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The heterogeneity of intraductal carcinoma of the prostate is associated with different efficacy of standard first-line therapy for patients with metastatic castration-resistant prostate cancer

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Abstract

Background: To explore whether metastatic castration-resistant prostate cancer (mCRPC) patients with distinct intraductal carcinoma of the prostate (IDC-P) subtypes respond differently to abiraterone and docetaxel treatment.

Methods: We retrospectively analyzed data of 170 mCRPC patients receiving abiraterone or docetaxel as first-line therapy. PSA response, PSA progression-free survival (PSA-PFS), radiographic progression-free survival (rPFS), and overall survival (OS) were analyzed based on the presence of IDC-P and its subpatterns.

Results: IDC-P was confirmed in 91/170 (53.5%) patients. Among them 36/91 (39.6%) and 55/91 (60.4%) harbored IDC-P patterns 1 and 2, respectively. Patients with IDC-P pattern 1 shared similar clinical outcomes to those without IDC-P in both abiraterone and docetaxel treatment. However, against cases without IDC-P or with IDC-P pattern 1, patients with IDC-P pattern 2 had markedly poorer prognosis in either abiraterone (mPSA-PFS: 11.9 vs. 11.1 vs. 6.1 months, $p < 0.001$; mrPFS: 18.9 vs. 19.4 vs. 9.6 months, $p < 0.001$) or docetaxel (mPSA-PFS: 6.2 vs. 6.6 vs. 3.0 months, $p < 0.001$; mrPFS: 15.1 vs. 12.6 vs. 5.5 months, $p < 0.001$) treatment. For patients without IDC-P, docetaxel had comparable therapeutic efficacy with abiraterone. However, the efficacy of docetaxel was significantly inferior to abiraterone in patients with either IDC-P pattern 1 (mPSA-PFS: 6.6 vs. 11.1 months, $p = 0.021$;

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mrPFS: 12.6 vs. 19.4 months, $p = 0.027$) or pattern 2 (mPSA-PFS: 3.0 vs. 6.1 months, $p = 0.003$; mrPFS: 5.5 vs. 9.6 months, $p = 0.007$).

Conclusion: Compared to docetaxel, abiraterone exhibited better efficacy in patients with IDC-P of either pattern. However, IDC-P pattern 2 responded unsatisfactorily to either abiraterone or docetaxel therapy. Novel therapeutic strategies for IDC-P pattern 2 need further investigations.

KEYWORDS

abiraterone, architectural pattern, docetaxel, intraductal carcinoma of the prostate, metastatic castration-resistant prostate cancer

1 | INTRODUCTION

Due to unique pathological characteristics and highly aggressive behavior, intraductal carcinoma of the prostate (IDC-P) was formally acknowledged by WHO as a distinct pathological entity of prostate cancer (PCa) in 2016.[1] The incidence of IDC-P increased from 2.1% in the low-risk localized PCa cohorts to 23.1%, 36.7%, and 56.0% in the intermediate-risk, high-risk, and metastatic PCa, respectively.[2]

The presence of IDC-P has now been widely acknowledged to be associated with poor prognosis throughout all stages of PCa.[3–9] For patients with localized PCa receiving either radical prostatectomy or radical radiation therapy, the existence of IDC-P was strongly correlated with rapid disease progression and shorter overall survival.[3,4] We also found that IDC-P was associated with unfavorable clinical outcomes even for patients with localized high-risk PCa.[5] Notably, tumoral heterogeneity also exists within IDC-P lesions. According to Epstein criteria and the 2016 WHO classification, IDC-P can be subclassified into two architectural patterns (pattern 1: loose cribriform or micropapillary; pattern 2: solid or dense cribriform).[10,11] Our recent studies uncovered that IDC-P pattern 2 exhibited more aggressive characteristics compared with IDC-P pattern 1 in patients with locally advanced PCa or metastatic hormone-sensitive prostate cancer (mHSPC).[5,12]

In our previous work, we found that IDC-P was still associated with poor prognosis in the metastatic castration-resistant prostate cancer (mCRPC) setting. For mCRPC patients receiving docetaxel (DOC) as first-line therapy, the presence of IDC-P in prostate biopsy specimen indicated poor clinical outcomes.[13] This finding was validated by another Japanese research.[14] Besides, the therapeutic efficacy of abiraterone (ABI) seemed to be superior to that of DOC as first-line therapy in mCRPC patients with IDC-P component. However, whether mCRPC patients with different IDC-P subpatterns had differential response to standard treatment of mCRPC is still unknown.

