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The presence of cribriform pattern in prostate biopsy and radical prostatectomy is associated with negative postoperative pathological features

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Introduction Prostate cancer is the second most common male cancer worldwide. Its rising incidence and high overtreatment rate drive the search for new prognostic factors. Histopathological variants, such as cribriform pattern (CP), are associated with poorer oncologic outcome. The aim of this study was to assess the correlation between CP in prostate biopsy and radical prostatectomy (RP) and postoperative pathological features.

Material and methods In this retrospective, single-centre study we analysed the reviewed medical records of 100 men who underwent minimally invasive RP in the years 2017–2019. RP histopathological examination was performed by a single expert pathologist, and preoperative biopsies were assessed by various professionals from different referral centres.

Results 48% of men underwent endoscopic RP with limited lymphadenectomy, whereas 52% underwent laparoscopic RP with extended lymphadenectomy. CP in biopsy was present in 6 patients: 3 in each of both groups (6.3% and 5.8%, respectively). Lymph node metastases were present in 50% and 10% of patients with and without CP in biopsy, respectively ($p = 0.028$). Postoperative histopathological examination revealed CP in 65%. CP in RP was associated with higher International Society of Urological Pathology (ISUP) ($p < 0.001$), extraprostatic extension (EPE) ($p = 0.001$), seminal vesicle invasion (SVI) ($p = 0.001$), and positive surgical margin (PSM) ($p = 0.004$). Thirteen (20%) of the patients with CP in the RP specimen had lymph node metastasis, and none of the patients without CP in the RP specimen had regional LN metastasis.

Conclusions The presence of CP in a biopsy specimen and RP is associated with negative postoperative features. Therefore, efforts should be made to increase CP reporting in biopsies because its identification could trigger a more radical surgical approach with extended lymphadenectomy.

Key Words: cribriform pattern ‹› prostate cancer ‹› radical prostatectomy ‹› prostate biopsy

INTRODUCTION

Prostate cancer (PCa) is the second most common male cancer worldwide. The high incidence and clinical impact of radical treatments on patients' quality of life stimulate clinicians to further improve diagnostic methods and seek parameters that could help better discriminate clinically significant (CSPCa) from non-significant prostate cancer (NSPCa). Currently, the shared decision-making process is still based on D'Amico risk group classification, which incorporates the following vari-

ables: serum prostate specific antigen (sPSA), clinical disease stage, and morphology of cancer cells in prostate biopsy. Nonetheless, those parameters are not ideal and carry the risk of both over- and underestimation of the disease. The 2014 International Society of Urological Pathology (ISUP) consensus conference on novel assessment of prostate biopsy and radical prostatectomy (RP) specimens acknowledged that cribriform pattern (CP) along with ill-formed glands, fused gland, and glomeruloid structures were to be recognized as a spectrum of Gleason 4 pattern. The reported prevalence of cribriform morphology varies significantly between studies from 8.9% [1] to 37% (cribriform architecture, not solely CP) [2] in prostate biopsy and from 25% [3, 4] to almost 70% in radical prostatectomy specimens [2, 5]. Until recently there was no uniform definition of CP. In 2021 the ISUP held a conference, and recognized experts in the field of uropathology developed a consensus definition of CP. Currently, CP is defined as a confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power [6]. There should be no intervening stroma or mucin separating individual or fused glandular structures [7]. To date, conducted studies have shown an association between CP in both prostate biopsy and RP specimens, and adverse pathological findings and clinical outcomes after RP such as more advanced disease stage, lymph node metastasis (LNs met), shorter biochemical recurrence (BCR)-free survival, higher risk of distant metastasis, and shorter disease-specific survival (DSS) [5, 8, 9, 10]. The negative impact of regional LN metastasis especially in multiple LNs on oncological outcomes in PCa patients has also been proven [11, 12]. The extent of lymphadenectomy (LND) during RP depends on the risk of lymph node involvement based on available nomograms. Limited LND (lLND) is restricted to obturator LNs, whereas extended pelvic lymphadenectomy (ePLND) additionally involves the removal of LNs overlying external and internal iliac vessels. Histopathological evaluation of removed lymphatic tissue provides valuable information on the disease stage and helps guide adjuvant treatment. At the same time, studies conducted to date have failed to confirm that LND is associated with any oncological benefit. ePLND provides more tissue for analysis but is associated with higher morbidity, especially lymphocele [13, 14]. The authors decided to conduct this study to evaluate the impact of CP at biopsy and RP on pathological adverse findings after RP and to assess real-life reporting of CP in prostate biopsy specimens.

