Original Article

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Prognostic Impact of Conglomerated Cribriform Morphology in Gleason Score 7 Prostate Adenocarcinoma

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Abstract

Objective: Cribriform architecture has increasingly been recognized as an adverse morphological feature in prostate adenocarcinoma. The present study aimed to describe a novel histopathological subtype of cribriform architecture, termed conglomerated cribriform morphology (CCM), and to investigate its association with clinicopathological parameters and oncological outcomes.
Materials and Methods: Radical prostatectomy specimens with Gleason score 7 and cribriform architecture were retrospectively reviewed. All cases were re-evaluated and categorized into two morphological groups: basic cribriform morphology and CCM. Clinicopathological variables and survival outcomes were compared between these groups.
Results: A total of 151 patients were included in the study, with a mean age of 67.6 years. CCM was detected in 21.2% of cases. This pattern was significantly associated with higher prostate-specific antigen levels, extraprostatic extension, lymph node metastasis, biochemical recurrence, and distant metastasis. Multivariate Cox regression analysis revealed tertiary Gleason pattern, lymphovascular invasion, and CCM as independent predictors of biochemical recurrence. Patients with CCM had significantly shorter biochemical recurrence-free survival.
Conclusion: Cribriform architecture is widely considered an unfavorable feature in prostate cancer. The newly described conglomerated cribriform subtype appears to be a particularly aggressive variant. Recognition of this morphology may contribute to improved prognostic stratification and influence clinical management strategies.
Keywords: Prostate adenocarcinoma, Gleason score 7, cribriform morphology, basic cribriform, conglomerated cribriform, biochemical recurrence

Introduction

In recent years, cribriform architecture has attracted considerable attention in prostate cancer research due to its association with unfavorable clinical outcomes. Several studies have demonstrated that tumors exhibiting cribriform growth patterns behave more aggressively compared with other Gleason pattern 4 morphologies (1-5). The International Society of Urological Pathology (ISUP) describes cribriform carcinoma as a confluent epithelial proliferation composed of malignant cells forming multiple gland-like luminal spaces that are clearly visible at low magnification and lack intervening stroma (6). Distinguishing invasive cribriform carcinoma from intraductal carcinoma of the prostate is an important diagnostic consideration. Intraductal carcinoma generally retains a surrounding basal cell layer, whereas invasive cribriform carcinoma lacks basal cells.

Beyond the simple presence of cribriform glands, several investigators have attempted to determine whether additional morphological characteristics may further refine prognostic assessment. In particular, gland size has been proposed as a potentially relevant parameter. Some reports suggest that larger cribriform glands are associated with worse clinical outcomes, whereas other studies have not confirmed this relationship, leading to ongoing debate regarding the prognostic significance of gland size (7,8). A recent study suggested that cribriform glands larger than 0.25 mm are correlated with adverse prognostic parameters (9).

Although diagnostic challenges exist, cribriform morphology is generally considered to demonstrate relatively good interobserver reproducibility compared with other Gleason pattern 4 patterns (10,11). Morphological features such as

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transluminal bridging and reduced peripheral luminal space have been proposed as useful criteria for recognizing cribriform carcinoma (12).

Most published studies have focused on the presence or size of cribriform glands or on differentiating invasive cribriform carcinoma from intraductal carcinoma. However, the potential heterogeneity within invasive cribriform architecture itself has not been extensively investigated. The present study aimed to evaluate distinct histopathological subtypes of invasive cribriform morphology and to assess their potential prognostic significance.

Materials and Methods

Patients who underwent radical prostatectomy between 2010 and 2020 and were diagnosed with Gleason score (GS) 7 (3+4 or 4+3) prostate adenocarcinoma were reviewed retrospectively. Only cases demonstrating cribriform architecture were included in the study. Ethical approval was obtained from the Eskişehir Osmangazi University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision no: 47, date: 27.01.2021, number: E-25403353-050.99-203691).

Pathological Evaluation

All histopathological slides were independently reviewed in a blinded manner by two experienced pathologists. After re-evaluation, 151 cases demonstrating cribriform morphology were included in the study. Data collected included GS, ISUP grade group (GG), presence of a tertiary pattern, lymphovascular and perineural invasion, extraprostatic extension (EPE), seminal vesicle invasion, pathological stage (pT), and lymph node metastasis.

Cribriform architecture was identified according to ISUP criteria (6). Cases were subsequently categorized into two morphological subgroups: basic cribriform morphology (BCM) and conglomerated cribriform morphology (CCM). The presence of even a single, invasive, conglomerated cribriform structure was considered sufficient for classification as CCM. To differentiate invasive cribriform carcinoma from intraductal carcinoma, p63 immunohistochemistry was performed in selected cases. BCM was defined as cribriform glands with round, oval, or irregular contours, clearly separated from the surrounding stroma (Figure 1). CCM was defined as large, invasive cribriform structures demonstrating expansile or infiltrative growth, frequently forming merged glandular masses and occasionally being associated with stromal or capillary components (Figure 2).