Therefore, the purpose of the current study is to explore whether patients with distinct subtypes of IDC-P (IDC-P pattern 1 and IDC-P pattern 2) display different response to ABI and DOC treatment, which might help physicians make more elaborative decisions in the treatment of mCRPC patients.

2 | MATERIALS AND METHODS

2.1 | Study design

Between 2014 and 2019, a total of 170 mCRPC patients were included in this study. All patients received random 12-core ultrasound-guided transperineal prostate biopsy at the time of initial diagnosis (the initial biopsy) and CRPC (the repeated biopsy) with written informed consents. All patients were treated with maximal androgen blockade at the initial diagnosis of metastatic PCa (medical or surgical castration plus bicalutamide 50 mg/day). After mCRPC was confirmed, 122 and 48 patients received ABI (abiraterone acetate 1000 mg/day plus prednisone 10 mg/day) and DOC (75 mg/m^2 q3w, plus prednisone 10 mg/day, maximized with 10 cycles) as first-line therapy, respectively. This study is based on a real-world cohort. For each CRPC patient, the treatment decision was determined based on several factors including patient's performance status, clinicians' suggestion, patient's desire, and patients' medical insurance. After the failure of first-line mCRPC treatment, 61/170 (35.9%) patients received sequential treatments.

Clinicopathological data of these patients were collected with institutional review board approval, including age, CRPC-free survival (CFS), IDC-P status, visceral metastasis, Eastern Cooperative Oncology Group (ECOG) score, baseline prostate-specific antigen (PSA) level at the time of CRPC, baseline serum hemoglobin (HGB) level, serum lactate dehydrogenase (LDH) level, and serum alkaline phosphatase (ALP) level at the time of mCRPC diagnosis, first-line therapy during mCRPC, and sequential treatments after disease progression. CRPC was defined according to 2014 EAU guidelines:[15] despite a castration testosterone level (<0.5 ng/ml), three consecutive rises in serum PSA, resulting in two 50% increases over the nadir, with a PSA > 2 ng/ml.

All biopsy pathological specimens were reviewed by two experienced urinary pathologists (Chen Ni and Nie Ling) independently, any disagreements were solved by discussion or consensus with a third urological pathologist. Previously we found that the incidence of IDC-P increased at the time of mCRPC against the initial diagnosis, which implies rebiopsy at mCRPC is more accurate to detect IDC-P than the initial biopsy.[8] Therefore, the detection of IDC-P was based on repeated biopsy and strictly defined by the Epstein criteria.[10] Gleason score was evaluated at initial diagnosis because it could not be evaluated accurately in CRPC

tissues due to response caused by androgen deprivation therapy (ADT). We performed immunohistochemical (IHC) staining and labeled basal cells with a triple antibody cocktail (AMACR/P63/HCK) for accurate diagnosis. IDC-P was separated into pattern 1-loose cribriform or micropapillary and pattern 2-solid or dense cribriform (Figure 1). Specimens containing both patterns were considered as pattern 2. Considering that the clinical significance of atypical intraductal proliferation (AIP) is debatable, our medical center does not routinely report the presence of AIP.

2.2 | Outcomes

The primary endpoints were PSA progression-free survival (PSA-PFS) and radiographic progression-free survival (rPFS), which were defined as the interval from the initial first-line therapy to PSA-progression or radiographic progression, respectively. PSA progression was defined as two consecutive rises in the PSA level of 25% or more above the nadir (and by ≥2 ng/ml) after the treatment initiation. Radiographic progression was defined as at least two new lesions on the first posttreatment scan, with at least two additional lesions on the next scan and/or progression in nodes or viscera on computer tomography (CT), aggravated bone pain, or death. The secondary endpoints were PSA response and overall survival (OS). PSA response was defined as ≥50% decline in PSA level from baseline, maintained for ≥4 weeks. OS was defined as the time from the initiation of first-line therapy after mCRPC to death from any cause.