MATERIAL AND METHODS

In this retrospective, single-centre study we analysed the reviewed medical records of 100 patients treated with minimally invasive RP for localised or locally advanced PCa from 2017 to 2019. Patients who were either primarily managed with external beam radiotherapy (EBRT) or received neoadjuvant androgen deprivation therapy (ADT) or in whom data from medical history regarding prostate biopsy or RP were incomplete were excluded from further analysis. Minimally invasive RP was performed by a single high-volume expert surgeon. The decision regarding the need for ePLND was based on the 2012 Briganti nomogram available online. When the risk of lymph node metastases < 5%, ePLND was omitted and lLND was performed. The histopathological examination was performed by a single expert pathologist following the 2014 ISUP criteria. Preoperative biopsy results were extracted from patients' medical records. Details regarding the prostate biopsy technique were not taken into consideration because in most cases those data were missing. Patients' clinical characteristics included the following: age at the time of surgery, preoperative sPSA, PSA density (PSAD), clinical disease stage according to the 2017 UICC TNM classification system, and multiparametric resonance imaging results (mpMRI). Extracted biopsy characteristics were as follows: ISUP according to 2014 ISUP recommendations, percentage of cores involved by the PCa, the presence of CP and intraductal carcinoma (IDC). Pathological assessment of RP specimen included the following: type of surgery, the extent of LND, pathological disease stage according to the 2017 UICC TNM classification system, ISUP according to 2014 ISUP recommendations, PCa extension (one vs. both lobes), extraprostatic extension (EPE), seminal vesicle invasion (SVI), positive surgical margin (PSM), lymph node metastases (LNs met), and the presence of CP and IDC. The examining expert uropathologist used the CP definition provided by the 2014 ISUP recommendations [15]. No attempt was made to identify large and small CPs. IDC was identified with the WHO 2016 definition. Basal cell immunostaining to distinguish between CP and IDC was left to the discretion of the examining expert uropathologist. The primary endpoint of this study was to assess the impact of CP in prostate biopsy and RP on disease stage and adverse pathological parameters in RP specimens. The secondary endpoint was concordance between biopsy and RP in the detection of CP.

Statistical analysis

Data on categorical variables were reported as frequencies (n) and percentages (%). Continuous variables were described as means ± standard deviations (SD) or median values and interquartile range (IQR). To assess continuous variables between CP and non-CP, a t-test was used if the normal distribution was confirmed; otherwise, the Mann-Whitney U test was used. The chi-square and Fisher exact tests were used to compare categorical variables between CP and non-CP. Prostatectomy findings on CP were considered as a gold standard to determine sensitivity and specificity of prostate biopsy. A P-value of <0.05 was considered significant. All statistical analyses were performed with jamovi (Version 2.3).

RESULTS

Baseline cohort characteristics

The entire cohort consisted of 100 patients. The mean age at the time of the surgery was 63.9 years (SD ±6.6). The mean sPSA level was 11.9 ng/ml (SD ±10.2). In 47 patients mpMRI was performed with a mean prostate volume of 44.9 cc (SD ±26). Thirty-nine of those men underwent mpMRI in the pre-biopsy setting. In 32 patients, data regarding the number of biopsy cores were missing, and in the remaining 68 cases the mean number of cores per patient was 7.9. In total, 48 men underwent extraperitoneal endoscopic radical prostatectomy (EERP) with lLND, whereas in 52 patients laparoscopic radical prostatectomy (LRP) with ePLND was performed. After RP, upgrading was observed in 47% and downgrading in 21% of patients, respectively.