Clinical Evaluation

Clinical variables included preoperative prostate-specific antigen (PSA) level, follow-up duration, adjuvant radiotherapy, distant metastasis, biochemical recurrence, biochemical recurrence-free survival (BRFS), disease-related mortality (DRM), and survival status. Biochemical recurrence was defined as a PSA level ≥0.2 ng/mL at least 8 weeks after surgery.

Immunohistochemistry

Sections were prepared from formalin-fixed, paraffin-embedded tissue blocks. After deparaffinization and rehydration, endogenous peroxidase activity was blocked using hydrogen peroxide. Antigen retrieval was performed using Tris-EDTA buffer. Slides were incubated with monoclonal p63 antibody and visualized using an EnVision detection system. Hematoxylin was used for counterstaining. The absence of basal cell staining around cribriform glands supported the diagnosis of invasive carcinoma.

Statistical Analysis

The Shapiro-Wilk test was used to evaluate the distribution of continuous variables. The Mann-Whitney U test was applied for comparisons between groups. Associations between categorical variables were assessed using Pearson's chi-square test, the Yates-corrected chi-square test, or Fisher's exact test, as appropriate. BRFS was analyzed using Kaplan-Meier survival analysis with the log-rank test. Multivariate Cox proportional hazards regression was performed to identify independent predictors of recurrence. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics version 25.

Results

Patient Characteristics

The study included 151 patients. Among these cases, 62.9% were classified as GG2 and 37.1% as GG3. The mean patient age was 67.6 years (range 52-83 years). Pathological staging revealed 33.7% pT2, 41.1% pT3a, and 25.2% pT3b. The mean PSA level was 15.8 ng/mL (range 3-181.9). Perineural invasion was observed in 66.2% of cases, while lymphovascular invasion was present in 25.2%. Positive surgical margins were detected in 29.1% of patients. Among the 129 patients who underwent

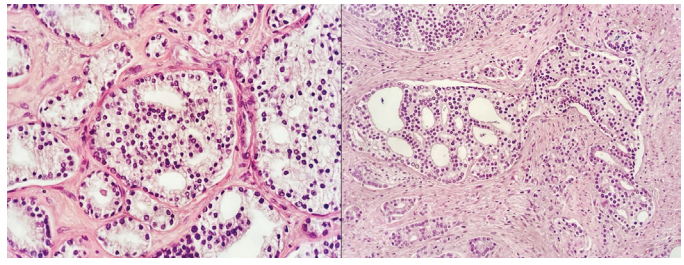

Figure 1. Example of invasive BCM, H&E

BCM: Basic cribriform morphology, H&E: Hematoxylin and eosin

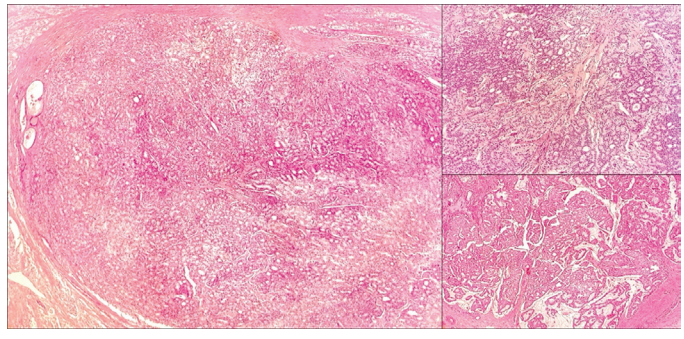

Figure 2. Example of invasive CCM, H&E

CCM: Conglomerated cribriform morphology, H&E: Hematoxylin and eosin

lymph node dissection, lymph node metastasis was identified in 22.5% of patients.

Cribriform Morphology

BCM was detected in 78.8% of cases, while CCM was identified in 21.2%. Most BCM cases (73.9%) were in GG2, whereas 78.1% of CCM cases were in GG3 (p<0.001). The mean cribriform gland percentage was 13.2% in BCM and was significantly higher at 42.8% in CCM (p<0.001). Preoperative PSA ≥10 ng/mL was observed in 45.4% of BCM and 75% of CCM cases (p=0.005). Mean PSA values were 12.8 ng/mL in BCM and 26.5 ng/mL in CCM (p<0.001). EPE was more frequent in CCM (84.4% vs. 61.3%, p=0.025). Surgical margin positivity was also higher in CCM (46.9%, p=0.023). Biochemical recurrence occurred in 62.5% of CCM patients (p<0.001). Lymph node metastasis was significantly more common in CCM (p=0.046). Distant metastases occurred in 5.3% of BCM cases and 34.4% of CCM cases (p<0.001). Although tertiary patterns were more frequent in CCM (18.8% vs. 14.3%), this difference was not statistically significant (p=0.581). Table 1 summarizes the associations between cribriform morphological subtypes and the evaluated prognostic parameters.

