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Original article

The association of the cribriform pattern with outcome for prostatic adenocarcinomas

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ABSTRACT

With the revision of the Gleason system at the 2005 International Society of Urological Pathology Consensus Conference, there was consensus that most cribriform glands should be classified as pattern 4. There is now increased understanding that invasive cribriform carcinoma is a relatively aggressive disease.

This study was based on 233 radical prostatectomy (RP) specimens collected at the Department of Pathology, Umraniye Education and Research Hospital, from 2006 to 2013. We assessed the cribriform foci associated with the more definitive patterns 3, 4, and 5 elsewhere on the RP specimens and evaluated the association of the presence of cribriform pattern (CP) with biochemical prostate-specific antigen recurrence (BPR).

In Cox regression model, taking into account the Gleason score (GS), pathologic stage, surgical margin (SM) status, presence of a CP, and preoperative prostate-specific antigen (PSA), a positive SM, and the presence of a CP were independent predictors of BPR after RP. We observed BPR more frequently in GS 3 + 3 cases with a CP than in those without a CP ($p = 0.008$). There was no significant difference in BPR status for cases with GS 3 + 4, 4 + 3, 4 + 5, and 5 + 4 when the patients were stratified by the presence of a CP.

On the basis of these data, we suggest that the classification of CP into Gleason pattern 4 has value in predicting BPR status after RP. However, as many of these modifications are empirical and supported by only a few studies, long-term follow-up studies with clinical endpoints are necessary to validate these recommendations.

Introduction

One of the most important items of input from the 2005 International Society of Urological Pathology consensus conference was the modification of Gleason pattern 4, which is now assigned to most cribriform patterns (CP)s, because there is increased understanding that invasive cribriform carcinoma is a relatively aggressive disease [1–4]. More stringent criteria have been proposed to help pathologists distinguish the new cribriform Gleason pattern 3 from pattern 4, a distinction that would significantly affect further therapeutic options and prognosis [5,6]. Cribriform Gleason pattern 3 is depicted as individual small round glands with regular contours and large, round, evenly spaced lumina as opposed to Gleason pattern 4, which is characterized by larger glandular formations with irregular contours or jagged edges and/or smaller, irregularly distributed lumina or slit-like lumina thought to be formed by the fusion of glands [5].

In a subsequent study involving 10 well-known uropathologists, it was determined that the diagnosis Gleason CP 3 virtually does not exist in practice. It has been recommended that the cribriform architecture should no longer be considered a component of Gleason pattern 3 [5]. The diagram of the modified Gleason system has been revised accordingly [7,8], yet the recommendation that all cribriform glands be classified as pattern 4 similarly lacks supporting outcome studies. The most immediate result of these changes has been improved inter-observer reproducibility among pathologists and improved correlation between the Gleason scores (GS)s of needle biopsy and corresponding radical prostatectomy (RP) specimens [8]. Butthe impact on the prognosis and clinical outcomes of these changes has not been well studied.

Based on the study of Epstein et al. [5], we considered all CPs as GS 4. We assessed the cribriform foci associated with more

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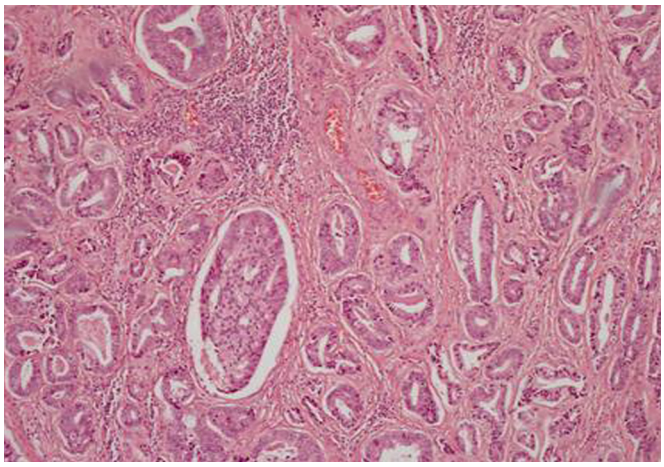

Fig. 1. Cribriform pattern – Gleason score 3 + 4 (H&E, x40)

definitive patterns 3, 4, and 5 elsewhere on the RP specimens and evaluated the association of the presence of a CP with biochemical prostate-specific antigen recurrence (BPR).

Material and methods

The study was based on consecutive 235 RP specimens, comprising 210 robotic and 25 radical retropubic prostatectomy specimens collected at the Department of Pathology, Ümraniye Education and Research Hospital, from 2006 to 2013.

None of the patients had a history of receiving cryotherapy, radiotherapy, or androgen deprivation. A postoperative serum prostate-specific antigen (PSA) level above 0.1 ng/mL was considered a BPR. Each prostate was sampled according to a standardized laboratory protocol. All slides of all cases were independently reviewed as blinded to outcome by two pathologists (Kir G, Sarbay BC), and then discrepant cases were jointly reviewed. Each case was assigned a Gleason grade according to the 2005 ISUP criteria [5].

