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Prognostic Significance of Cribriform Architecture of Pattern 4 Prostatic Adenocarcinomas

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Abstract:-

- ***Objective:***

Among prostate cancer patients, the Gleason score is associated with adverse clinical outcomes. We aimed to determine whether cribriform architecture in prostate cancer patients without a history of treatment was related to prognosis in patients with Gleason pattern 4 of prostate cancer.

- ***Material and Methods:***

A prospective cross-sectional study included (n=450) consecutive prostate biopsy specimens between June 2014 and May 2015, out of which (n=237) had pattern 4 prostate adenocarcinoma. Demographic, clinical, and follow-up details were obtained. Patients (n = 86) with a treatment history were excluded from the study.

- ***Results:***

Univariate Cox regression analysis of diagnostic biopsies from (n=151) patients with pattern 4 of prostate cancer who had been followed for an average of 70.3 months demonstrated that the cribriform architecture of prostate cancer with pattern 4 was independently associated with poorer disease-specific survival in biopsies with a hazard ratio (HR) of 3.1, 95% Confidence Interval (CI) of 0.9-10.6, and P value of <0.001.

- ***Conclusion:***

It is concluded that a cribriform architecture of prostate cancer in biopsies with pattern 4 adenocarcinoma is associated with a lower disease-specific survival rate. Therefore, it is essential to report the presence and percentage of cribriform architecture in patients with pattern 4 prostate cancer.

Keywords:- *Prostate Cancer, Gleason Score, Cribriform Architecture, Prognosis, Prostatic Adenocarcinoma.*

I. INTRODUCTION

Prostate cancer is a widespread cancer, especially among men worldwide. In 2020, there were around 1.4 million new cases of prostate cancer globally. It is the fourth most common cancer overall and the second most common cancer among men (1). Prostate cancer is relatively common in Pakistan, too. A meta-analysis found that its prevalence in the country is approximately 5.20% (2). The prognosis of prostatic adenocarcinoma depends on factors such as tumor stage, Gleason score, PSA level, age, and biochemical markers (3). The Gleason score is an essential determinant of clinical outcomes in men with prostate cancer. Cribriform architecture in Pattern 4 prostatic adenocarcinomas is thought to be a crucial factor in determining the prognosis. The cribriform pattern of glands is assigned a Gleason score of 4. The modified Gleason score groups with cribriform pattern 4 include Grade Group 2 (Gleason score 3 + 4 = 7), Grade Group 3 (Gleason score 4 + 3 = 7), Grade Group 4 (Gleason score 4+4=8), and Grade Group 5 (Gleason scores 4+5 or 5+4=9) (4,5). The cribriform pattern is characterized by glandular structures with luminal spaces that resemble a sieve. Shah et al. attempted to define the cribriform architecture as "A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification ×10). There should be no intervening stroma or mucin separating individual or fused glandular structures" (6). An analysis of (n=450) consecutive prostate biopsy specimens was conducted by a team of three histopathologists with expertise in genitourinary pathology using Gleason scores and Grade Group guidelines of the International Society of Urological Pathology (ISUP) 2019 and World Health Organization (WHO) 2022 to evaluate all cases of prostatic adenocarcinoma with the primary objective of identifying cases with cribriform architecture pattern 4 of prostatic adenocarcinoma and suggest that it can be predictive of biochemical recurrence, metastasis-free survival, and disease-specific survival (7). Other Studies have shown that men with cribriform architecture have adverse pathological and clinical outcomes, including a greater likelihood of biochemical failure, metastasis, and death from disease. Thus, the importance of treating these men more aggressively is demonstrated (8). This study aimed to identify cribriform growth patterns in prostate cancer patients and their relationship with prognosis in the Pakistani Population.

II. MATERIALS AND METHODS

A prospective cross-sectional study was conducted at Chughtai Institute of Pathology, Lahore, Pakistan, following approval from the institutional review board (CIP/IRB/1081A). The Institutional Review Board of the Chughtai Institute of Pathology, Lahore, Pakistan, approved the study, and informed consent was obtained from the participants. Patients with pattern 4 prostate adenocarcinoma (n=237) diagnosed on biopsy specimens between January 2014 and December 2015 were selected for inclusion in this study. We excluded patients (n = 86) undergoing treatment before surgery, including radiotherapy or hormone therapy.