Survival Analysis

Radiotherapy was administered to 25.5% of patients. Distant metastasis developed in 11.6% of patients, and biochemical recurrence developed in 31%. Six patients lacked follow-up data. The mean follow-up period was 68 months (range 12-153 months). DRM occurred in 1.4% of patients. Kaplan-Meier analysis demonstrated that BRFS was significantly shorter in CCM than in BCM (51.2 vs. 117.9 months, p<0.001). BRFS in CCM was 3.87-fold shorter than in BCM (Figure 3). Multivariate analysis identified lymphovascular invasion, tertiary pattern, and CCM as independent predictors of recurrence (Table 2).

Discussion

The Gleason grading system remains one of the most important prognostic indicators in prostate adenocarcinoma. Moreover, it serves as a primary method for guiding the selection of optimal therapeutic strategies for patients. Gleason pattern 4 encompasses several architectural patterns including poorly formed glands, fused glands, glomeruloid structures, and CM (13). While these morphological subtypes were not routinely reported in the past, recent studies have consistently shown that invasive CM carries worse prognostic implications (1,3,8,14). In radical prostatectomy specimens with a GS of 7, the presence of cribriform architecture has been linked to reduced 5-year BRFS (7). Consequently, both the Genitourinary Pathology Society and the ISUP now recommend documenting CM in prostate biopsies and radical prostatectomies (15,16).

Although some studies suggest that large cribriform glands are associated with poor prognosis (7), others have reported that size does not matter (8,17). The concept of expansile cribriform architecture has also been proposed to describe large cribriform structures with numerous luminal spaces or dimensions exceeding those of adjacent benign glands. These lesions have been associated with increased rates of EPE, lymph node metastasis, and seminal vesicle invasion (18). While a recent study described cribriform diameter >0.25 mm as a potential prognostic marker, morphological features of the glands were not addressed (9). Importantly, most of these studies did not exclude intraductal carcinoma, and a standard definition for large, small, or expansile cribriform glands has yet to be established.

While earlier studies mainly evaluated the prognostic role of cribriform architecture in GS7 tumors, subsequent research has demonstrated that this architectural pattern retains independent prognostic significance in higher-grade prostate cancers, including GS8 and 9-10 (4,8,19). In addition to morphological differences, cribriform prostate carcinoma has been shown to harbor distinct molecular alterations. These include increased

Table 1. Relationship between the cribriform pattern subgroups and other prognostic parameters

	Basic cribriform pattern (n=119)	Conglomerated cribriform pattern (n=32)	p-value
ISUP group grade n (%)			
2	88 (73.9)	7 (21.9)	**<0.001***
3	31 (26.1)	25 (78.1)	
PSA value n (%)			
<10 ng/mL	65 (54.6)	8 (25)	**0.005***
≥10 ng/mL	54 (45.4)	24 (75)	
PSA value, mean (ng/mL) 95% CI	12.89 11.09-14.69	26.59 15.06-38.13	**<0.001****
Extraprostatic extension n (%)			
Present	73 (61.3)	27 (84.4)	**0.025***
Absent	46 (38.7)	5 (15.6)	
Surgical margin n (%)			
Positive	29 (24.4)	15 (46.9)	**0.023***
Negative	90 (75.6)	17 (53.1)	
Lymphovascular invasion n (%)			
Present	23 (19.3)	15 (46.9)	**0.003***
Absent	96 (80.7)	17 (53.1)	
Tertiary pattern n (%)			
Present	17 (14.3)	6 (18.8)	**0.581*****
Absent	102 (85.7)	26 (81.3)	
Biochemical recurrence n (%)			
Present	25 (22.1)	20 (62.5)	**<0.001***
Absent	88 (77.9)	12 (37.5)	
Lymph node metastasis n (%)			
Present	18 (17.6)	11 (36.7)	**0.046*****
Absent	81 (82.4)	19 (63.3)	
Distant organ metastasis n (%)			
Present	6 (5.3)	11 (34.4)	**<0.001*****
Absent	108 (94.7)	21 (65.6)	

*: Yates test, **: Mann-Whitney U test, ***: Fisher's exact test, CI: Confidence interval, PSA: Prostate-specific antigen

frequencies of PTEN and p27 loss, as well as changes affecting DNA repair pathways (20). Moreover, key genetic changes implicated in cribriform prostate cancer involve deregulation of the MYC, mTORC1, MAPK, KRAS, JAK-STAT, and epidermal growth factor receptor pathways. Epigenetic modifications may further contribute to this deregulation, as cribriform morphology has been linked to increased EZH2 expression and heightened levels of DNA methylation (20-22).

