Annals of Diagnostic Pathology 39 (2019) 59–62

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Prostatic ductal adenocarcinoma with cribriform architecture has worse prognostic features than non-cribriform-type

Sammy Au[a,*], Carlos F. Villamil[b], Reza Alaghehbandan[c], Gang Wang[b]

[a] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
[b] Department of Pathology and Laboratory Medicine, BC Cancer Agency, Vancouver, BC, Canada
[c] Department of Pathology, Royal Columbian Hospital, New Westminster, BC, Canada

ARTICLE INFO

Keywords:
Prostate cancer
Prostatic ductal adenocarcinoma
Prostatic neoplasms

ABSTRACT

Prostatic ductal adenocarcinoma (PDA) is a rare histologic subtype of prostate cancer characterized by large glands lined with tall columnar pseudostratified epithelium. PDA has several architectural patterns, with papillary and cribriform being the most common. The cribriform pattern of acinar carcinoma has shown to be associated with a worse prognosis in terms of disease progression and disease-specific mortality. However, the significance of cribriform pattern in PDA is unknown. In this study, we sought to compare the adverse pathologic features between cribriform-type and non-cribriform-type PDA, and between PDA and acinar carcinoma with Gleason scores 8–10. We identified PDA cases diagnosed between 2008 and 2018 and 428 radical prostatectomy (RP) specimens containing Gleason 8–10 acinar carcinoma. The slides of all PDA cases were reviewed, and pathologic features were recorded. We found that the vast majority of PDA contained admixed acinar carcinoma, with a median percentage of the ductal component of 50% (range 5–100). 29% of PDA was graded as Grade Group 4 and 35.5% as Grade Group 5. At the time of RP, 45.2% of cases presented as pathologic stage T3a and 29% as T3b. Cribriform-type PDA demonstrated a significantly higher likelihood of extraprostatic extension (84% vs 33.3%, $p = 0.01$), seminal vesical invasion (36% vs 0%, $p = 0.04$), lymphovascular invasion (40% vs 0%, $p = 0.03$) and advanced pathologic stage (84% vs 33.3%, p = 0.01) compared to PDA without cribriform architecture. The proportion of stage ≥ pT3 tumors in PDA was similar compared to that in Gleason 8–10 acinar carcinoma (74.2% vs 70.8%, $p = 0.68$).

1. Introduction

Prostatic ductal adenocarcinoma (PDA) is a rare but aggressive subtype of prostate cancer characterized by tall columnar epithelium with elongated nuclei [1-3]. PDA has several architectural patterns, with papillary and cribriform being the most common [1,2,4]. PDA is often found admixed with acinar carcinoma, with the PDA component typically graded as Gleason grade 4, as it has demonstrated to behave similar to Gleason 4 + 4 acinar carcinoma [1,3,4].

In conventional acinar carcinoma, there is a growing body of evidence that the cribriform pattern of Gleason grade 4 carcinoma is associated with a worse prognosis in terms of disease progression and disease-specific mortality [5]. In radical prostatectomy (RP) specimens, the presence of invasive cribriform carcinoma has shown to be a predictive factor for distant metastasis and death from prostate cancer [6]. Cribriform pattern is also seen in PDA. However, the significance of cribriform architecture in PDA is unknown. In this study, we aimed to compare the adverse pathologic features between cribriform-type and non-cribriform-type PDA, and between PDA and acinar carcinoma with Gleason scores 8–10.

2. Materials and methods

The study had research ethics approval by the institutional review boards (#H18-01526). Cases of PDA and acinar carcinoma were identified via Sunset (searchable database of all pathology reports in British Columbia). We identified all cases of PDA diagnosed on needle core biopsies, transurethral resections (TUR) and/or radical prostatectomies between May 2008 and May 2018. Thirty-one cases underwent RP. Cases of PIN-like ductal adenocarcinoma were excluded from the study as they have been shown to behave similar to Gleason 3 + 3 prostate cancer [7]. For the acinar carcinoma group, we identified 428 radical prostatectomy specimens with Gleason scores 8–10 between May 2012 and May 2018.