2.3 | Statistical analysis

X^2 test was applied to compare the baseline characteristics and assessed PSA response. PSA-PFS, rPFS, and OS were assessed by Kaplan–Meier method. Log-rank test was used to compare the differences between the survival curves. The value of different clinicopathological factors in predicting PSA-PFS, rPFS, and OS were analyzed by Cox proportional hazards model. Parameters with $p < 0.10$ in univariate analyses were further tested in multivariate analyses. For continuous data, cut points of PSA and CFS were their median value, whereas cut points of LDH, ALP, and HGB were their upper or lower limit of normal. All statistical analyses were performed by SPSS version 25.0. A $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The baseline characteristics of 170 mCRPC patients are summarized in Table 1. In total, IDC-P was confirmed in 91/170 (53.5%) patients; 122 and 48 patients received ABI and DOC, respectively. Among the IDC-P carriers, 36/91 (39.6%) and 55/91 (60.4%) had IDC-P pattern 1 and pattern 2, respectively. Patients harboring IDC-P pattern 2 were relatively younger against those with IDC-P pattern 1 (Table 1). Other baseline factors were well balanced among different groups. The median time from the initial diagnosis to CRPC (CFS) was 13.5 months. The median follow-up time was 34.4 months for the whole cohort; 104/170 (61.2%) patients died during the follow-up. As shown in Table S1, 49/122 (40.2%) of our patients in ABI group and 12/48 (25.0%) in DOC group received one or more sequencing treatments after first-line therapy, including ABI ($n = 11$), DOC ($n = 35$), enzalutamide ($n = 7$), olaparib ($n = 6$), proxalutamide ($n = 3$), pembrolizumab ($n = 1$), pazopanib ($n = 1$), and everolimus ($n = 2$).

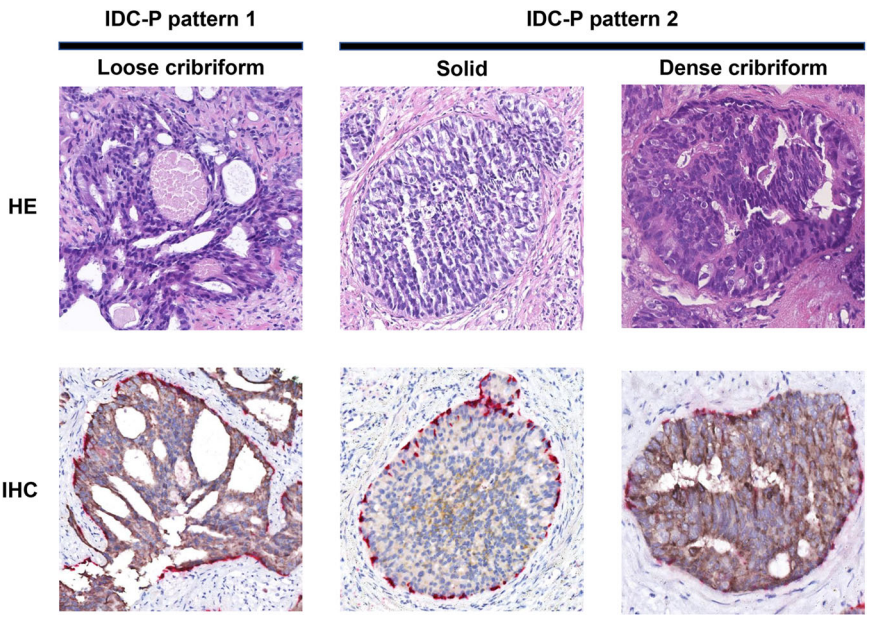

FIGURE 1 Histopathological features of intraductal carcinoma of the prostate architectural patterns. HE, hematoxylin–eosin staining; IHC, immunohistochemistry [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics of the total cohort