Our study aimed to define histopathological subgroups of invasive CM that may have prognostic significance, particularly in GG2 and GG3 cases where treatment strategies may vary. For routine use, we selected key histopathological criteria that are frequently used to define morphological subtypes. CCM was statistically associated with higher GG, increased EPE, positive surgical margins, advanced pT stage, lymph node metastasis, elevated PSA, biochemical recurrence, and distant metastasis compared with BCM.

Although CM demonstrates the highest interobserver reproducibility among Gleason pattern 4 morphologies (54-79%), diagnostic variability persists (10). Cribriform carcinoma consists of cohesive epithelial sheets forming rounded or irregular trabeculae with multiple lumina. However, this definition does not clearly distinguish CM from complex fused glands, papillary proliferations, glomeruloid growth, or tumors with cribriform-like mucinous morphology. van Leenders et al. (23) defined CM as tumor cell sheets with minimal stromal contact, limited peripheral luminal space, and clearly visible lumina on H&E sections. Shah et al. (12) identified consensus diagnostic criteria including transluminal bridging, lack of stromal contact, absence of intraglandular mucin, <50% peripheral luminal space, and dense cellular proliferation. Parameters with higher disagreement included partial bridging, stromal contact, mucinous fibroplasia, glomeruloid-like patterns, and >50% peripheral luminal space (12). In our study, we applied simplified and well-defined criteria to minimize diagnostic variability. Nevertheless, further studies are required to achieve higher interobserver concordance. Additionally, distinguishing BCM, which is more common in GG2, from intraductal carcinoma or cribriform PIN remains challenging without immunohistochemical basal cell markers. Many prognostic studies on CM do not address this distinction.

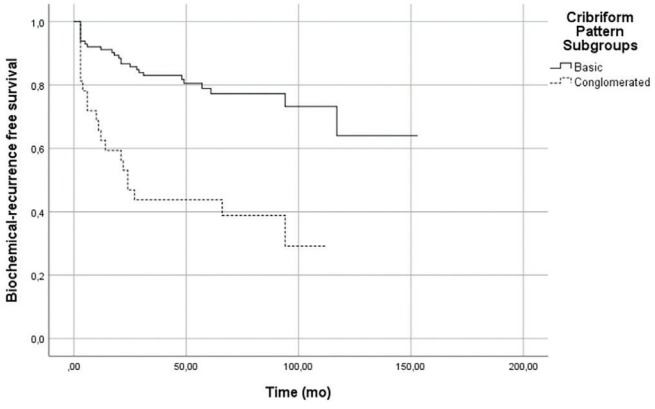

Figure 3. BRFS curves for patients with GG2 and 3 disease, categorized according to the morphology of invasive cribriform glands (BCM vs. CCM) (p<0.001)

BRFS: Biochemical recurrence-free survival, GG: Grade group, BCM: Basic cribriform morphology, CCM: Conglomerated cribriform morphology

Table 2. Cox regression analysis of biochemical recurrence-free survival in patients with GG2 or 3 prostate cancer with invasive cribriform pattern

Multivariate analysis	Hazard ratio (95% CI)	p-value
Cribriform morphology Basic Conglomerated	(Reference) 2.97 (1.59-5.55)	**0.001**
Lymphovascular invasion Absent Present	(Reference) 2.95 (1.55-5.62)	**0.001**
Tertiary pattern Absent Present	(Reference) 3.14 (1.59-6.19)	**0.001**

GG: Grade group, CI: Confidence interval

Study Limitations

This study has several limitations. First, the study was conducted at a single institution and included a relatively small number of cases. Second, the follow-up period was limited for some patients. Because this is the first study describing this morphological subtype, comparative data in the literature are limited. Larger multicenter studies with longer follow-up periods are necessary to validate these findings.

Conclusion

This study represents the first attempt to evaluate the prognostic significance of histopathological subgroups within invasive CM. Our findings suggest that CCM is associated with aggressive tumor behavior, including higher rates of lymph node metastasis and biochemical recurrence, and poorer BRFS. Identification of this morphological pattern in prostate biopsies or prostatectomy specimens may provide valuable prognostic information, particularly in patients with GG2 and 3 disease. Recognition of this subtype could influence treatment planning and follow-up strategies. Further large-scale studies are required to confirm these observations.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Eskişehir Osmangazi University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision no: 47, date: 27.01.2021, number: E-25403353-050.99-203691).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ö., C.C., Concept: E.Y., N.S.Ş., Design: E.Y., N.S.Ş., Data Collection or Processing: E.Y., N.S.Ş.,

A.Ö., Analysis or Interpretation: E.Y., E.Ç., Literature Search: E.Y., M.A., Writing: E.Y., M.A.

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