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We collected demographic and clinical information regarding age, Gleason score, and treatment history, as these factors are significant for predicting prognosis in prostate cancer. Follow-up was defined as beginning with the diagnosis of prostate cancer in this study until the last available follow-up or death. Cox regression analysis was used to estimate disease-specific survival rates. IBM SPSS version 21 (Chicago, IL, USA) was used for the statistical analysis. P values less than 0.001 were considered significant.

III. RESULTS

According to the analysis of patients with prostatic adenocarcinoma with pattern 4 of prostate cancer without prior history of treatment (n=151), 93 (61.5%) had cribriform pattern 4 of prostate cancer, and 58 (38.41%) had prostate cancer without cribriform architecture pattern 4. Patients with cribriform architecture of pattern 4 had a median age of 71.1 years, and patients without cribriform architecture of pattern 4 had a median age of 68.6 years. The median follow-up period was 70.3 months. These findings have been demonstrated in Table 1 and Figure 1.

A univariable Cox regression analysis indicates that the presence of cribriform pattern 4 is associated with a significantly higher hazard ratio for disease-specific mortality.

The analysis found a hazard ratio of 3.1 with a p-value of less than 0.001, indicating that patients with this pattern face a substantially greater risk of dying from prostate cancer compared to those without it. This underscores the aggressive nature of cribriform pattern 4 and highlights its importance in guiding treatment decisions. Thus, disease-specific survival (HR, 3.1; 95% CI, 0.9 to 10.6; p <0.001) of men with cribriform pattern 4 of prostatic carcinoma was significantly lower than that of men without cribriform architecture, also shown in Table 2 and Figure 2.

Table 1: An Overview of the Cribriform Pattern 4 of Prostate Adenocarcinomas on Biopsies

Characteristic	**Value**	**Median Age of Patients**
Cribriform Pattern Present, n (%)	93 (61.5%)	71.1 years
Cribriform Pattern Not Present, n (%)	58 (38.41%)	68.6 years