Clinicopathological features in patients with and without cribriform pattern in prostate biopsy

Among 100 men, biopsy revealed CP in 6 cases. Neither PSA nor PSAD differed significantly between patients with and without CP in prostate biopsy. One-third of patients with (n = 2) and 13% without (n = 12) CP in prostate biopsy, respectively, had clinically locally advanced disease. Fifty per cent of patients with CP in prostate biopsy underwent either EERP with lLND or LRP with ePLND. CP was significantly associated with lymph node metastasis (LNs met) (p = 0.028) and the presence of IDC in the RP specimen. There was no statistically significant correlation between CP and other negative pathological features. (Table 1)

Clinicopathological features in patients with and without cribriform pattern in radical prostatectomy specimen

Patients with CP in the RP specimen were more likely to have clinically more advanced disease ($p< 0.001$). Moreover, CP in RP was associated with higher ISUP ($p < 0.001$). Pathological negative prognostic factors such as EPE (p = 0.001, RR 1.68 [1.26–2.25]), SVI (p = 0.001, RR 1.47 [1.22–1.76]), PSM (p = 0.004, RR 1.32 [1.13–1.54]) were also more commonly encountered in CP-positive patients. Thirteen (20%) patients with CP in the RP specimen had regional LNs met.

Table 1. *Clinicopathological characteristics of patients with and without cribriform pattern in prostate biopsy*

RP	CP in Bx	non-CP in Bx	p-value
Number, n (%)	6 (6)	94 (94)	
Age (mean ± SD)	64.8 ±8.57	63.8 ±6.54	0.721[&]
MRI PV (cc) (mean ±SD)	40.4 ±28.2	45.5 ±26.0	0.309[*]
PSA (ng/mL) (mean ±SD)	12.1 ±11.1	11.8 ±10.2	0.667[*]
cTNM, n (%)			
cT1	2 (33)	46 (49)	
cT2a/b	2 (33)	26 (27)	
cT2c	0	10 (10)	
cT3	2 (33)	12 (13)	0.369[*], 0.308[&]
Surgery, n (%)			
EERP + lLND,	3 (50)	45 (48)	
LRP + ePLND	3 (50)	39 (41)	1.000[#]
Lobe, n (%)			
One	2 (33)	46 (49)	
Both	4 (67)	41 (44)	0.425[#]
ISUP, n (%)			
1	0 (0)	4 (4)	
2	1 (17)	41 (44)	
3	2 (33)	37 (39)	
4	2 (33)	6 (6)	
5	1 (17)	6 (6)	0.053[#]
Upgrading, n (%)	1 (17)	46 (49)	0.210[#]
ECE, n (%)	4 (67)	35 (37)	0.205[#]
SVI, n (%)	3 (50)	20 (21)	0.133[#]
PSM, n (%)	1 (17)	17 (18)	1.000[#]
N1, n (%)	3 (50)	10 (10)	0.028[#]
IDC, n (%)	3 (50)	9 (10)	0.022[#]

Bx – prostate biopsy, RP – radical prostatectomy, CP – cribriform pattern, MRI – magnetic resonance imaging , PV – prostate volume, ISUP – International Society of Urological Pathology classification, PSAD – PSA density, EERP – endoscopic extraperitoneal radical prostatectomy, LPR – laparoscopic radical prostatectomy, lLND – limited lymphadenectomy, ePLN – extended pelvic lymphadenectomy, ECE – extraprostatic extension, SVI – seminal vesicle invasion, PSM – positive surgical margin, N1 – regional lymph node metastasis: obturator, external iliac, internal iliac, IDC – intraductal carcinoma
[&]t-test; [*]Mann-Whitney U-test; [#]Fisher's exact test

Cribriform pattern and intraductal carcinoma in prostate biopsy and radical prostatectomy specimens

The prevalence of CP in RP specimens was 65%, which was much higher than in biopsies (6%) (Table 1, Table 2). In patients with CP in the prostate biopsy, RP confirmed the diagnosis in 5 cases. Additionally, CP was detected in another 60 patients without CP in the biopsy. In one case cribriform structures were only found on core biopsy material, not in the material from RP. Sensitivity and specificity of CP detection in prostate biopsy were 7.7% and 97%, respectively. RP specimen evaluation identified IDC in 50% and 10% of patients with and without CP in prostate biopsy ($p = 0.02$), respectively. Altogether there were 68 patients with CP/IDC in RP specimens (Table 1, Table 2).

