was re-reviewed for Gleason score and cribriform patterns, with large cribriform defined as cribriform acini with greater than 12 lumens and simple cribriform as 12 or fewer lumens. Differences in Decipher score were analyzed in a generalized linear model controlling for pathology stage and tumor margin status. A multivariable Cox proportional hazards model was performed for BCR-free survival.

Results: Of 337 cases, 118 were Gleason 3+4=7. The mean Decipher scores in 3+4=7 cases without cribriform, with simple cribriform, and with large cribriform were 0.41, 0.54, and 0.62, respectively. In a multivariable model with pathology stage, margin tumor length, and percentage pattern 4 as covariates, compared to cases without cribriform, simple cribriform was associated with 0.10 increase in Decipher (p=0.03) and 4.7-fold hazard ratio of BCR (95% confidence interval [CI], 0.4–56.5; p=0.22) and large cribriform was associated with 0.17 increase in Decipher (p<0.001) and 16.0-fold hazard ratio of BCR (95% CI, 1.4–181.2; p=0.02).

Conclusions: Among Gleason 3+4=7 carcinomas, large cribriform was associated with higher Decipher scores and greater BCR risk. Our results support that large cribriform is an aggressive pattern 4 subtype and should be considered a contraindication for active surveillance.

Keywords: Active surveillance; Prostate cancer; Prostatectomy

INTRODUCTION

In prostate cancer, the Gleason scoring system is a major determinant of clinical decision making. Patients with Gleason score 3+3=6 (Grade Group 1) on biopsy generally should be followed with active surveillance, whereas patients with

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Gleason score 4+3=7 (Grade Group 3) or higher are typically offered definitive therapy. The optimal treatment strategy for patients with Gleason score 3+4=7 (Grade Group 2) prostate cancer is still an area of uncertainty, as some cancers in this group prove entirely indolent whereas others progress rapidly. This highlights the need to further improve upon the classification of these tumors with a number of strategies currently being undertaken, such as improving clinical risk classifiers, improving histologic grading and the use of commercially available tissue based risk classifiers, such as OncotypeDx and Decipher.

For improving tumor grading, a number of important observations have been made related to the different histologic growth patterns of carcinoma that are assigned the Gleason grade 4 [1-6]. In particular, cribriform pattern has been associated with the worst outcomes, compelling experts in urologic pathology to recommend specifically reporting cribriform patterns when present in prostate cancers [7,8]. However cribriform growth also has extreme variability in size that is not routinely taken into account clinically, although a recent study has shown poorer outcomes when larger cribriform structures are present [9].

While commercially available tissue based molecular classifiers will contain contributions from the various Gleason patterns in their output, these various subtypes were not considered in the design of these assays and considering such patterns in addition to risk classifier scores may provide additional important information not currently being considered. For example, with the Decipher radical prostatectomy genomic classifier, a RNA based whole transcriptome microarray assay that predicts metastatic risk [10,11], the presence of cribriform pattern 4 was found to be significantly associated with Decipher score [12]. In another study in which large cribriform and glomeruloid Gleason pattern 4 were compared, large cribriform was found to be associated with higher Decipher scores and with greater risk of biochemical recurrence (BCR) [13]. Large cribriform has also been found to be associated with higher scores than simple cribriform in a study on prostate biopsies that received OncotypeDx testing, a reverse transcriptase-polymerase chain reaction test performed on prostate biopsies that is designed to predict adverse pathology at prostatectomy [14].

In this study we sought to examine the relationships between Decipher radical prostatectomy score, cribriform Gleason pattern 4 subtype, and risk of BCR in a cohort of prostate cancer patients with Gleason score 3+4=7 (Grade Group 2) tumor.

MATERIALS AND METHODS

1. Study design

This study was approved by the Institutional Review Board of UCSF (University of California, San Francisco) (approval number: 15-15823). Consent was waived by the Institutional Review Board. In a retrospective cohort study, the pathology case database of UCSF was searched for prostatectomy reports from January 2016 to March 2020 that had received Decipher testing. The decision to perform Decipher testing was at the discretion of the treating urologist. The formalin-fixed paraffin-embedded block with the largest area of highest-grade tumor had previously been selected after review by a genitourinary pathologist and sent for Decipher testing.