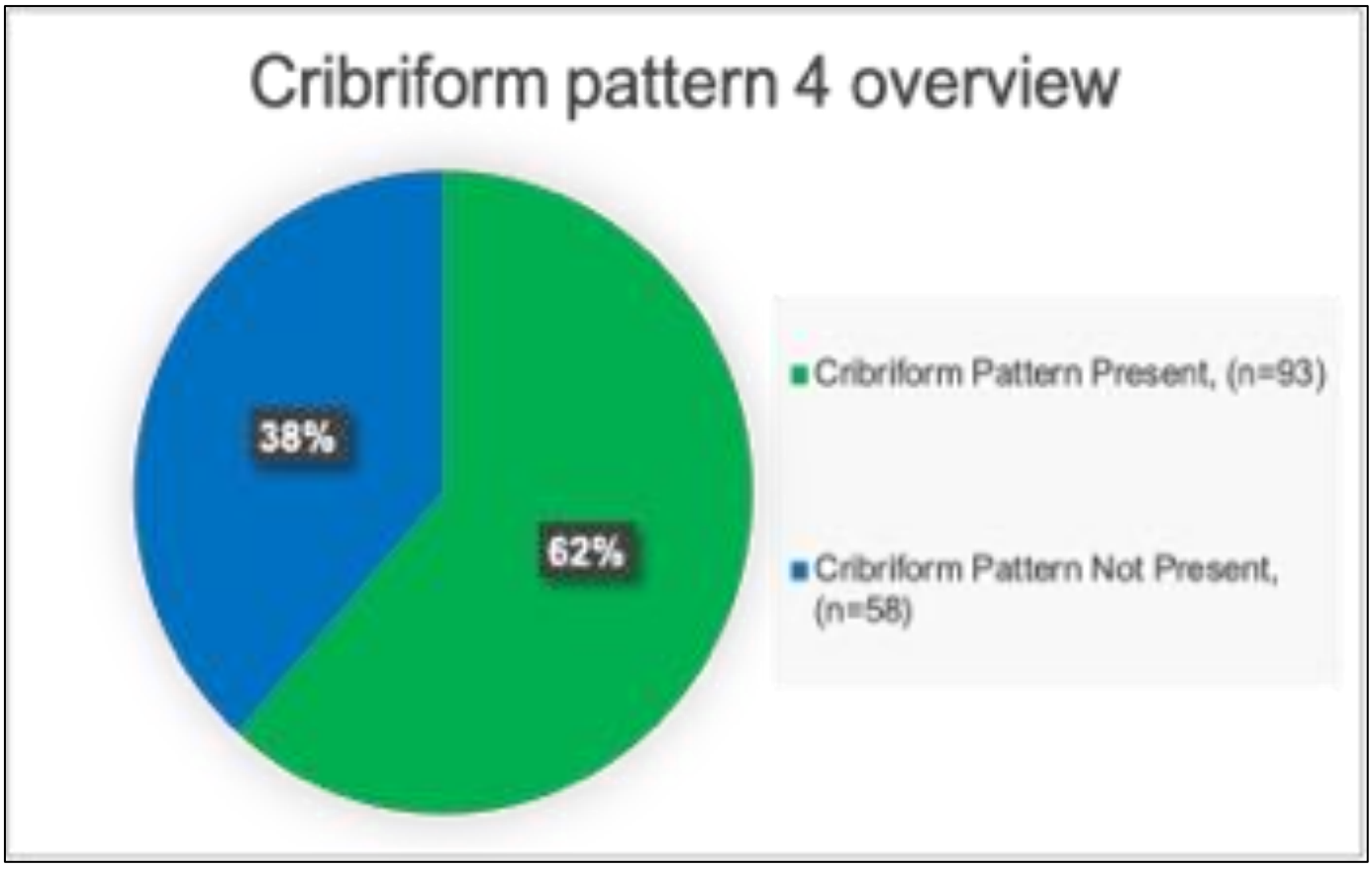

Fig 1: An Overview of the Cribriform Pattern 4 of Prostate Adenocarcinomas on Biopsies

Table 2: Univariable Cox Regression Analysis for Disease-Specific Survival of Cribriform Pattern 4 of Prostatic Adenocarcinoma

Characteristic	Hazard Ratio	95% Confidence Interval	P value
Cribriform pattern 4 of Prostatic adenocarcinoma	93 (61.5%)	71.1 years	<0.001