Table 2. *Clinicopathological characteristics of patients with and without cribriform pattern in radical prostatectomy*

RP	CP in RP	non-CP in RP	p-value	RR (95% CI)
Number, n (%)	65 (65)	35 (35)		
Age (mean ±SD)	64.1 ±6.3	63.5 ±7.29	0.634[&]	
MRI PV (cc) (mean ± SD)	41 ±19.4	51.3 ±33.7	0.319*	
PSA (mean ±SD)	14.2 ±11.9	7.52 ±3,06	0.012*	
PSAD (mean ±SD)	0.322 ±0.327	0.176 ±0.096	0.176*	
cTNM, n (%)				
cT1	23 (35)	25 (71)		
cT2a/b	20 (31)	8 (23)		
cT2c	9 (14)	1 (3)		
cT3	13 (20)	1 (3)	< 0.001*	
Surgery, n (%)				
EERP+lLND	26 (40)	22 (63)		
LRP+ePLND	39 (60)	13 (37)	0.37[@]	2.54 (1.09–5.92)
Lobe, n (%)				
One	26 (40%)	22 (63%)		
Both	34 (52%)	11 (31%)	0.032[@]	1.54 (1.06–2.24)
ISUP, n (%)				
1	0 (0)	4 (11)		
2	19 (29)	19 (54)		
3	33 (51)	10 (35)		
4	6 (9)	2 (6)		
5	7 (11)	0 (0)	< 0.001*	
ECE, n (%)	33 (51)	6 (17)	0.001[@]	1.68 (1.26–2.25)
SVI, n (%)	22 (34)	1 (3)	0.001[@]	1.47 (1.22–1.76)
PSM, n (%)	17 (26)	1 (3)	0.004[@]	1.32 (1.13–1.54)
N1, n (%)	13 (20)	0		
IDC, n (%)	9 (14)	3 (9)	0.533[@]	1.71 (0.43–6.79)

RP – radical prostatectomy, CP – cribriform pattern, RR – relative risk, CI – confidence interval, MRI – magnetic resonance imaging, PV – prostate volume, ISUP – International Society of Urological Pathology classification, PSAD – PSA density, EERP – endoscopic extraperitoneal radical prostatectomy, LPR – laparoscopic radical prostatectomy, ILND – limited lymphadenectomy, ePLND – extended pelvic lymphadenectomy, ECE – extraprostatic extension, SVI – seminal vesicle invasion, PSM – positive surgical margin, N1 – regional lymph node metastasis: obturator, external iliac, internal iliac, IDC – intraductal carcinoma
[&]t-test; *Mann-Whitney U-test; [@]chi-square test

DISCUSSION

We performed this study to evaluate the impact of CP in prostate biopsy and RP on adverse pathological findings after RP and to assess real-life reporting of CP in biopsy in a retrospective cohort. The results show that the presence of CP in prostate biopsy as well as RP is a negative pathological prognostic factor and that in our setting CP detection in biopsy specimens seems to be underreported. Additionally, patients positive for CP in biopsy had significantly more frequently concurrent IDC in RP.

In our study, CP was identified in 6% and 65% in prostate biopsy and matched RP specimens, respectively. The 2014 ISUP conference consensus concluded that Gleason 4 pattern spectrum includes 4 different submorphologies: CP, ill-formed glands, fused glands, and glomeruloid structures [15]. Although combined in one group, these patterns seem to have different malignant potential, which was not included in recent guidelines [5, 9]. Until recently there was no uniform CP definition. With the new consensus CP definition there are still inconsistencies amongst pathologies regarding the minimal size of lesions containing cribriform structures. Moreover, sole microscopic examination can be challenging in distinguishing between CP and IDC. Therefore, immunohistochemical staining for basal cells is recommended in equivocal cases. Multiple studies showed conflicting results regarding the true prevalence of CP in both RP and prostate biopsy. Elfandy et al. assessed the prevalence of CP in RP specimens based on the analysis of The Cancer Genome Atlas cohort (TCGA) and identified CP in 62% of cases, but they made no attempt to distinguish CP from IDC [16]. Boettcher et al. assessed combined CR/IDC presence in the same cohort, and despite inclusion of IDC, fewer CP/IDC cases were detected (31%) [17]. According to Masoomian et al., the prevalence of CP/IDC in prostate biopsy and RP was 26.9 % and 51.8%, respectively. Keefe et al. proved good interobserver agreement ($K = 0.79$) in CP identification in prostate biopsy specimens [18]. Satisfactory interobserver reproducibility in terms of CP detection in contrast to the other GP 4 patterns such as ill-formed or fused glands was also

