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ORIGINAL PAPER

Prostate cancer with cribriform pattern: Exclusion criterion for active surveillance?

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Summary

Introduction: Following the 2014 International Society of Urological Pathology meeting, a rapidly growing body of evidence by several researchers has been demonstrating a poor prognosis in association with cribriform morphology. The aim of our study was to describe the presence of cribriform foci in specimens of radical prostatectomies and to evaluate whether demographic and clinical characteristics are associated with the presence of cribriform pattern.

Materials and methods: This cohort study was based on 70 radical retropubic prostatectomies specimens collected between 2012 and 2016 and evaluated for the association of the cribriform pattern with age, prostate-specific antigen at surgery day, Gleason on biopsy, Gleason after radical prostatectomy, extracapsular extension, vesicles invasion, margins, multiparametric magnetic resonance imaging, and post-operative radiotherapy.

Results; From the univariable analysis, biochemical prostate-specific antigen recurrence (p = 0.001), extracapsular extension (p = 0.003), pre-operative prostate-specific antigen (p = 0.017), vesicles invasion, (p = 0.038) and post-operative radiotherapy (p < 0.001) showed an association with the presence of cribriform pattern. There was also a significant difference of cribriform pattern and Gleason 7 in needle biopsy (p = 0.020) and cribriform pattern and Gleason 8 or 9 in radical prostatectomy specimen (p = 0.036).

Conclusions: In our study, the increase in preoperative prostate-specific antigen had a high association with cribriform pattern. Further evidence is needed to discriminate preoperative prostate specific antigen values that might potentially be associated with the presence of cribriform pattern. Raising our knowledge about the cribriform pattern can be an excellent opportunity to correctly identify and treat patients who will eventually die from prostate cancer, sparing treatment in those who will not.

KEY WORDS: *Cribriform pattern; Prostate cancer; Radical prostatectomy.*

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INTRODUCTION

The *Gleason pattern* (GP) 4 has been assigned to most cribriform patterns, because of the understanding that invasive cribriform carcinoma is relatively aggressive (1). Cribriform is characterized by a "*solid proliferation with multiple, punched out lumina without intervening stroma*" (2).
Following the 2014 *International Society of Urological Pathology* (ISUP) meeting, a rapidly growing body of evidence by several researchers has been demonstrating a poor prognosis in association with cribriform morphology (3).
Dong et al. (4) showed that, after 10 years of follow-up, 13% of patients with cribriform architecture morphology at *radical prostatectomy* (RP) developed metastasis compared to 2.6% with GP 4 without cribriform morphology. Other studies supported the information that the presence of any cribriform was associated with higher biochemical recurrence (5-6). Cribriform lesions in their pure form on RP specimens were found to be poorly visible on *multi-parametric magnetic resonance imaging* (mpMRI), namely only 17% of foci were visible (7).
Sarbay et al. (8) demonstrate that diagnosing all cribriform patterns, at least GP 4, would significantly affect further therapeutic options and prognosis.
The aim of our study is to access the cribriform foci on the RP specimens, and to evaluate whether demographic and clinical characteristics are associated with the presence of cribriform pattern (CP).

MATERIALS AND METHODS

This cohort study was based in 70 radical retropubic prostatectomies specimens collected between 2012 and 2016 in our *Department*. All the patients had a mpMRI pre-operatively. The study was approved by institutional ethics committee, and informed consent was obtained from all patients. Patients treated with cryotherapy, radiotherapy, or androgen deprivation pre-operatively were excluded.
The *prostate-specific antigen* (PSA) was measured at the day of the surgery and in the last consultation before the beginning of the study. A postoperative serum PSA above 0.2 ng/mL was considered as a *biochemical prostate-specific antigen recurrence* (BPR) (9).
Each prostate was sampled according to the standardized laboratory's protocol by the original reporting pathologist: specimens fixed in 10% neutral buffered formalin for at least 24h, serial sectioning into 0.3 mm thick sections of the whole prostate, paraffin embedding and 4 µm thick sections stained with H&E.
All the specimens were evaluated by the same pathologist with the aim of identifying the presence of a cribriform pattern. This pattern was considered to be present

No conflict of interest declared.