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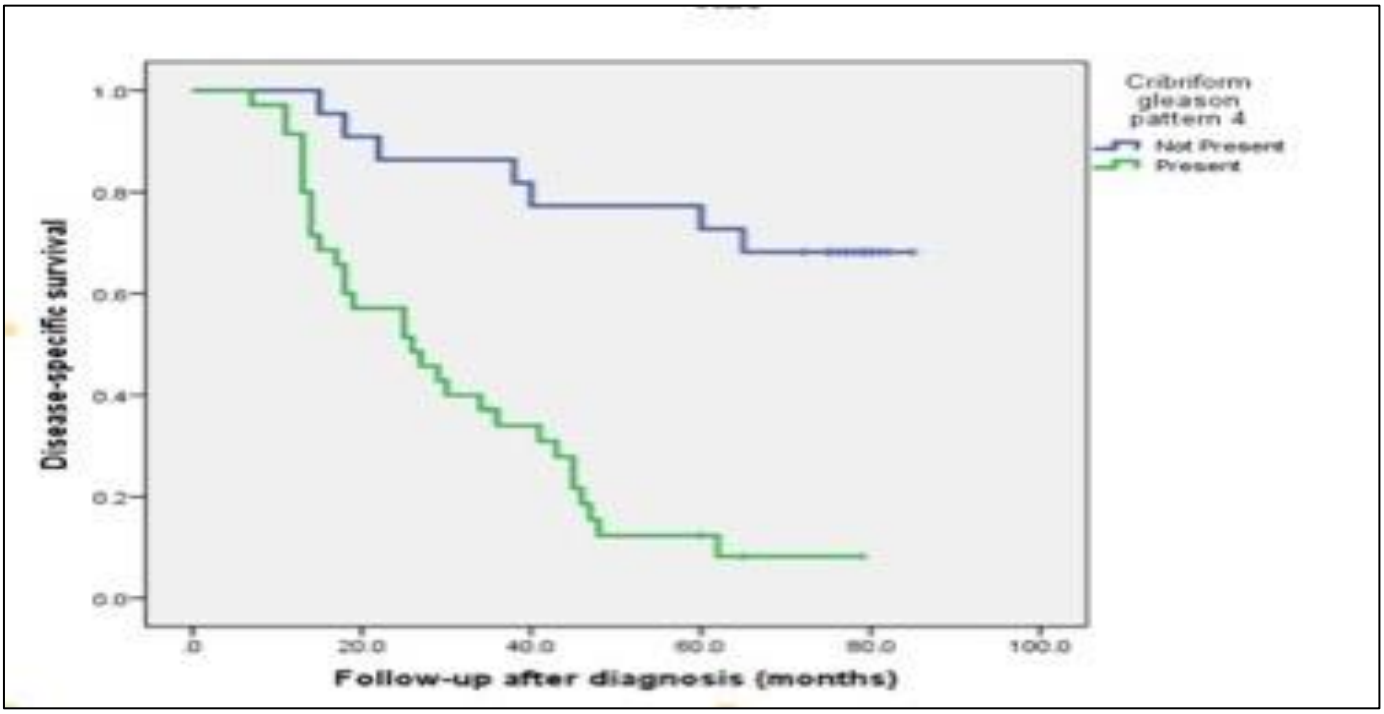

Fig 2: Disease-Specific Survival Rate Stratified by Cribriform Pattern 4.

IV. DISCUSSION

The prognosis for prostatic adenocarcinoma depends on various clinical and pathological factors that help guide treatment and predict outcomes. Critical factors for prognosis include the tumor stage, Gleason score, and prostate-specific antigen (PSA) levels at diagnosis. These factors form the basis for assessing the likelihood of disease progression and overall patient survival. Our study examined the presence of cribriform pattern 4 in prostatic adenocarcinomas and its relationship to prognostic factors. The cribriform and non-cribriform pattern of the prostate is shown in Figures 3,4,5 and 6. Disease-specific survival was independently predicted by cribriform architecture. Our study showed 61.5% of adenocarcinomas with Gleason pattern 4 had cribriform architecture and poor clinical outcomes.