Cancer volume was determined using the grid method [9] and was calculated as the sum of the volume of individual cancer foci [9].

We defined the CP as the presence of confluent epithelial proliferation with multiple lumina, without intervening stroma, and without comedonecrosis or the solid proliferation of GS 5 (Fig. 1).

Based on the modified Epstein criteria, we assessed the cribriform foci (regardless of contour, size, shape of the glands, and shape of the lumens) associated with the more definitive patterns 3, 4, and 5 (pattern 3, single, small, separate, or undulating branched acini; pattern 4, poorly formed or fused glands; pattern 5, individual cells or sheet-like solid proliferation) elsewhere on the RP specimens and evaluated the association of the presence of CP, GS, extraprostatic extension (EPE), surgical margin (SM) status, pathologic stage, and preoperative PSA with BPR status. We defined all CPs with comedonecrosis as Gleason pattern 5. We applied immunohistochemistry (p63) to all equivocal cribriform areas with smooth contours to exclude high-grade prostatic intraepithelial neoplasia (PIN) and intraductal adenocarcinoma. We stained 6 equivocal cases with p63. Four of them were unstained, 2 of them were stained with p63 (myoepithelial cells). These cases were evaluated as PIN and excluded from the study. There was no case with intraductal carcinoma. Finally, the study included 233 RP specimens (208 robotic and 25 radical retropubic prostatectomy). We examined 109, 85, 26, 9, and 4 cases with GSs of 3 + 3, 3 + 4, 4 + 3, 4 + 5, and 5 + 4, respectively, and any case with GS 4 + 4. This was due to the absence of GS 4 + 4 cases.

Table 1
Patient characteristics.

GS; *n* (%)	3 + 3	109 (46.8)
	3 + 4	85 (36.5)
	4 + 3	26 (11.7)
	4 + 5	9 (3.9)
	5 + 4	4 (1.7)
EPE; *n* (%)	Negative	157 (67.4)
	Positive	76 (32.6)
SM;*n* (%)	Negative	189 (81.1)
	Positive	44 (18.9)
CP; *n* (%)	Negative	89 (38.2)
	Positive	144 (61.8)
pStage, *n* (%)	T2	169 (72.5)
	T3	64 (27.5)
BPR; *n* (%)	Negative	206 (88.4)
	Positive	27 (11.6)
Preop PSA (per ng/dL)	Min–max (median)	0.38–136 (6.19)
	Mean ± SD	9.01 ± 12.30
Follow-up time (month)	Min–max (median)	3–71 (34)
	Mean ± SD	33.47 ± 16.08

BPR, biochemical prostate-specific antigen recurrence; CP, cribriform pattern; pStage, pathologic stage.
EPE, extraprostatic extension; GS, Gleason score; SM, surgical margin; PSA, prostate-spesific antigen.

EPE, microscopic bladder neck invasion, pathologic stage, seminal vesicle invasion, and SM status were defined according to the 2005 ISUP Consensus Conference Working Group 3, 4, 5 [10–12].

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (NCSS LLC, Kaysville, Utah, USA) were used for statistical analysis.

A key outcome measure of the study was the BPR status after RP, with a median follow-up of 3.5 (range 1–7, mean 3.78 ± 1.46) years.

To compare qualitative parameters, the Yates' continuity correction test, Fisher's exact test, and Fisher–Freeman–Halton test were used. A p-value of <0.05 was considered significant. To determine whether failure was related to the presence of the CP as well as to the pathologic stage, grade, EPE, SM status, and preoperative PSA univariate and multivariate analyses were used. Nonparametric tests were used to determine the associations of BPR with pathologic parameters. Multivariate survival analysis was performed using Cox hazard models with forward stepwise selection of statistically significant independent variables. All tests were 2-sided, and significance levels were set at a p-value of <0.05.

Results

The pathologic characteristics of the study population are presented in Table 1. Of the 233 specimens, 109 (46.8%), 85 (36.5%), 26 (11.7%), 9 (3.9%), and 4 (1.7%) were GS 3 + 3, 3 + 4, 4 + 3, 4 + 5, and 5 + 4, respectively; no case was GS 4 + 4. This was due to the absence of GS 4 + 4 cases. Furthermore, 76 (32.6%), 44 (18.9%), and 144 (61.8%) of the cases had EPE, positive SM, and CP, respectively, and 64 cases (27.5%) were stage pT3. By our definition of PSA failure, 27 (11.6%) of 233 patients showed BPR. Significant differences included associations of failure with GS ($3+3 \times 3+4 \times 4+3 \times 4+5 \times 5+4$, and $3+3x \geq 7$) ($p < 0.001$ and $p = 0.012$, respectively), EPE ($p = 0.013$), and positive SM ($p < 0.001$), presence of CP ($p < 0.001$), high pathologic stage ($p < 0.001$), and preoperative PSA ($p < 0.001$) (Table 2).