2. Histopathologic review and Decipher assay

The original H&E-stained slide from the block sent for Decipher testing was reviewed blinded to original reported Gleason score in order to determine which patients had Gleason score 3+4=7 on the highest grade tumor nodule on the block sent for testing. The H&E slide was also reviewed in a blinded manner for the presence of various growth patterns indicative of Gleason pattern 4, including cribriform (Fig. 1). Large cribriform was defined in this study as large cribriform acini with greater than 12 lumen spaces,

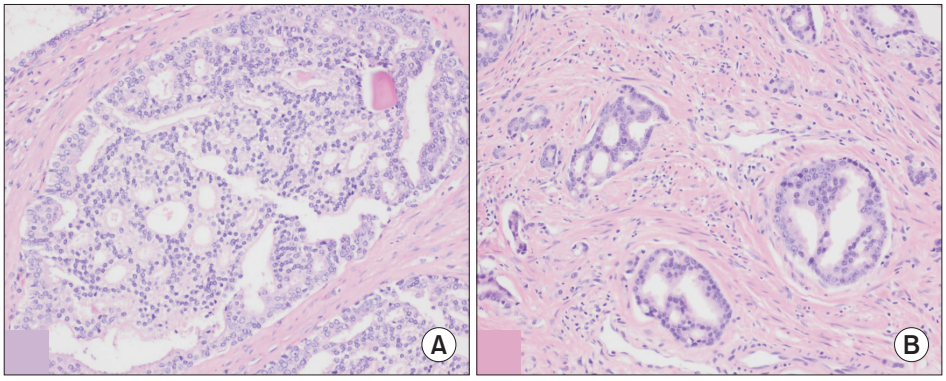

Fig. 1. (A) Large cribriform was defined as large cribriform acini with greater than 12 lumen spaces. (B) Simple cribriform was defined as cribriform acini with 12 or fewer lumen spaces (H&E, ×20).

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and simple cribriform was defined as cribriform acini with 12 or fewer lumen spaces. Patients were classified as either having no cribriform, simple cribriform without any large cribriform, or large cribriform (with or without simple cribriform).

The H&E-stained slides were also evaluated in a blinded manner for the presence of intraductal carcinoma (IDC). Immunohistochemistry for basal cell markers was not performed, as the deeper level sections of the block had been used to perform the Decipher assay. The presence of IDC was determined via published morphologic criteria [15], with the additional requirement of obvious basal cells at the periphery of the suspect glands.

The Decipher test (Decipher Biosciences, Inc., Vancouver, BC, Canada) is an expression array-based assay that uses RNA extracted from FFPE radical prostatectomy specimens to calculate a risk score from 0 to 1 and validated risk category for risk of metastases within 5 years after prostatectomy [10,16]. Scores less than 0.45 correspond to the low risk category, scores from 0.45 to 0.6 correspond to the intermediate risk category, and scores above 0.6 correspond to the high risk category.

3. Biochemical recurrence, tumor T and N stages, tumor margin status, and percentage Gleason pattern 4

Prostatectomy tumor T and N stages, length of tumor at margin, prostatectomy overall percentage Gleason pattern 4, and BCR data were obtained from the medical record, with BCR defined as two consecutive prostate-specific antigen (PSA) levels of 0.2 ng/mL or more starting 8 weeks after prostatectomy. Prostate biopsy Gleason Grade Group information was obtained from the medical record.

4. Statistical analyses

The association between Gleason score and Decipher scores was tested using a one-way ANOVA with linear post-test for trend. For the Gleason score 3+4=7 cases, the difference between Decipher scores for cribriform subtype was assessed using the Wilcoxon rank sum test, adjusted for multiple comparisons using the Holm method. The difference between Decipher scores for pT stage was assessed using the Wilcoxon rank sum test, adjusted for multiple comparisons using the Holm method. In a multivariable analysis, a generalized linear model with Decipher score as the dependent variable and pT and pN stages, length of tumor at margin, and prostatectomy percentage Gleason pattern 4 as covariates was used. Kaplan–Meier analysis was performed to assess the outcome of freedom from BCR, with statistical significance assessed by log-rank test and censoring on date of last PSA test. We then performed multivariable Cox proportional hazards models of time to BCR with pT and pN stages, length of tumor at margin, and prostatectomy percentage Gleason pattern 4 as covariates. Time to BCR models with and without Decipher score as a covariate were compared via ANOVA analysis. The association between cribriform subtype at prostatectomy and Grade Group 1–2 versus 3–5 on biopsy was evaluated using chi-squared test. Statistics were performed using R, using "ggpubr", "ggbeeswarm", "survival", and "survminer" packages, or GraphPad Prism software (Version 8.1.1; GraphPad Software Inc., San Diego, CA, USA), and statistical significance was considered at $p<0.05$.