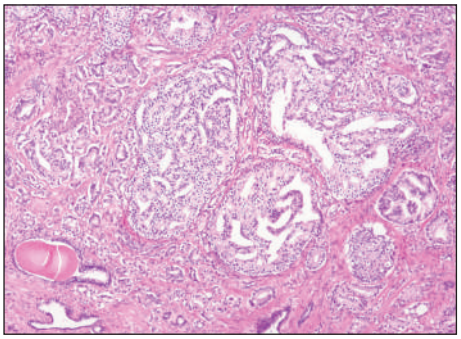

Figure 1. *Confluent epithelial proliferations with multiple lumina and no intervening stroma.*

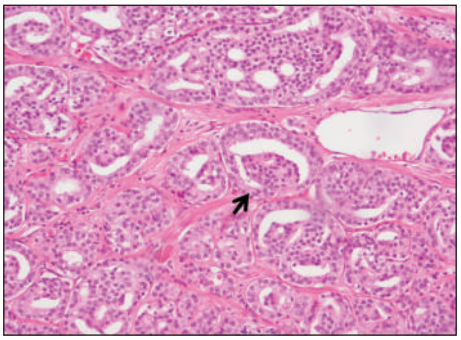

Figure 2. *Cribriform formation attached to only one edge of the gland, resulting in the less common glomeruloid pattern.*

when confluent epithelial proliferations with multiple lumina and no intervening stroma were observed (Figure 1), and also when the cribriform formation was attached to only one edge of the gland, resulting in the less common glomeruloid pattern (Figure 2).
Cases with comedonecrosis were not observed. For some cases with cribriform areas with smooth contours, immunohistochemistry (p63 and CK34βe12) was applied to distinguish from high-grade *prostate intraepithelial neoplasia* (PIN) and intraductal carcinoma.

Statistical analysis

Characteristics of study patients were described using the median and interquartile range (IQR: 25th percentile-75th percentile) for continuous variables and frequencies (percentages) for categorical variables.
To study the association between cribriform foci and clinical and demographic variables, logistic regression models were used. Odd ratios were estimated with corresponding 95% *confidence intervals* (CI).
The following variables were considered in the univariable analysis: age, PSA at surgery day, Gleason on biopsy, Gleason after radical prostatectomy, extracapsular extension, vesicles invasion, margins, mpMRI, and post-operative radiotherapy.
Those variables attaining a p-value < 25 in the univariable analysis were selected as candidates for the multivariable model.
Discriminative ability and calibration of the model were assessed by the area under the receiver-operating characteristic curve (AUC) and the Hosmer-Lemeshow test (Figure 3), respectively.
The level of significance α = 0.05 was considered. All data were analyzed using the *Statistical Package for the Social Sciences for Windows 22.0* (*IBM Corp. Released 2013. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.*).

Results

Out of 70 specimens of patients with radical retropubic prostatectomy included in the study, 23 (32.9%) had a cribriform pattern. The median age at diagnosis was 66 years (range 60-70) for patients with cribriform pattern and 65 years (range 60-68) for patients who do not have cribriform pattern at radical prostatectomy specimen.
The pathologic characteristics of the study sample are presented in Table 1. The grade group distribution of the 70 specimens was as follow: 14 (20%), 27 (38.6%), 14 (20%), 5 (7.1%), 6 (8.6%), 3 (4.3%) and 1 (1.4%) were Gleason 3+3, 3+4, 4+3, 4+4, 4+5, 5+4 and 3+5, respectively.
Furthermore, for cases with CP, 14 (60.9%), 12 (52.2%) and 5 (21.7%) had *extraprostatic extension* (EPE), surgical margin (SM) and vesicles invasion, respectively.
On the other hand, for cases without CP, 11 (23.4%), 15 (31.9%) and 2 (4.3%) had EPE, SM and vesicles invasion, respectively. By previous definition of PSA failure, 7 (30.4%) of the patients with CP and only 1 (2.2%) without CP showed BPR. Of those who had BPR, 7 (87.5%) had cribriform pattern, while from those who did not had BPR, only 16 (26.2%) had cribriform pattern. Concerning radiotherapy, 16 (69.6%) of the patients with CP have done adjuvant radiotherapy, while only 7 (30.4%) with CP have not been submitted to RT.
From the univariable analysis, BPR (p = 0.001), EPE (p = 0.003), pre-operative PSA (p = 0.017), vesicles invasion (p = 0.038) and RT (p < 0.001) showed an association with the presence of cribriform pattern (Table 2).
There was no statistically significant difference between the presence of CP and positive margins (p = 0.105), mpMRI PIRADS 4 (p = 0.609) and 5 (p = 0.254), Gleason Score 7 in RP Specimen (p = 0.131) or Gleason score 8 or 9 in needle biopsy (p = 0.429). On the other hand, there was a significant difference with CP pattern and Gleason 7 in needle biopsy (p = 0.020) and with CP and Gleason 8 or 9 in RP specimen (p = 0.036) (Table 2).