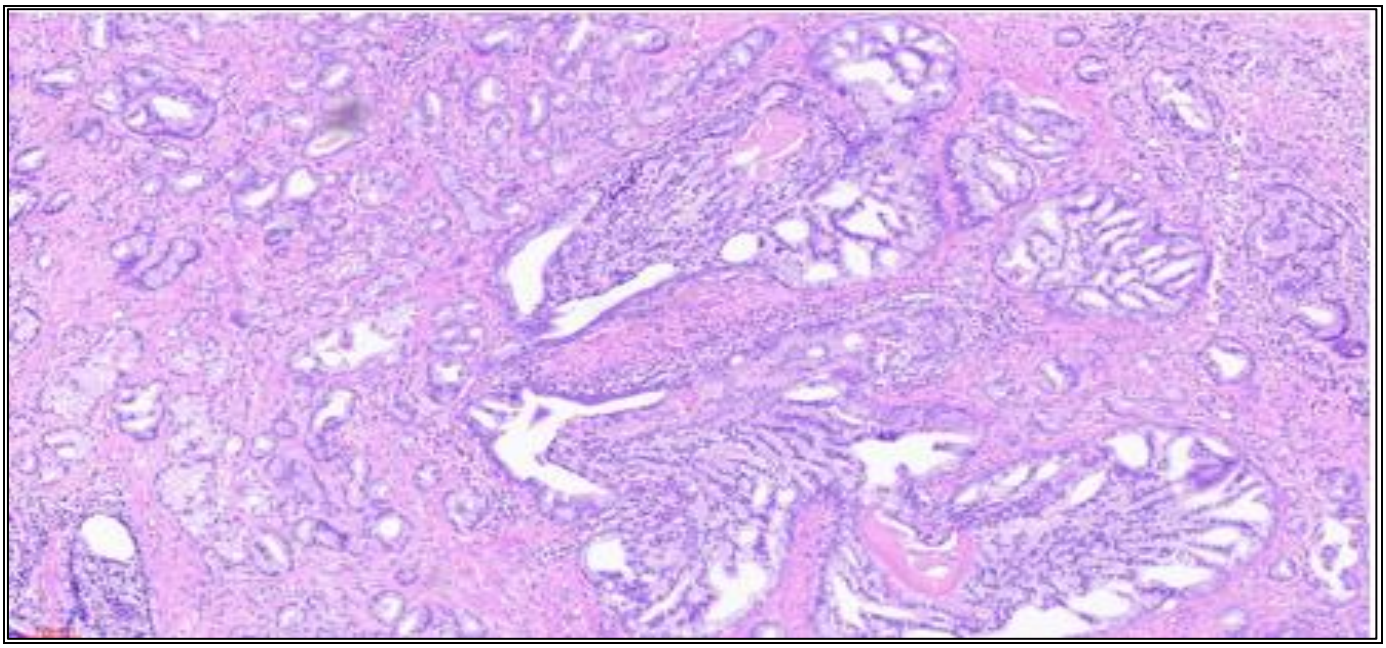

Fig 3: Cribriform Gleason Pattern 4 (hematoxylin-eosin ×200x)

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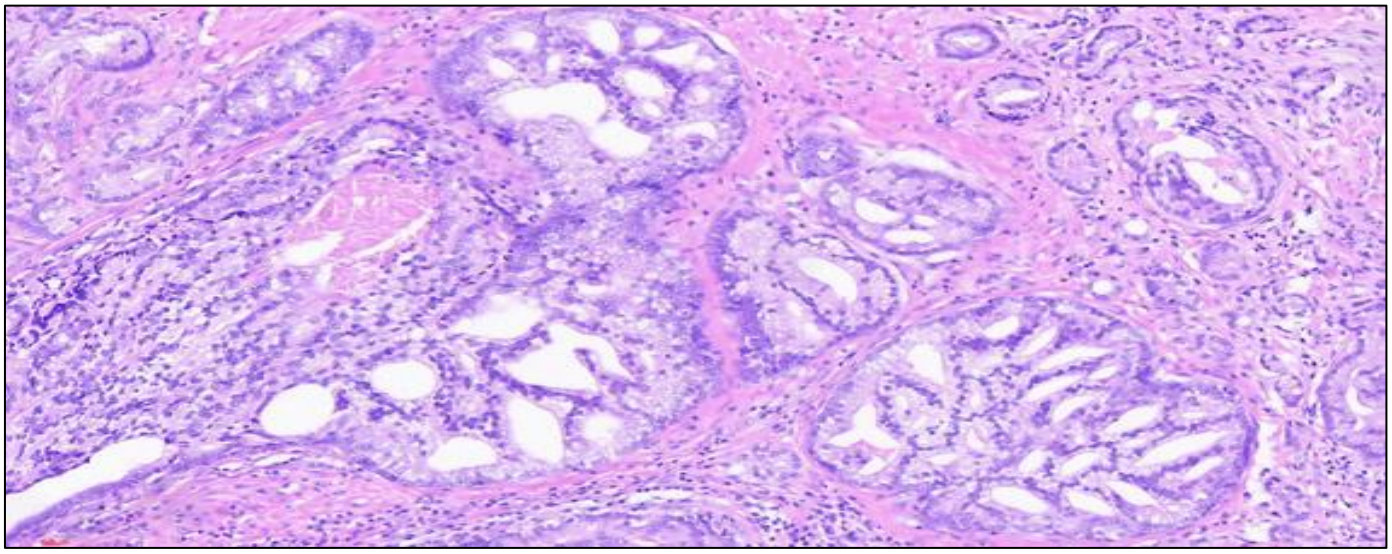

Fig 4: Cribriform Gleason Pattern 4 (hematoxylin-eosin ×400x).