Variables	Total (*n* = 170)	Without IDC-P (*n* = 79)	With IDC-P (*n* = 91)		*p*
			Pattern 1 (*n* = 36)	Pattern 2 (*n* = 55)	
Age (years)					0.039
Median (IQR)	71.0 (65.0–76.0)	73.0 (68.0–78.0)	70.5 (62.0–76.25)	69.0 (64.0–73.0)	
≥70	99 (58.2%)	54 (68.4%)	19 (52.8%)	26 (47.3%)	
<70	71 (41.8%)	25 (31.6%)	17 (47.2%)	29 (52.7%)	
CFS (months)					0.761
Median (IQR)	13.5 (7.7–24.8)	14.4 (9.3–25.6)	13.4 (7.4–29.8)	11.6 (6.2–21.1)	
≥14	84 (49.4%)	41 (51.9%)	18 (50.0%)	25 (45.5%)	
<14	86 (50.6%)	38 (48.1%)	18 (50.0%)	30 (54.5%)	
GS, no.					0.046
<8	16 (9.4%)	9 (11.4%)	4 (11.1%)	3 (5.5%)	
8	18 (10.6%)	13 (16.5%)	4 (11.1%)	1 (1.8%)	
9–10	136 (80.0%)	57 (72.2%)	28 (77.8%)	51 (92.7%)	
Visceral metastasis, no.					0.793
Without	154 (90.6%)	71 (89.9%)	32 (88.9%)	51 (92.7%)	
With	16 (9.4%)	8 (10.1%)	4 (11.1%)	4 (7.3%)	
ECOG score, no.					0.415
0–1	152 (89.4%)	68 (86.1%)	33 (91.7%)	51 (92.7%)	
≥2	18 (10.6%)	11 (13.9%)	3 (8.3%)	4 (7.3%)	
PSA (ng/ml)					0.641
Median (IQR)	13.1 (4.4–66.9)	13.2 (4.8–94.2)	11.0 (5.1–27.4)	13.6 (4.1–46.6)	
≥13, no. (%)	86 (50.6%)	40 (50.6%)	16 (44.4%)	30 (54.5%)	
<13, no. (%)	84 (49.4%)	39 (49.4%)	20 (55.6%)	25 (45.5%)	
HGB (g/L)					0.836
Median (IQR)	128.0 (116.0–136.0)	127.0 (114.3–135.0)	128.5 (115.5–139.3)	129.0 (119.0–139.5)	
≥120, no. (%)	120 (70.6%)	54 (68.4%)	26 (72.2%)	40 (72.7%)	
<120, no. (%)	50 (41.7%)	25 (31.6%)	10 (27.8%)	15 (27.3%)	
LDH (IU/L)					0.585
Median (IQR)	206.0 (179.0–239.0)	207.5 (185.0–238.0)	209.5 (188.3–245.8)	189.0 (167.5–233.0)	
≥250, no. (%)	35 (20.6%)	17 (21.5%)	9 (25.0%)	9 (16.4%)	
<250, no. (%)	135 (79.4%)	62 (78.5%)	27 (75.0%)	46 (83.6%)	
ALP (IU/L)					0.898
Median (IQR)	109.0 (80.0–191.0)	113.0 (82.0–203.0)	108.0 (84.0–175.3)	104.0 (79.0–166.5)	
≥160, no.	47 (27.6%)	23 (29.1%)	9 (25.0%)	15 (27.3%)	
<160, no.	123 (72.4%)	56 (70.9%)	27 (75.0%)	40 (72.7%)	
Proportional ratio of sequential therapy					0.047
Yes	61 (35.9%)	27 (34.2%)	8 (22.2%)	26 (47.3%)	
No	109 (64.1%)	52 (65.8%)	28 (77.8%)	29 (52.7%)	

Abbreviations: ALP, alkaline phosphatase; CFS, castration-resistant prostate cancer-free survival; ECOG, Eastern Cooperative Oncology Group; GS, Gleason score; HGB, hemoglobin; IDC-P, intraductal carcinoma of the prostate; IQR, interquartile range; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

3.2 | Clinical outcomes of mCRPC in the whole cohort

For the total 170 patients, the median PSA-PFS, rPFS, and OS were 7.9, 13.7, and 24.8 months, respectively. The presence of IDC-P was associated with unfavorable clinical outcomes compared to those without IDC-P (PSA response rate: 42/91 [46.2%] vs. 50/79 [63.3%], $p = 0.025$, mPSA-PFS: 6.6 vs. 10.6 months, $p = 0.001$; mrPFS: 11.2 vs. 18.0 months, $p < 0.001$; mOS: 21.9 vs. 30.0 months, $p = 0.076$) (Figure S1). Among patients treated with ABI ($n = 122$), PSA response was achieved in 71/122 (58.2%) cases, the median PSA-PFS, rPFS, and OS were 9.1, 14.8, and 27.4 months, respectively. In DOC treatment, cohort ($n = 48$), PSA response occurred in 21/48 (43.8%) men, the median PSA-PFS, rPFS, and OS were 5.6, 8.9, and 21.5 months, respectively (Table S2).

3.3 | The prognostic value of IDC-P architectural patterns in patients treated with ABI

Among patients treated with ABI, PSA response was similar between cases with and without IDC-P (52.4% [33/63] vs. 64.4% [38/59], $p = 0.245$) (Figure S2A). However, IDC-P was associated with shorter median PSA-PFS (7.9 vs. 11.9 months, $p = 0.012$), rPFS (11.9 vs. 18.9 months, $p = 0.003$), and OS (25.4 vs. 31.1 months, $p = 0.031$) (Figure S2B–D). Multivariate Cox regression further confirmed that IDC-P, together with CFS, GS, HGB level, and ALP level, was one of the independent prognosticators predicting worse clinical outcomes in the first-line ABI treatment of mCRPC (PSA-PFS: HR = 1.90, 95% CI: 1.24–2.93, $p = 0.004$; rPFS: HR = 1.75, 95% CI: 1.14–2.69, $p = 0.011$; OS: HR = 1.46, 95% CI: 0.89–2.40, $p = 0.138$) (Table 2).