Figure 3.
Good discriminative ability to distinguish between patients with and without cribriform pattern with an AUC = 0.79 (95% CI: 0.67-0.91).

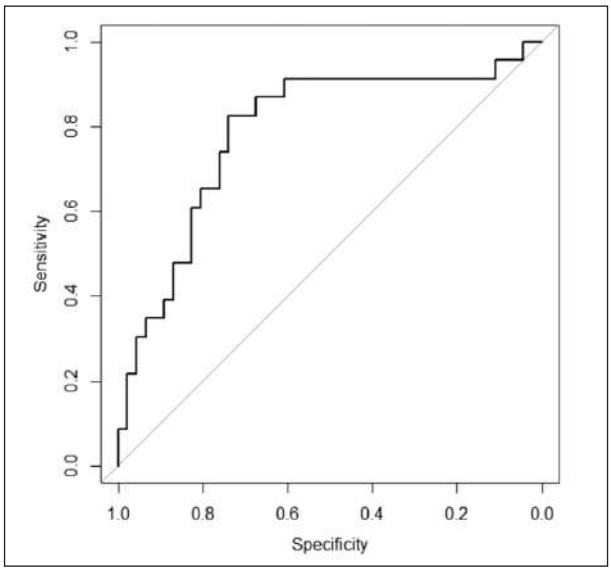

Table 1.
Clinical characteristics of the patients by group.

	With cribriform pattern n = 23	Without cribriform pattern
Preop PSA (per ng/dL)*	9.10 (6.04-15.44)	6.04 (4.86-8.45)
EPE, n (%)		
Positive	14 (60.9)	11 (23.4)
Negative	9 (39.1)	36 (76.6)
BPR, n (%)		
Yes	7 (30.4)	1 (2.2)
No	16 (69.6)	45 (97.8)
RT, n (%)		
Yes	16 (69.6)	11 (23.9)
No	7 (30.4)	35 (76.1)
SM, n (%)		
Positive	12 (52.2)	15 (31.9)
Negative	11 (47.8)	32 (68.1)
Vesicles Invasion, n (%)		
Positive	5 (21.7)	2 (4.3)
Negative	18 (78.3)	45 (95.7)

** Values are expressed as median (interquartile range); BPR, biochemical prostate-specific antigen recurrence; EPE, extraprostatic extension; SM, surgical margin; PSA, prostate specific antigen.*

Table 2.
Univariable regression analysis, dependent variable: cribriform pattern.

Variables	Odds ratio estimates	95% CI		p-value
Age (years)*	1.01	0.93	1.10	0.811
Preop PSA	1.14	1.02	1.27	0.017
Gleason in needle biopsy**				
7	3.82	1.24	11.80	0.020
8 or 9	2.17	0.32	14.71	0.429
Gleason in RP Specimen**				
7	3.50	0.69	17.76	0.131
8 or 9	7.00	1.14	42.97	0.036
EPE	5.09	1.74	14.93	0.003
Vesicle invasion	6.25	1.11	35.20	0.038
Margins	2.33	0.84	6.47	0.105
mpMRI***				
4	1.40	0.39	5.08	0.609
5	2.80	2.59		0.254
Adjuvant RT	7.27	2.38	22.23	< 0.001

** For each one-year increase of age; ** Reference category: 6; *** Reference category: 2 or 3; CI, Confidence Interval; EPE, Extracapsular extension; PSA, Prostate Specific Antigen; RT, Radiotherapy; p-values obtained by logistic regression models.*

Results of multivariable model showed that for each unit increase in pre-operative PSA, there was a 14.2% increase (OR-estimate = 1.14; 95% CI: 1.01-1.29; p = 0.033) in the odds of cribriform pattern. It was also observed that patients with extracapsular extension have a 5-fold increase in the odds of having cribriform pattern (OR-estimate = 5.35; 95% CI: 1.68-17.02; p = 0.005).
The multivariable model showed a good discriminative ability to distinguish between patients with and without cribriform pattern with an AUC = 0.79 (95% CI: 0.67-0.91) (Figure 3). The Hosmer-Lemeshow goodness-of-fit test showed a good calibration (p = 0.377).