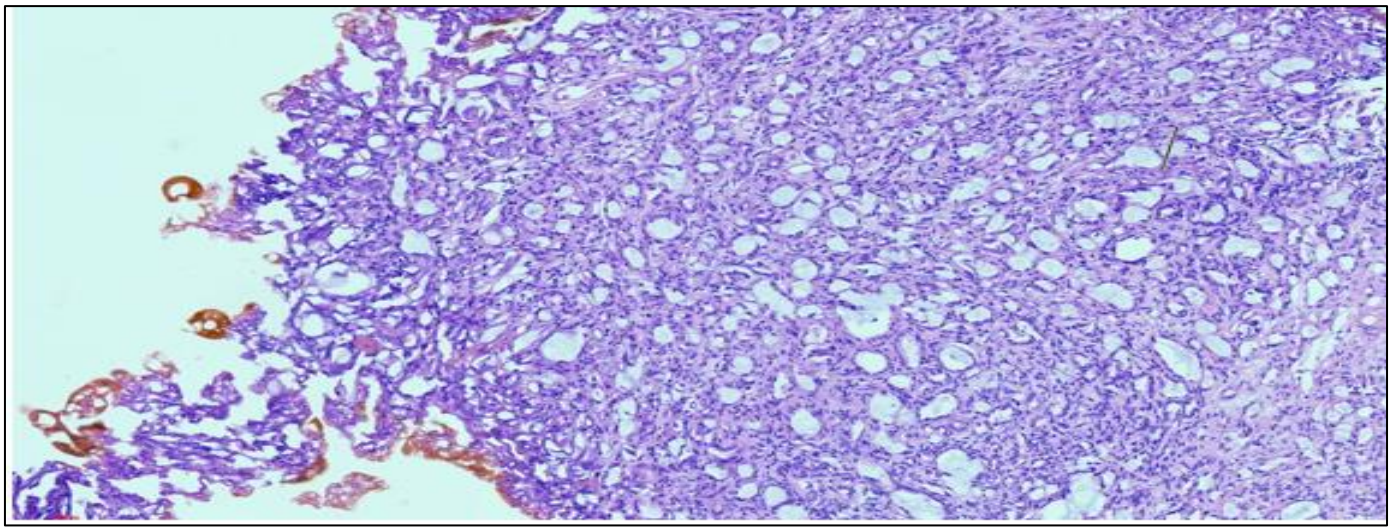

Fig 5: Non-Cribriform Gleason Pattern 4. (hematoxylin-eosin ×200x).