* Corresponding author.
E-mail addresses: sammyau@alumni.ubc.ca (S. Au), carlos.villamil@bccancer.bc.ca (C.F. Villamil), gang.wang1@bccancer.bc.ca (G. Wang).

https://doi.org/10.1016/j.anndiagpath.2019.02.007

1092-9134/ © 2019 Elsevier Inc. All rights reserved.

Slides from all cases of PDA were retrieved and reviewed by at least one urologic pathologist. In addition to patient's age and pre-treatment prostate specific antigen (PSA) level, the following pathologic features were recorded: percentage of PDA component in mixed tumors, architecture of PDA, Gleason grade of acinar carcinoma component, overall Gleason score, pathologic stage, presence of extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymphovascular invasion (LVI), margin involvement, lymph node metastases, and presence of intraductal carcinoma (IDC). The PDA components were assigned Gleason Pattern 4, and the areas of comedonecrosis in PDA were graded as Gleason 5.

The adverse pathologic features and pathologic stage were compared between cribriform-type and non-cribriform-type PDA. In addition, the pathologic stage was compared between PDA and Gleason 8–10 acinar carcinoma.

Statistical analyses were performed using the software STATA 13 (StataCorp, College Station, Texas). Data were summarized using mean or median for continuous variables and number or percentage for categorical variables. Comparison between groups was performed using Fisher's exact test. Statistical significance was set at a p-value of 0.05.

3. Results

The median age at diagnosis for PDA was 71 years (range 43–91) with a median pre-treatment PSA of 8.4 ng/mL (range 1.3–28). Of the 45 cases of PDA, 16 (35.6%) were diagnosed on needle biopsy, 10 (22.2%) on TUR, and 19 (42.2%) on radical prostatectomy. Twelve (46.2%) of the 26 PDA cases diagnosed on needle biopsy or TUR underwent subsequent radical prostatectomy for a total of 31 RP specimens in the PDA group.

At RP, the vast majority (30/31, 96.8%) of cases contained PDA admixed with acinar carcinoma. The median percentage of the ductal component was 50% (range 5–100). Cribriform pattern of acinar carcinoma was present in 23.3% (7/30) of mixed PDA cases, and IDC was identified in 32.3% (10/31). The Grade Group (GG) distribution was as follows: 16.1% (5/31) were graded as GG2, 19.4% (6/31) as GG3, 29% (9/31) as GG4, and 35.5% (11/31) as GG5. The pathologic stage at RP was as follows: 26% (8/31) were stage pT2, 45.2% (14/31) were pT3a and 29% (9/31) were pT3b. 74.2% (23/31) of cases were positive for extraprostatic extension and 29% (9/31) for seminal vesical invasion (Fig. 1). 54.8% (17/31) of cases had positive margins and 16.1% (5/31) had lymph node metastases. LVI was present in 32.3% (10/31) of cases. 19.4% (6/31) of PDA had papillary architecture only, 3.2% (1/31) had cribriform architecture only, and 77.4% (24/31) had both papillary and cribriform architecture.

The clinicopathologic features of cribriform-type and non-cribriform-type PDA at RP are shown in Table 1. There was no significant difference in mean age and mean PSA between the two groups ($p = 0.30$ and $p = 0.46$, respectively). There was a statistically significant difference in Grade Group distribution ($p = 0.02$), with lower proportions of Grade Groups 2 and 4 and higher proportions of Grade Groups 3 and 5 in the cribriform PDA group. Cribriform acinar carcinoma was present in 5 of 25 cribriform PDA and 2 of 6 PDA without cribriform architecture. IDC was identified in 7 of 25 cribriform PDA and 3 of 6 PDA without cribriform architecture.