RESULTS

Of 337 patients in the cohort who underwent prostatectomy from January 2016 to March 2020 and had received Decipher testing on their prostatectomy specimen, the median age was 66.8 years (range, 40.4–79.0 y), the average age was 64.3 years (standard deviation [SD], 7.5 y), and the average Decipher score was 0.64 (SD, 0.2) (Supplementary Table 1). Increasing Gleason score correlated with Decipher score (linear test for trend $p<0.0001$, Supplementary Fig. 1). Cases with Gleason score 3+4=7 (Grade Group 2) on the highest grade tumor nodule on the block sent for testing comprised the largest group, with 118 cases (Table 1). Of these 118 Gleason score 3+4=7 patients, the median age was 53.3 years (range, 40.4–77.1 y) and the average age was 56.3 (SD, 9.2) (Table 1); 40 were classified as high risk by Decipher testing, 33 as intermediate risk, and 45 as low risk. Among these Gleason score 3+4=7 cases, pT and pN stage correlated with Decipher score (Supplementary Fig. 2, Supplementary Table 2). There were 50 patients with positive surgical margin and 18 patients with IDC (Supplementary Table 3). The association between cribriform subtype at prostatectomy and Grade Group 1–2 versus 3–5 on prostate biopsy was examined by chi-squared test. The p-value was 0.06, which is not statistically significant, but may suggest an association between large cribriform at prostatectomy and higher Gleason Grade Group at biopsy (Supplementary Tables 4, 5).

Among the Gleason score 3+4=7 cases, 41 patients had no cribriform pattern on the block sent for Decipher testing, 27 patients had only simple cribriform on the block sent for Decipher testing, and 50 patients had large cribriform in addition to simple cribriform pattern on the block sent for Decipher testing. The highest average Decipher scores were seen in cases with large cribriform, with average Decipher

scores of 0.41, 0.54, and 0.62 for cases without cribriform (41 patients), with simple cribriform (and no large cribriform) (27 patients), and with large cribriform (50 patients), respectively (Table 1, Fig. 2). In a multivariable model with T and N stages, length of tumor at margin, and prostatectomy percentage Gleason pattern 4 as covariates, compared to cases without cribriform, simple cribriform was associated with a 0.10 increase in Decipher score (p=0.03) and 4.7-fold hazard ratio of BCR (95% CI, 0.4–56.5; p=0.22), whereas large cribriform was associated with a 0.17 increase in Decipher score (p<0.001) and 16.0-fold hazard ratio of BCR (95% CI, 1.4–181.2; p=0.02) (Fig. 3, Table 2) (table of the models including all covariates in Supplementary Table 6-1, 6-2).

In a second multivariable model with the addition of Decipher score as a covariate, simple cribriform was associated with a 4.2-fold hazard ratio of BCR (95% CI, 0.3–57.9; p=0.28) and large cribriform was associated with a 15.6-fold hazard ratio of BCR (95% CI, 1.2–211.0; p=0.04). Using an ANOVA analysis comparing the two multivariable models, the addition of Decipher score was associated with a p-value of 0.12 for improved prediction of BCR risk.

A significant difference in Decipher score was seen in the 18 Gleason score 3+4=7 cases with IDC and in the 100 Gleason score 3+4=7 cases without recognizable IDC (0.73 vs. 0.49; p<0.001). However, no significant difference in BCR risk

Table 1. Age, ethnicity, cribriform type, and presence of IDC for Gleason score 3+4=7 patients

Variable	Value	Decipher score
Age (y)	53.3 (40.4–77.1)	
	56.3±9.2	
Race		
Caucasian	99 (83.9)	
Asian/API	6 (5.1)	
Black/African American	6 (5.1)	
Hispanic	1 (0.8)	
Native American	1 (0.8)	
Other/unknown	5 (4.2)	
Cribriform type		
None	41	0.41±0.14
Simple	27	0.54±0.21
Large	50	0.62±0.18
Presence of IDC		
Absent	100	0.49±0.18
Present	18	0.73±0.14

Values are presented as median (range), mean±standard deviation, number (%), or number only.
API, Asian/Pacific Islander; IDC, intraductal carcinoma.