The therapeutic efficacy of ABI treatment in patients with different IDC-P subpatterns was further explored. Clinical outcomes of patients with IDC-P pattern 1 and those without IDC-P were similar (Figure 2). On the contrary, cases with IDC-P pattern 2 were associated with much poorer prognosis than patients with IDC-P pattern 1 (mPSA-PFS: 6.1 vs. 11.1 months, $p = 0.001$; mrPFS: 9.6 vs. 19.4 months, $p < 0.001$; mOS: 23.1 vs. 27.0 months, $p = 0.596$) or those without IDC-P (mPSA-PFS: 6.1 vs. 11.9 months, $p < 0.001$; mrPFS: 9.6 vs. 18.9 months, $p < 0.001$; mOS: 23.1 vs. 31.1 months, $p = 0.037$) (Figure 2B–D). Multivariate Cox regression after adjusting other prognosticators further strengthened these findings (Table 2).

3.4 | The prognostic value of different IDC-P architectural patterns in patients treated with DOC

Among patients treated with DOC, IDC-P was also a predictor of poor prognosis (Figure S3 and Table S3). IDC-P-carriers had shorter median PSA-PFS (5.1 vs. 6.2 months, $p = 0.038$), rPFS (6.8 vs. 15.1 months, $p = 0.011$) against the noncarriers (Figure S3B,C). Yet only numerically lower PSA response rate and shorter OS time were found in patients with IDC-P than those without IDC-P (PSA response: 9/28 [32.1%] vs. 12/20 [60.0%], $p = 0.055$; mOS: 17.8 vs. 22.3 months, $p = 0.569$) (Figure S3A,D). Multivariate Cox regression further confirmed that the presence of IDC-P, together with CFS and visceral metastasis, was an independent factor predicting rapid disease progression in DOC treatment (PSA-PFS: HR = 2.04, 95% CI: 1.08–3.85, $p = 0.029$; rPFS: HR = 2.37, 95% CI: 1.22–4.61, $p = 0.011$) (Table S3).

Subgroup analysis revealed that patients with IDC-P pattern 1 and without IDC-P shared similar clinical outcomes in DOC treatment, whereas cases with IDC-P pattern 2 had much poorer PSA-PFS and rPFS (mPSA-PFS: 3.0 vs. 6.6 vs. 6.2 months, $p < 0.001$; mrPFS: 5.5 vs. 12.6 vs. 15.1 months, $p < 0.001$) (Figure 3). Multivariate Cox regression after adjusting other prognosticators also confirmed this finding (Table S3).

3.5 | Comparison of efficacy between ABI and DOC for IDC-P (–), IDC-P pattern 1, and IDC-P pattern 2 patients

For mCRPC patients without IDC-P ($n = 79$), the therapeutic efficacy of ABI and DOC were comparable. No significant difference on PSA response rate (38/59 [64.4%] vs. 12/20 [60.0%], $p = 0.724$), median PSA-PFS (11.9 vs. 6.2 months, $p = 0.157$), rPFS (18.9 vs. 15.1 months, $p = 0.213$), and OS (31.1 vs. 22.3 months, $p = 0.188$) was found between ABI and DOC treatment (Figure S4).

Notably, among patients with IDC-P pattern 1 ($n = 36$), ABI brought significantly longer PSA-PFS (11.1 vs. 6.6 months, $p = 0.021$) and rPFS (19.4 vs. 12.6 months, $p = 0.027$) compared to DOC. Despite lacking statistical significance, the OS of patients with IDC-P pattern 1 receiving ABI treatment was numerically longer than those treated with DOC (27.0 vs. 14.4 months, $p = 0.535$) (Figure S5B,C). The PSA response rate was similar between ABI and DOC treatment (14/23 [60.9%] vs. 5/13 [38.5%], $p = 0.299$) (Figure S5A) in IDC-P pattern 1 carriers. Additionally, multivariate Cox regression suggested ABI was superior to DOC in prolonging PSA-PFS (HR = 2.90, 95% CI: 1.22–6.90, $p = 0.016$) and rPFS (HR = 3.61, 95% CI: 1.50–8.65, $p = 0.004$) among patients with IDC-P pattern 1 (Table 3).