Compared to PDA without cribriform architecture, those with cribriform pattern demonstrated a significantly higher likelihood of EPE (84% vs 33.3%, $p = 0.01$), seminal vesical invasion (36% vs 0%, $p = 0.04$), LVI (40% vs 0%, $p = 0.03$) and advanced pathologic stage (pT3a or higher) (84% vs 33.3%, p = 0.01). There was no statistically significant difference in positive margins (52% vs 66.7%, $p = 0.52$) or lymph node metastases (20% vs 0%, $p = 0.12$).

Of the cases with EPE, 73.9% (17/23) had PDA with cribriform pattern in the EPE component. The remainder of the cases with EPE had Gleason 4 acinar carcinoma (4/23, 17.4%), Gleason 3 acinar carcinoma (1/23, 4.3%), and PDA with papillary architecture (1/23, 4.3%) in the EPE component. Of the cases with positive margins, 29.4% (5/17) had PDA with cribriform pattern at the margin. The remainder of the cases had acinar type carcinoma at the margin (23.5% Gleason 3, 35.3% Gleason 4 and 11.8% Gleason 5).

There were 12 cases showing pure PDA on initial biopsy or TUR. One case demonstrated invasion into the bladder wall on the TUR specimen. Four cases underwent subsequent RP, with three cases showing an admixed acinar component. The one RP specimen showing pure PDA was graded as Grade Group 5 with Gleason Pattern 5 comedonecrosis.

The pathologic stage distribution of the purely acinar carcinoma group was as follows: 29.2% (125/428) were stage pT2, 33.2% (142/428) were pT3a and 37.6% (161/428) were pT3b. The Grade Group distribution was: 36.7% (157/428) Grade Group 4 and 63.3% (271/428) Grade Group 5. The proportion of cases with advanced pathologic stage in this acinar carcinoma group was similar to that in the PDA group (70.8% vs 74.2%, $p = 0.68$). Similarly, there was no significant difference in the proportion of cases with advanced pathologic stage between cribriform PDA and Gleason 8–10 acinar carcinoma (84% vs 70.8%, $p = 0.15$).

4. Discussion

Prostatic ductal adenocarcinoma is an unusual variant of prostate cancer with a more aggressive behavior than conventional acinar carcinoma [1-3]. In this study, 64.5% of cases with a PDA component presented as Grade Group 4 or 5. Similarly, a study by Samaratunga et al. [8] found that 65% of their PDA cases had Gleason scores of 8–10.

PDA has been shown to behave similar to Gleason 4 + 4 acinar carcinoma [1,3,9]. In this study, we found that the majority of PDA cases presented at advanced pathologic stage, similar to the findings from other studies [1,3,4,8,10]. A review of the surveillance, epidemiology and end results (SEER) program data in the United States revealed that PDA had a greater proportion presenting with higher stages, a higher likelihood of metastatic disease, and an almost threefold higher rate of death than acinar carcinoma [3,11]. Samaratunga et al. [8] reported a high rate of advanced disease at the time of RP, with 73% extraprostatic extension, in PDA. Another study showed similar results, with 66.7% of cases showing EPE and 66.7% with positive surgical margins [4].

Compared to Gleason 8–10 acinar carcinoma, we found that PDA had a similar percentage of tumors with stage ≥T3. A study by Packiam et al. [12] reported more favorable pathologic features in PDA compared to Gleason 8–10 acinar carcinoma, with a smaller percentage, with stage ≥T3 (39% vs 52%, $p < 0.001$), with lymph node metastases (4% vs 11%, $p < 0.001$), and with positive margins (25% vs 33%, $p < 0.001$). This difference could be due to different Gleason scores of PDA cases included in each study and/or a different percentage of cases having cribriform morphology, either in Gleason pattern 4 acinar carcinoma or in PDA. Despite this, the study found similar outcomes in terms of mortality and disease-specific survival between PDA and acinar carcinoma of Gleason scores 8–10.