reported by Kweldam et al. [19]. Hollemans et al. found cribriform architecture in 30% (55/186) of prostate biopsies and 69% (128/186) of matched RPs, with a sensitivity of 43% and specificity of 97%; it is worth mentioning that in the study both biopsy and RP specimens were reviewed by 3 investigators [2]. Downes et al. showed comparable results in terms of sensitivity and specificity (30% and 97%) in CP identification in prostate biopsy [20]. To further improve pathological identification of CP, in 2021 the ISUP held a conference, and recognized experts in the field of uropathology developed a consensus definition of CP [6]. In our study, the high specificity (97%) was in line with aforementioned results. However, the very low sensitivity (7.7%) was unexpected. We assume that a major factor contributing to this surprisingly low sensitivity is the origin of the biopsy data. In our cohort prostate biopsy was performed in different centres across the country. The information regarding prostate biopsy was derived from patients' medical records, and therefore it raised questions about the quality of tissue sampling, pathological evaluation, and reporting. The problem of CP presence reporting in prostate biopsy was reflected by the results of a pre-meeting survey for the Genitourinary Pathology Society (GUPS), which took place in 2019 and revealed that only 40% of US pathologists confirmed inclusion of CP in biopsy PCa diagnosis. A study by Hollemans et al. showed that biopsy undersampling may lead to false negative results in up to 40% of cases [2].

CP is considered as a highly aggressive PCa morphology. The presence of CP in RP has been shown to be associated with both adverse pathological and oncological outcomes such as the following: advanced disease stage, PSM, shorter BCR-free survival, shorter MFS-free survival, and shorter OS [9, 10, 21]. CP in prostate biopsy has also been found to be a negative prognosticator after RP: postoperative disease upgrading, upstaging, and LN metastasis [18, 22]. We found no association between CP in prostate biopsy and EPE, SVI, PSM, and disease upgrading after RP, probably as a result of low CP prevalence. Fifty per cent of patients with CP in prostate biopsy underwent either lLND or ePLND. LN metastases were identified in 50% (n = 3) and 10% (n = 10) of patients with and without CP in prostate biopsy, respectively (p = 0.03). The extent of LND is determined by the risk of harbouring LN metastasis. Widely available externally validated nomograms such as the Briganti nomogram, the Roach formula, or the Partin and MSKCC nomograms help clinicians in preoperative assessment of LN invasion [23]. Those nomograms include various variables such as sPSA, clinical disease stage, biopsy ISUP, and the number of positive cores. A recently developed risk calculator by Briganti includes mpMRI findings to better discriminate the high-risk population. However, none of those nomograms incorporates prostate cancer cell morphology. Moreover, EAU guidelines do not consider inclusion of CP in the decision-making process regarding the extent of LND. In the case of elevated probability of LN metastasis, ePLND is recommended. Although this study showed that LN metastases were statistically more common in patients with CP in prostate biopsy, only half of them underwent LRP with ePLND. LNs met, especially in multiple LNs, are a known negative prognostic factor associated with worse BCR-free survival, MET-free survival, and OS [24–25]. Whether LND during RP influences oncological outcomes remains controversial; however, it provides detailed information on the disease stage and may guide adjuvant treatment [26].

CP is characterized by distinct genetic and epigenetic alternations, which are indicative of its highly aggressive behaviour. Based on the analysis of the TGCA cohort, cribriform morphology was characterized by deletions of multiple genes: PTEN (10q23.3), NKX3–1 (8p21.2), and MAP3K7 (6q15), which, as tumour suppressor genes, play crucial roles in malignant transformation. PTEN and NKX3–1 loss is more commonly encountered in metastatic castration resistant PCa (mCRPC) [27]. Moreover, expression alternations also affect other tumour suppressor genes such as RB1 and TP53, which are also known to be associated with more aggressive PCa behaviour and therapy resistance [28, 29]. The methylation level is higher in patients with cribriform morphology compared to non-cribriform. Significant hypermethylation affect multiple genes such as CYP26A, ZNF853, DDIT4L, B3GAT1 and RASL12. Methylation profile alternations have also been found in other genes such as EVX1, EPHX3 (ABHD9) and IRAK3 [27]. All these epigenetic changes show that cribriform morphology methylation profile resembles mCRPC. Genetic changes in CP also affect RNA expression. Long noncoding RNA SChLAP1 has been found to be increased in case of CP [30]. At the same time overexpression of SChLAP1 has been linked to increased metastatic burden [31]. There are multiple genetic pathways in which CP acquires its malignant behaviour.