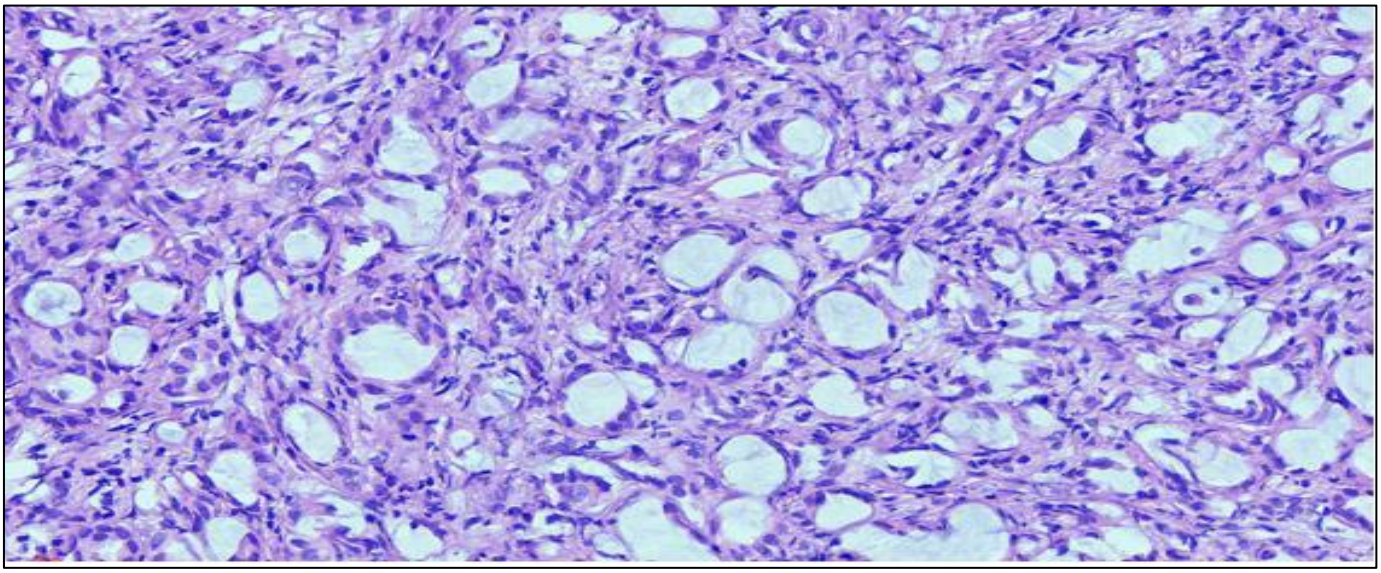

Fig 6: Non-Cribriform Gleason Pattern 4. (Hematoxylin-Eosin ×400x).

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According to Sayan et al.'s study, specific genes, including KRT13, KRT5, KRT15, COL17A1, KRT14, KRT16, and TP63, showed significantly lower mRNA expression levels in patients with cribriform pattern 4 than those without, suggesting that complex genetic changes are responsible for cribriform pattern 4 of prostate cancer (9). Oufattole et al. found that cribriform morphology in Gleason patterns is a predictive factor of biochemical recurrence after radical prostatectomy and is associated with a higher frequency of lymphovascular invasion. As demonstrated by Okubo et al., the cribriform morphology of Gleason 4 adenocarcinomas is a predictive risk factor for lymph node metastasis (10). The cribriform pattern is reported to be more common among cancers with Gleason scores 4 + 3 than cancers with Gleason scores 3 + 4, and there is an association between Gleason pattern 4 percentage and biochemical recurrence (11). A significant increase in adverse outcomes has been reported in patients with prostate cancer with large cribriform glands (more than 0.25 mm in diameter) compared to those with small cribriform glands (less than 0.25 mm in diameter) or without cribriform glands (12). A study conducted by Chen et al. also demonstrated that patients with Gleason 7 prostate cancer with cribriform Gleason pattern 4 were more likely to exhibit adverse pathological characteristics such as extraprostatic extension and positive surgical margins as well as shorter survival times when the cribriform gland was large or more significant than twenty percent (13). According to Choy et al., patients with a Gleason score of seven and cribriform architecture experienced a reduction in biochemical recurrence-free survival over five years. In contrast, patients with non-cribriform patterns, including glomeruloid architecture, experienced higher biochemical recurrence-free survival over that same period. (14). There is a greater likelihood of lymph node metastasis and extraprostatic spread among patients with prostate cancer with Gleason group grade 2 and cribriform architecture, according to Hollemans et al. In addition, the size of the invasive cribriform tumor correlates with its pathologic stage, and patients with large invasive cribriform tumors had more positive lymph nodes than patients with small invasive cribriform tumors (15). The findings of our study contribute to the growing body of literature that supports the importance of Gleason 4 cribriform patterns in terms of prognosis and are in line with the previous work of Keldem et al. in which they conducted a multivariate Cox regression and log-rank analysis of diagnostic biopsies obtained from 1031 patients who had been followed for an average of 13 years (16). The findings of the study by Keldem et al. demonstrated that invasive cribriform and intraductal carcinomas were independently associated with poorer disease-specific survival in pre-treatment biopsies with a hazard ratio of 2.6, 95% Confidence Interval of 1.4–4.8, and a P value of 0.002 (17).

- **Acknowledgment:** None

- **Disclosure of Conflict of Interest:** None

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