Based on the current analysis, ABI still showed relatively better clinical efficacy than DOC in patients harboring IDC-P pattern 2. Higher PSA response, prolonged PSA-PFS, rPFS, and OS were found in patients treated with ABI versus DOC (PSA response: 19/40 [47.5%] vs. 4/15 [26.7%], $p = 0.163$; mPSA-PFS: 6.1 vs. 3.0 months, $p = 0.003$; mrPFS: 9.6 vs. 5.5 months, $p = 0.007$; mOS: 23.1 vs. 17.8 months, $p = 0.890$) (Figure S6). Multivariate Cox regression also showed the first-line therapy significantly impact PSA-PFS (HR = 2.61, 95% CI: 1.39–4.88, $p = 0.003$) and rPFS (HR = 2.32, 95% CI: 1.17–4.59, $p = 0.016$) among patients with IDC-P pattern 2. However, it cannot be neglected that even though ABI showed superior efficacy than DOC in cases with IDC-P pattern 2, it still only provides very limited benefits for this group of patients (Figure 4). Honestly speaking, patients with IDC-P pattern 2 was actually associated with rapid disease progression and poorer response to the current standard of care for mCPRC.

TABLE 2 Univariate and multivariate analyses of PSA-PFS, rPFS, and OS for patients treated with abiraterone

	PSA-PFS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years), ≥70 vs. <70	0.98 (0.65–1.48)	0.918		
CFS (months), ≥14 vs. <14	0.76 (0.52–1.13)	0.179		
GS, 9–10 vs. <8	3.05 (1.31–7.09)	0.009	2.75 (1.17–6.45)	0.020[a]
GS, 9–10 vs. 8	2.23 (1.10-4.50)	0.025	1.60 (0.78–3.28)	0.201[a]
Visceral metastasis, with vs. without	1.00 (0.55–1.83)	0.998		
ECOG score, ≥2 vs. 0–1	0.99 (0.40–2.43)	0.980		
PSA (ng/ml), ≥13 vs. <13	1.01 (0.73–1.60)	0.712		
HGB (g/L), ≥120 vs. <120	0.60 (0.40–0.91)	0.017	0.56 (0.36–0.88)	0.011[a]
LDH (IU/L), ≥250 vs. <250	1.37 (0.86–2.17)	0.184		
ALP (IU/L), ≥160 vs. <160	1.93 (1.24–2.99)	0.004	1.81 (1.15–2.85)	0.010[a]
IDC-P (+) vs. IDC-P (−)	1.66 (1.11–2.48)	0.013	1.90 (1.24–2.93)	0.004[a]
Pattern 1 vs. IDC-P (−)	0.88 (0.49–1.56)	0.652		
Pattern 2 vs. IDC-P (−)	2.82 (1.78–4.47)	<0.001	3.00 (1.85–4.88)	<0.001[b]
Pattern 2 vs. 1	3.22 (1.74–5.95)	<0.001	2.92 (1.57–5.43)	0.001[b]
	rPFS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years), ≥70 vs. <70	0.78 (0.51–1.20)	0.265		
CFS (months), ≥14 vs. <14	0.64 (0.42–0.97)	0.033	0.65 (0.42–1.00)	0.048[c]
GS, 9–10 vs. <8	3.47 (1.40–8.62)	0.007	3.57 (1.43–8.93)	0.007[c]
GS, 9–10 vs. 8	2.79 (1.27–6.13)	0.011	2.09 (0.94–4.67)	0.072[c]
Visceral metastasis, with vs. without	1.13 (0.62–2.08)	0.684		
ECOG score, ≥2 vs. 0–1	1.07 (0.39–2.92)	0.895		
PSA (ng/ml), ≥13 vs. <13	1.16 (0.78–1.75)	0.465		
HGB (g/L), ≥120 vs. <120	0.72 (0.47–1.11)	0.142		
LDH (IU/L), ≥250 vs. <250	1.00 (0.61–1.63)	0.992		
ALP (IU/L), ≥160 vs. <160	1.80 (1.15–2.81)	0.010	1.83 (1.15–2.92)	0.011[c]
IDC-P (+) vs. IDC-P (−)	1.86 (1.23–2.81)	0.003	1.75 (1.14–2.69)	0.011[c]
Pattern 1 vs. IDC-P (−)	1.00 (0.56–1.78)	0.997		
Pattern 2 vs. IDC-P (−)	3.33 (2.07–5.37)	<0.001	3.55 (2.15–5.88)	<0.001[d]
Pattern 2 vs. 1	3.33 (1.81–6.17)	<0.001	4.08 (2.16–7.75)	<0.001[d]
	OS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years), ≥70 vs. <70	1.04 (0.63–1.70)	0.888		
CFS (months), ≥10 vs. <10	0.54 (0.33–0.88)	0.013	0.53 (0.32–0.87)	0.013[c]
GS, 9–10 vs. <8	10.31 (1.42–76.92)	0.021	11.63 (1.59–83.33)	0.016[c]
GS, 9–10 vs. 8	2.67 (1.14–6.33)	0.024	2.16 (0.87–5.35)	0.097[c]