When pure PDA is identified in a needle biopsy of the prostate, it is possible that some areas of the tumor, potentially containing an admixed acinar component, may not have been sampled in the biopsy. In our study, among the initial biopsies and TURs showing PDA without combined acinar carcinoma, three of the four cases that underwent subsequent RP demonstrated an admixed acinar component in the RP specimen. Some studies have shown that patients with pure PDA may have a better prognosis than those with mixed tumors, with reported mean survivals of 13.9 and 8.9 years, respectively [13]. However, pure PDA is uncommon; PDA is almost always found combined with acinar carcinoma [4]. In our study, only one of the RP cases showed pure PDA with the remainder showing mixed ductal and acinar carcinoma.

Conversely, PDA may be missed on initial biopsy, with the biopsy sample showing only the acinar carcinoma component. Indeed, 42% of

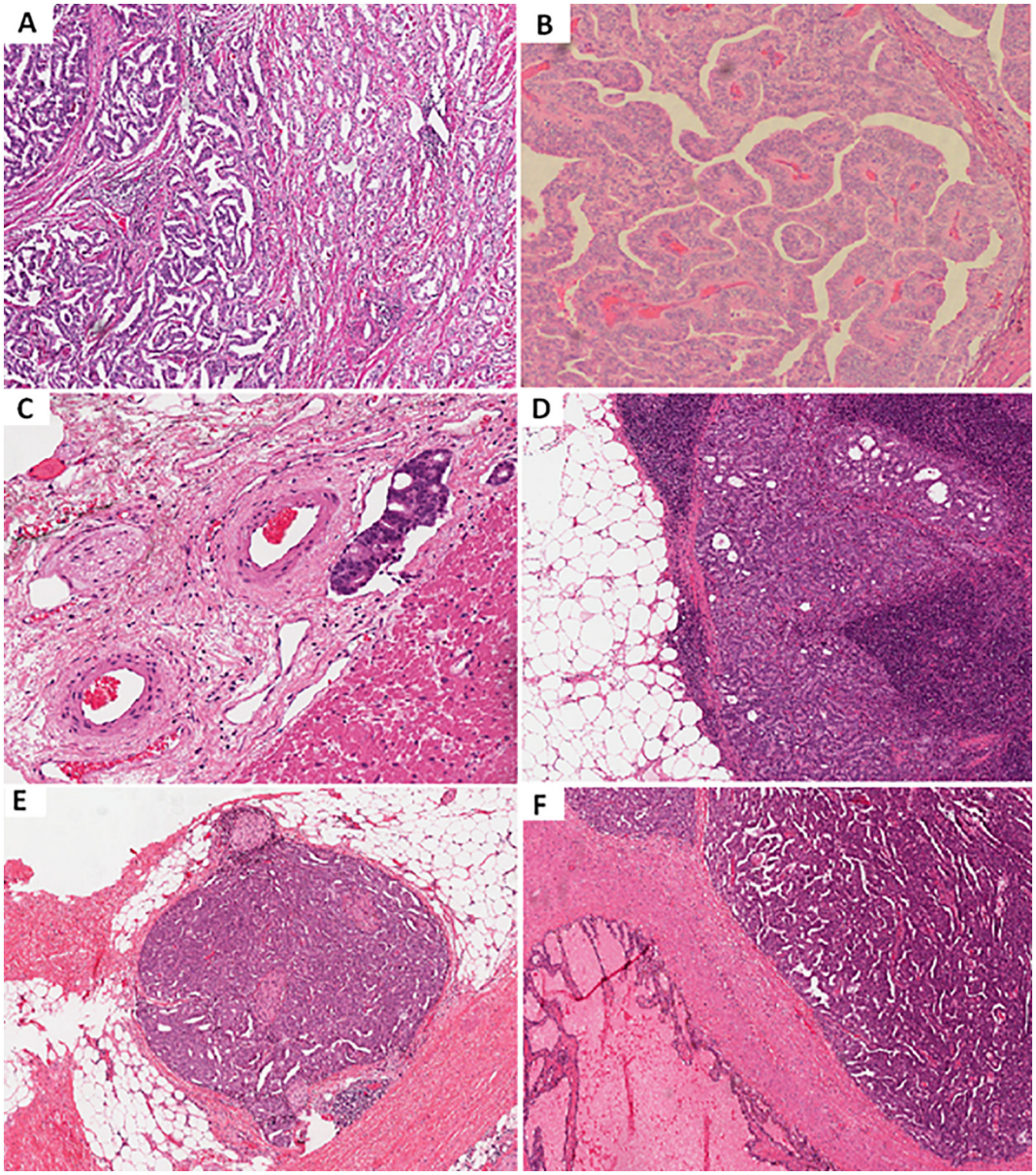

Fig. 1. Prostatic ductal adenocarcinoma. A. PDA and acinar type carcinoma in the same tumor. B. PDA with papillary architecture. C. Cribriform-type PDA with lymphovascular invasion. D. Cribriform-type PDA with lymph node metastasis. E. Cribriform-type PDA with extraprostatic extension. F. Cribriform-type PDA with seminal vesical invasion.

PDA cases in this study were diagnosed only at RP, with an initial biopsy or TUR showing adenocarcinoma without a PDA component. Similarly, Tu et al. [13] found that 54% of PDA cases were diagnosed only at the time of RP.

The two most common architectural forms seen in PDA are papillary and cribriform [1,2,4,14,15]. To our knowledge, this is the first study to evaluate the significance of cribriform pattern in PDA. In conventional acinar carcinoma, there is a growing body of evidence that cribriform pattern is more aggressive than the other patterns of Gleason grade 4 carcinoma [5,6]. In this study, we found that PDA with cribriform architecture, with or without admixed papillary architecture, were significantly more likely to present at advanced pathologic stage and had a significantly higher likelihood of lymphovascular invasion, seminal vesical invasion and extraprostatic extension compared to PDA without cribriform architecture. Moreover, the extraprostatic component consisted of cribriform-type PDA in 73.9% of cases. Further studies are needed to compare the long-term outcomes between cribriform-type and non-cribriform-type PDA.