MpMRI plays a crucial role in the process of PCa diagnosis and further management. There are inconclusive results on the issue of CP visibility on mpMRI. Seyrek et al. and Tuna et al. reported that CP-containing lesions are visible in mpMRI [32, 33]. The lesions were also characterized by low ADC values. Mikoshy et al., on the other hand, concluded

that mpMRI detectability is more depended on relative fractions of cells, stroma, and luminal space rather than typical architectural pattern [34].

In our study IDC in RP specimens was detected in 50% and 10% of patients with and without CP in prostate biopsy, respectively (p = 0.022). According to the 2014 ISUP consensus, IDC is a separate histopathological pattern that is not included in the grade group system [15]. In 2016 the WHO released a novel pathological classification of prostate tumours and provided a unified definition of IDC, a newly recognized entity, which is defined as an intra-acinar and/or intraductal neoplastic epithelial proliferation, which has some features of high-grade prostatic intraepithelial neoplasia (HGPIN) but exhibits much greater architectural and/or cytological atypia [35]. IDC in prostate biopsy and RP has been shown to be associated with adverse outcomes, more advanced disease stage, LN metastasis, shorter BCR-free survival, and worse cancer-specific survival (CSS) [36, 37, 38]. Masoomian et al. confirmed the negative impact of the presence of CP/IDC at biopsy on more advanced disease stage (p = 0.013). The authors also highlighted in meticulous and careful evaluation of specimens that CP/IDC presence in prostate biopsy in both true positive and false negative cases was linked with more advanced PCa stage [39]. Kweldam et al. showed that CP/IDC in prostate biopsy was associated with worse disease-specific survival (DSS). ISUP 2 patients without CP/IDC had DSS comparable to men with ISUP 1 PCa. On the other hand, ISUP 2 patients with CP/IDC had significantly worse survival than ISUP 2 patients without CP/IDC, and hence they should be discouraged from AS [23].

The malignant potential of CP is reflected in the current EAU guidelines, which recommend mandatory reporting of the presence of CP/IDC in prostate biopsy. Additionally, both CP and IDC are considered as an absolute contraindication for active surveillance (AS) [26]. The American Urological Association (AUA) also discourages AS in CP/IDC-positive patients [40]. The question regarding the best radical treatment option in patients with CP remains to be answered.

Our study has caveats that need to be addressed. Firstly, it was a retrospective and single-centre study with a small cohort. A lack of data led to the disqualification of a considerable number of patients treated for PCa in the given timespan. Secondly, the absence of biopsy re-evaluation and data collection from patients' medical records impacted the study bias. In our setting – a tertiary referral department of urology – we manage patients who underwent prostate biopsy outside our department, which in turn makes biopsy slides practically inaccessible. This study, however, presents a real-life scenario, in which the true prevalence of CP in prostate biopsies seems to be underreported. Moreover, identification of CP in RP specimens was based on a single expert opinion. At least 2 expert genitourinary pathologists would be optimal. In light of this study, we assume that uropathologists should place more emphasis on detailed and careful evaluation of both prostate biopsies and RP specimens because the cancer cell morphology has an impact on the patients' prognosis.

CONCLUSIONS

CP is a negative pathological feature after RP. Although cancer cell morphology is not currently incorporated in any tools predicting LN involvement, it may provide additional information on the disease stage and guide the extent of LNs during radical treatment. Additionally, pathological evaluation of both prostate biopsies and RP specimens requires special expertise and vigilance from uropathologist in the detection of CP because its presence matters and may have an impact on decisions regarding the patients' treatment and prognosis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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