TABLE 2 (Continued)

	OS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Visceral metastasis, with vs. without	1.27 (0.67–2.43)	0.466		
ECOG score, ≥2 vs. 0–1	0.49 (0.11–2.08)	0.333		
PSA (ng/ml), ≥13 vs. <13	1.28 (0.80–2.05)	0.298		
HGB (g/L), ≥120 vs. <120	0.82 (0.50–1.33)	0.417		
LDH (IU/L), ≥250 vs. <250	1.20 (0.70–2.06)	0.499		
ALP (IU/L), ≥160 vs. <160	2.06 (1.26–3.38)	0.004	2.03 (1.21–3.40)	0.007[c]
IDC-P (+) vs. IDC-P (−)	1.68 (1.04–2.72)	0.033	1.46 (0.89–2.40)	0.138[c]
Pattern 1 vs. IDC-P (−)	1.54 (0.81–2.92)	0.186		
Pattern 2 vs. IDC-P (−)	1.78 (1.04–3.03)	0.035	1.63 (0.93–2.87)	0.089[d]
Pattern 2 vs. 1	1.15 (0.60–2.23)	0.673	1.31 (0.67–2.57)	0.434[d]

Abbreviations: ALP, alkaline phosphatase; CFS, CRPC-free survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GS, Gleason score; HGB, hemoglobin; HR, hazard ratio; IDC-P, intraductal carcinoma of the prostate; LDH, lactate dehydrogenase; OS, overall survival from first-line therapy to death; PSA, prostate-specific antigen; PSA-PFS, PSA-progression-free survival; rPFS, radiographic progression-free survival.

[a]Adjusted for GS, HGB, ALP, and IDC-P (+) versus IDC-P (−).

[b]Adjusted for GS, HGB, ALP, and IDC-P pattern 2 versus pattern 1 versus IDC-P (−).

[c]Adjusted for CFS, GS, ALP, and IDC-P (+) versus IDC-P (−).

[d]Adjusted for CFS, GS, ALP, and IDC-P pattern 2 versus pattern 1 versus IDC-P (−).