One of the common differential diagnoses for cribriform-type PDA is intraductal carcinoma (IDC) [16]. The cribriform pattern of PDA is composed of tall pseudostratified columnar epithelium and back-to-back large glands forming slit-like lumens [1]. Likewise, the intraductal growth of PDA has cellular features of PDA, such as columnar epithelium with stratified elongated nuclei [4]. In contrast, IDC is composed of more rounded, cuboidal cells and cribriform patterns with rounded lumens [17]. Further complicating this distinction, it has been reported that IDC co-exists with PDA in 16% of RP specimens, and > 31.4% of PDA also show intraductal growth [18].

There are several limitations in this study. Although we were able to identify and review all cases that were diagnosed as PDA, we may not have captured undiagnosed cases of PDA, particularly if only a needle biopsy was performed as this could miss sampling of a PDA component of the tumor. Additionally, radical prostatectomies that were not completely submitted for histologic assessment may have created a source of bias, such as underrepresenting the PDA component of the tumor, particularly if of small volume. In this study, 77.4% (24/31) of

Table 1
Clinicopathologic features of prostatic ductal adenocarcinoma at radical prostatectomy.

Clinicopathologic features	PDA with cribriform pattern ($N = 25$)	PDA without cribriform pattern ($N = 6$)	p-value
Age, years			
Mean (range)	67 (43–76)	70 (64–73)	0.30
PSA, ng/mL			
Mean (range)	7.1 (1.8–23.3)	8.5 (1.5–26.6)	0.46
Grade group, n (%)			
2	2 (8)	3 (50)	0.01
3	6 (24)	0	0.19
4	6 (24)	3 (50)	0.22
5	11 (44)	0	0.04
pT category, n (%)			
2	4 (16)	4 (66.7)	0.17
≥3	21 (84)	2 (33.3)	0.01
Extraprostatic extension, n (%)	21 (84)	2 (33.3)	0.01
Seminal vesical invasion, n (%)	9 (36)	0	0.04
Positive margins, n (%)	13 (52)	4 (66.7)	0.52
Lymphovascular invasion, n (%)	10 (40)	0	0.03
Lymph node metastases, n (%)	5 (20)	0	0.12
Percentage of PDA component, %			
Mean (range)	53 (5–100)	32 (5–80)	0.24

the RP cases were completely submitted. Another limitation is that the group of Gleason 8–10 acinar carcinoma included in the study may have varying proportions of Grade Groups 4 and 5 and subtypes of Gleason 4. However, we included all RP specimens during the study time period in order to provide a representative sample.