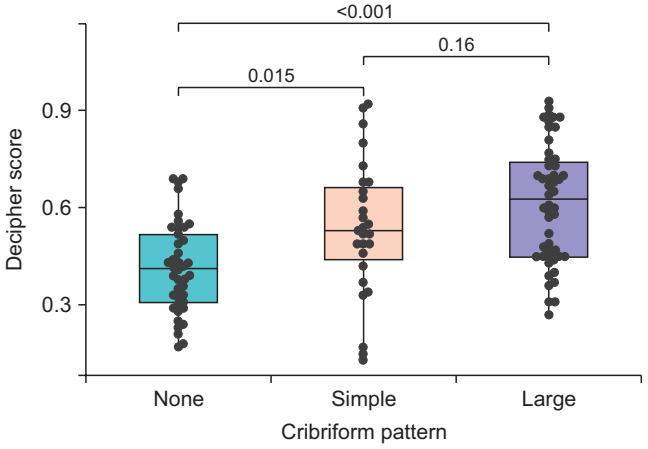

Fig. 2. Cribriform type (41 patients with none, 27 patients with simple cribriform [but no large cribriform], 50 patients with large cribriform) and Decipher score for Gleason score 3+4=7 cases.

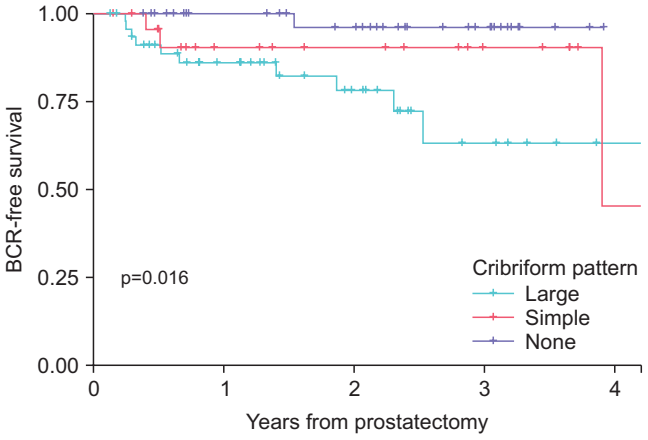

Fig. 3. Cribriform type (41 patients with none, 27 patients with simple cribriform, 50 patients with large cribriform) and biochemical recurrence (BCR)-free survival for Gleason score 3+4=7 cases.

Table 2. Cribriform type and Decipher score and BCR

Cribriform type	Increase in Decipher score	p-value	Hazard ratio (95% CI) of BCR	p-value
Simple cribriform vs. no cribriform	0.10	0.03	4.7-fold (0.4–56.5)	0.22
Large cribriform vs. no cribriform	0.17	<0.001	16.0-fold (1.4–181.2)	0.02

BCR, biochemical recurrence; CI, confidence interval.
To evaluate for increase in Decipher score for Gleason score 3+4=7 cases, a generalized linear model with Decipher score as the dependent variable and pT and pN stages, length of tumor at margin, and prostatectomy percentage Gleason pattern 4 as covariates was used. To evaluate hazard ratio of BCR, multivariable Cox proportional hazards models of time to BCR with pT and pN stages, length of tumor at margin, and prostatectomy percentage Gleason pattern 4 as covariates was used.

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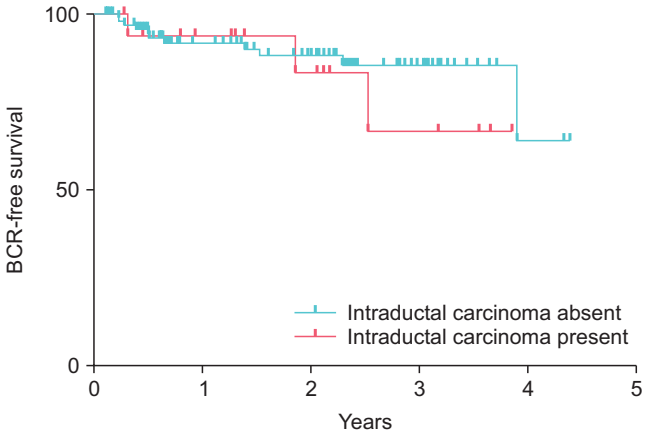

Fig. 4. Presence or absence of intraductal carcinoma and biochemical recurrence (BCR)-free survival for Gleason score 3+4=7 cases. No significant difference in BCR risk was observed between the two groups (hazard ratio, 1.7-fold risk; 95% CI, 0.4–7.8; p=0.47).

was observed between the two groups (hazard ratio, 1.7-fold risk; 95% CI, 0.4–7.8; p=0.47) (Fig. 4).