Discussion

Cribriform tumours are now recognized as highly aggressive and with worse prognosis compared to other morphologies. This means that enhancing the understanding of cribriform cancer biology is of the utmost importance to precisely identify and treat men that will eventually die of prostate cancer, while sparing treatment in those who will not (10).
What could be the implication of a cribriform pattern in clinical practice? In a study by *Kenneth et al.* (11) that involved 153 men who underwent RP, 76 with PSA failure (> 0.2 ng/mL) were matched to 77 men without failure. In high-grade pattern frequencies, 54.9% showed a CP. This pattern was also present in 61% of PSA failure cases. According to the multivariable analysis, the CP had the highest odds ratio for PSA failure.
In another study, 241 consecutive RP specimens were reviewed. The presence of poorly formed glands, fused glands, and CP was recorded for each case. The types of architectural patterns presented were associated with patient outcome. Twenty-two of 165 patients (13.3%) with CP adenocarcinoma develop metastasis, whereas 2 of 76 (2.6%) without a CP developed metastasis at a median postoperative follow-up of 10.0 years. They concluded that the presence of a CP was an independent predictor for BPR as well as metastasis after RP (12).
In the present study, we investigated the association of age, preoperative PSA, Gleason on biopsy, Gleason after RP, EPE, vesicles invasion, positive margins, BPR, mpMRI and post-operative radiotherapy with the presence of CP.
In the univariable analysis, EPE, vesicles invasion, preoperative PSA and adjuvant RT showed significant association in the presence of CP. There was also a statistical significance between CP and BPR. Of those who had BPR, 87.5% had CP, while those who did not had BPR, only 26.2% had CP. In the multivariable analysis, only EPE and pre-operative PSA revealed a statistically significant association with CP.
Use of active surveillance in select favorable intermediate-risk patients (Gleason 3+4) has been proposed (13). Some groups have argued that cribriform morphology itself outperforms the percentage of Gleason pattern 4 involvement for prognostication and should be used to determined candidates for active surveillance. In this context, CP might be a valuable additional parameter in selecting patients for active surveillance.
In this study, we found that RP specimens with CP had a significantly higher likelihood of seminal vesicle invasion and extraprostatic extension compared to specimens without CP. The presence of CP was also associated with an advanced pathological stage (Gleason 8 or 9) compared to those without CP.
Presently, the only way accepted to identify the presence of the cribriform morphology is through tissue analysis. *Holemans et al.*, identified PSA as independent predictor (*Odds Ratio 3.5; 95% Confidence Interval 1.2-9.4, P = 0.02*) for cribriform architecture on radical prostatectomy (14). In our study, the increase in preoperative PSA had a high association with CP. Further evidence is needed to discriminate preoperative PSA values that might potentially be associated with the presence of CP. We believe it is also worth to explore the value of prostate-specific membrane antigen ligands, to accurately detect the presence of the cribriform morphology and possibly treat it. Since tumors

with CP are characterized by specific genetic and molecular alterations, it would be possible to define the molecular profile of the neoplasm either in the tissue or in liquid biopsies (urine or blood) (9). It is important to differentiate these patients that would otherwise be selected for active surveillance and abstained of immediate treatment.

Conclusions

According our study, we found that patients with CP had higher preoperative PSA levels, higher rate of EPE, Seminal Vesicles Invasion, positive SM in final pathology, higher rate of adjuvant radiation therapy and BCR in postoperative course.

The evidence for the distinct adverse prognostic impact of invasive cribriform cancer has increased rapidly in recent years, so it is really important to ask our pathologists to specifically report the presence of CP in the pathology report. Excessive treatment of non-lethal prostate cancer has been a critical area in the approach to prostate cancer treatment, so raising our knowledge about the cribriform pattern can be an excellent opportunity to correctly identify and treat patients who will eventually die from prostate cancer, sparing treatment in those who will not. It might be important to consider cribriform growth as an exclusion criterion for active surveillance in Gleason score 3+4 = 7 patients.

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