To conclude, the majority of PDA presented as Grade Group 4 or 5 and with advanced stage at RP. The presence of cribriform architecture in PDA is associated with a significantly higher likelihood of extraprostatic extension, seminal vesical invasion, lymphovascular invasion and advanced pathologic stage compared to non-cribriform-type PDA.

Declarations of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors have no funding sources to disclose.

References

[1] Seipel AH, Delahunt B, Samaratunga H, et al. Ductal adenocarcinoma of the prostate: histogenesis: biology and clinicopathological features. Pathology 2016;48:398–405.
[2] Humphrey PA. Histological variants of prostatic carcinoma and their significance. Histopathology 2012;60:59–74.
[3] Meeks JJ, Zhao LC, Cashy J, et al. Incidence and outcomes of ductal carcinoma of the prostate in the USA: analysis of data from the Surveillance, Epidemiology, and End Results program. BJU Int 2012;109:831–4.
[4] Seipel AH, Wiklund F, Wiklund NP, et al. Histopathological features of ductal adenocarcinoma of the prostate in 1,051 radical prostatectomy specimens. Virchows Arch 2013;462:429–36.
[5] Siadat F. Cribriform morphology in prostate pathology. Diagn Histopathol 2018;24(6):215–9.
[6] Kweldam CF, Wildhagen MF, Steyerberg EW, et al. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Mod Pathol 2015;28:457–64.
[7] Tavora F, Epstein JI. High-grade prostatic intraepithelial neoplasia like ductal adenocarcinoma of the prostate: a clinicopathologic study of 28 cases. Am J Surg Pathol 2008;32:1060–7.
[8] Samaratunga H, Duffy D, Yaxley J, et al. Any proportion of ductal adenocarcinoma in radical prostatectomy specimens predicts extraprostatic extension. Hum Pathol 2010;41:281–5.
[9] Brinker DA, Potter SR, Epstein JI. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. Am J Surg Pathol 1999;23:1471–9.
[10] Lee TK, Miller JS, Epstein JI. Rare histological patterns of prostatic ductal adenocarcinoma. Pathology 2010;42:319–24.
[11] Morgan TM, Welty CJ, Vakar-Lopez F, et al. Ductal adenocarcinoma of the prostate: increased mortality risk and decreased serum prostate specific antigen. J Urol 2010;184:2303–7.
[12] Packiam VT, Patel SG, Pariser JJ, et al. Contemporary population-based comparison of localized ductal adenocarcinoma and high-risk acinar adenocarcinoma of the prostate. Urology 2015;86:777–82.
[13] Tu SM, Lopez A, Leibovici D, et al. Ductal adenocarcinoma of the prostate: clinical features and implications after local therapy. Cancer 2009;115:2872–80.
[14] Amin A. Prostate ductal adenocarcinoma. Appl Immunohistochem Mol Morphol 2018;26(7):514–21.
[15] Hertel JD, Humphrey PA. Ductal adenocarcinoma of the prostate. J Urol 2011;186:277–8.
[16] Seipel AH, Delahunt B, Samaratunga H, et al. Diagnostic criteria for ductal adenocarcinoma of the prostate. Interobserver variability among 20 expert uropathologists. Histopathology 2014;65:216–27.
[17] Wobker SE, Epstein JI. Differential diagnosis of intraductal lesions of the prostate. Am J Surg Pathol 2016;40:e67–82.
[18] Herawi M, Epstein JI. Immunohistochemical antibody cocktail staining (p63/HMWCK/AMACR) of ductal adenocarcinoma and Gleason pattern 4 cribriform and noncribriform acinar adenocarcinomas of the prostate. Am J Surg Pathol 2007;31:889–94.