DISCUSSION

Among men with Gleason score 3+4=7 cancers, the presence of large cribriform pattern was associated with increased Decipher scores and portended increased risk of BCR. The presence of large cribriform pattern conveyed greater risk than simple cribriform alone, and these effects persisted even after adjustment for T and N stage, length of tumor at margin, and percentage Gleason pattern 4. Indeed, the addition of Decipher testing conveyed only marginally increased information about BCR risk in this cohort when cribriform subtyping was considered, diminishing the potential value of this molecular classifier. These findings support the mounting evidence that large cribriform is a distinct and more aggressive subtype of Gleason pattern 4 and that patients with this feature should be considered for more aggressive treatment.

Various definitions of large cribriform and simple cribriform have been used in the literature [3,9,17]. There is currently no Genitourinary Pathology Society (GUPS) recommendation on the size criteria differentiating simple cribriform and large cribriform [7]. In this study we used Iczkowski et al.'s [3] definition of greater than 12 lumen spaces due to its ease in reproducibility among pathologists. In the Hollemans et al.'s study [9] the authors were able to see a difference in BCR between simple and large cribriform using a definition of large cribriform as large cribriform acini with a diameter of at least twice large that of adjacent benign glands. One limitation of this definition, in turn, is that benign glands can have significant variation in size. Despite using a different definition of large cribriform than the Hollemans et al.'s study [9] however, our study came to the same conclusion, that larger cribriform structures are associated with worse outcomes.

Literature reports of the clinical significance of simple cribriform versus large cribriform are conflicting, with one study reporting no correlation between cribriform size and upgrading or stage at radical prostatectomy [18] and another reporting no correlation between cribriform size and BCR [3]. In the Hollemans et al.'s study [9], however, large cribriform was shown to be an independent predictor of BCR-free survival. While our findings and the results of the Hollemans et al.'s study [9] support that large cribriform is more aggressive than simple cribriform, a consensus definition among genitourinary pathologists would be useful for future studies to confirm the difference in aggressiveness between simple cribriform and large cribriform. Subdividing cribriform pattern into large cribriform and simple cribriform could potentially improve current tumor grading methods and nomograms, independent of the use of molecular classifier tests.

One shortcoming of our study is the relatively short follow-up time, limiting evaluation of metastatic relapse. To detect recurrences, a follow-up time of at least 5 to 10 years is optimal. However, in our study no patients had follow-up time greater than 5 years, as the oldest prostatectomy specimens were from January 2016. Blocks sent for molecular testing had been selected after review by a genitourinary pathologist based on the largest area of highest-grade tumor, however it is theoretically possible that another section not evaluated would have shown more extensive cribriform pattern. If present, this bias would tend to underestimate the effect of cribriform on BCR risk.

While a significant difference in Decipher score was seen in the Gleason score 3+4=7 cases with and without IDC, no significant difference in BCR was observed between the two groups. However, one drawback of our study with regards to IDC is that immunohistochemistry for basal cells was not performed, and thus there is a potential that some of the areas designated as large cribriform are in fact IDC. While staining for basal cells would have been preferred to confirm the presence of IDC, staining on immediately adjacent level sections was not possible, as Decipher testing was performed on those level sections. While only 18 patients had IDC in our study, our results are concordant with the Hollemans et al.'s study [9], which did not find IDC to be an independent predictive factor for BCR-free survival in a multivariable model.

CONCLUSIONS

In summary, in this study of patients with Gleason score 3+4=7 on the block sent for Decipher prostatectomy testing, higher Decipher scores and greater risk of BCR were seen in patients with large cribriform. Our findings support that large cribriform is a more aggressive variant of Gleason pattern 4 and patients with large cribriform on biopsy should be treated rather than remain on active surveillance.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Nancy Y. Greenland, Jeffry P. Simko, and Bradley A. Stohr. Data acquisition: Nancy Y. Greenland, Jeffry P. Simko, and Bradley A. Stohr. Statistical analysis: Nancy Y. Greenland. Data analysis and interpretation: Nancy Y. Greenland, Matthew R. Cooperberg, Emily Chan, Jeffry P. Simko, and Bradley A. Stohr. Drafting of the manuscript: Nancy Y. Greenland, Matthew R. Cooperberg, Anthony C. Wong, Emily Chan, Peter R. Carroll, Jeffry P. Simko, and Bradley A. Stohr. Critical revision of the manuscript: Nancy Y. Greenland and Bradley A. Stohr. Obtaining funding: No funding, not applicable. Administrative, technical, or material support: Nancy Y. Greenland received administrative support from the UCSF Department of Pathology. Approval of the final manuscript: Nancy Y. Greenland.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210262.

REFERENCES

1. Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, van Leenders GJ. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Mod Pathol 2015;28:457-64.
2. McKenney JK, Wei W, Hawley S, Auman H, Newcomb LF, Boyer HD, et al. Histologic grading of prostatic adenocarcinoma can be further optimized: analysis of the relative prognostic strength of individual architectural patterns in 1275 patients from the Canary retrospective cohort. Am J Surg Pathol 2016;40:1439-56.
3. Iczkowski KA, Torkko KC, Kotnis GR, Wilson RS, Huang W, Wheeler TM, et al. Digital quantification of five high-grade prostate cancer patterns, including the cribriform pattern, and their association with adverse outcome. Am J Clin Pathol 2011;136:98-107.
4. Choy B, Pearce SM, Anderson BB, Shalhav AL, Zagaja G, Eggener SE, et al. Prognostic significance of percentage and architectural types of contemporary Gleason pattern 4 prostate cancer in radical prostatectomy. Am J Surg Pathol 2016;40:1400-6.
5. Kweldam CF, Kümmerlin IP, Nieboer D, Verhoef EI, Steyerberg EW, van der Kwast TH, et al. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. Mod Pathol 2016;29:630-6.
6. Kweldam CF, Kümmerlin IP, Nieboer D, Verhoef EI, Steyerberg EW, Incrocci L, et al. Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. Eur J Cancer 2016;66:26-33.
7. Epstein JI, Amin MB, Fine SW, Algaba F, Aron M, Baydar DE, et al. The 2019 Genitourinary Pathology Society (GUPS) white paper on contemporary grading of prostate cancer. Arch Pathol Lab Med 2021;145:461-93.
8. Epstein JI, Kryvenko ON. A comparison of Genitourinary Society Pathology and International Society of Urological Pathology prostate cancer guidelines. Eur Urol 2021;79:3-5.
9. Hollemans E, Verhoef EI, Bangma CH, Rietbergen J, Helleman J, Roobol MJ, et al. Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. Mod Pathol 2019;32:139-46.
10. Spratt DE, Zhang J, Santiago-Jiménez M, Dess RT, Davis JW, Den RB, et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. J Clin Oncol 2018;36:581-90.
11. Den RB, Santiago-Jimenez M, Alter J, Schliekelman M, Wagner JR, Renzulli Ii JF, et al. Decipher correlation patterns post prostatectomy: initial experience from 2 342 prospective patients. Prostate Cancer Prostatic Dis 2016;19:374-9.
12. Taylor AS, Morgan TM, Wallington DG, Chinnaiyan AM, Spratt DE, Mehra R. Correlation between cribriform/intraductal prostatic adenocarcinoma and percent Gleason pattern 4 to a 22-gene genomic classifier. Prostate 2020;80:146-52.
13. Greenland NY, Cowan JE, Zhang L, Carroll PR, Chan E, Stohr BA, et al. Expansile cribriform Gleason pattern 4 has

histopathologic and molecular features of aggressiveness and greater risk of biochemical failure compared to glomerulation Gleason pattern 4. Prostate 2020;80:653-9.
14. Greenland NY, Zhang L, Cowan JE, Carroll PR, Stohr BA, Simko JP. Correlation of a commercial genomic risk classifier with histological patterns in prostate cancer. J Urol 2019;202:90-5.
15. Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. Mod Pathol 2006;19:1528-35.
16. Karnes RJ, Bergstralh EJ, Davicioni E, Ghadessi M, Buerki C, Mitra AP, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-53.
17. Trudel D, Downes MR, Sykes J, Kron KJ, Trachtenberg J, van der Kwast TH. Prognostic impact of intraductal carcinoma and large cribriform carcinoma architecture after prostatectomy in a contemporary cohort. Eur J Cancer 2014;50:1610-6.
18. Keefe DT, Schieda N, El Hallani S, Breau RH, Morash C, Robertson SJ, et al. Cribriform morphology predicts upstaging after radical prostatectomy in patients with Gleason score 3 + 4 = 7 prostate cancer at transrectal ultrasound (TRUS)-guided needle biopsy. Virchows Arch 2015;467:437-42.