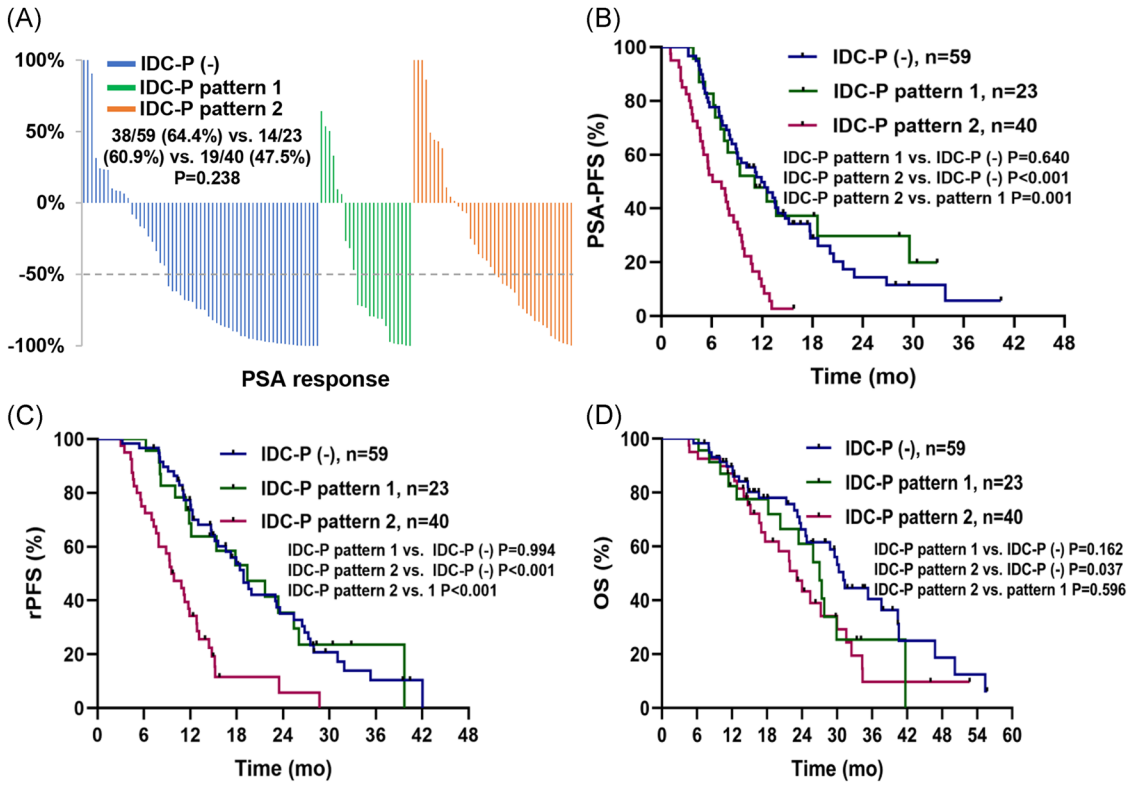

FIGURE 2 Waterfall chart of prostate-specific antigen (PSA) response (A) and Kaplan–Meier curves of prostate-specific antigen-progression-free survival (B), radiographic progression-free survival (C), and overall survival (D) in the cohort treated with abiraterone as the first-line therapy (without IDC-P vs. with IDC-P pattern 1 vs. with IDC-P pattern 2) [Color figure can be viewed at wileyonlinelibrary.com]

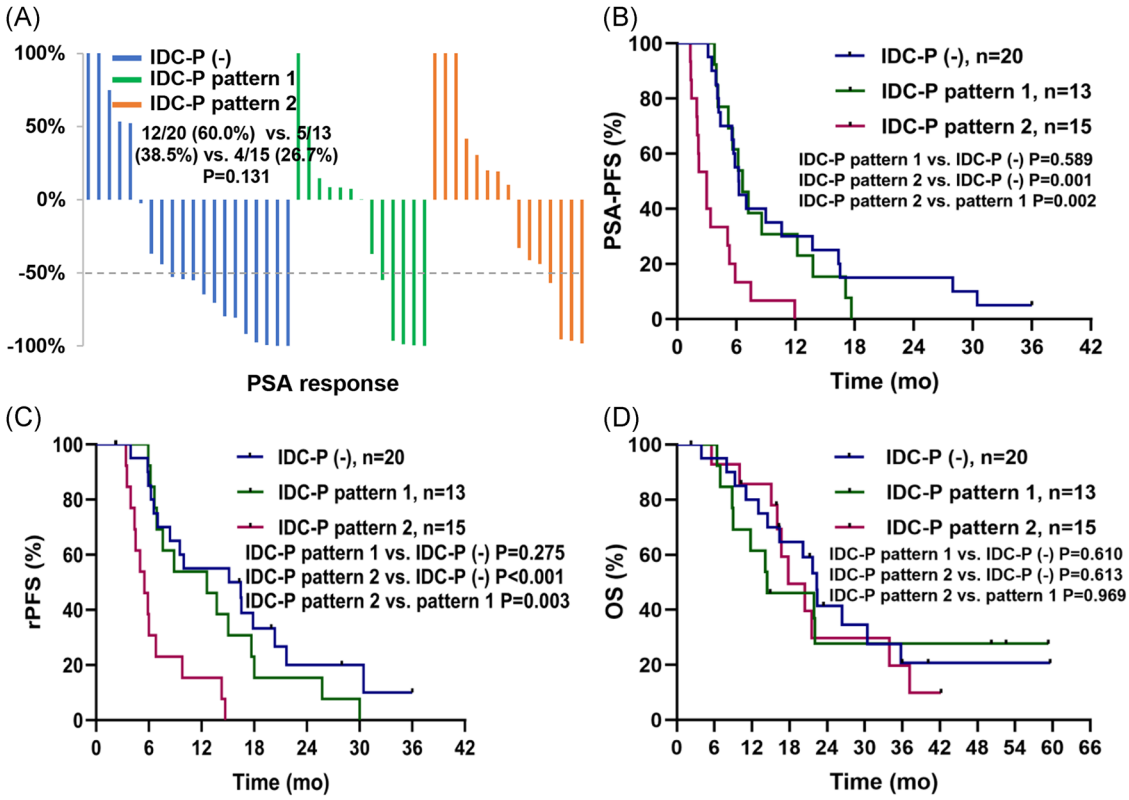

FIGURE 3 Waterfall chart of prostate-specific antigen (PSA) response (A) and Kaplan–Meier curves of PSA-progression-free survival (B), radiographic progression-free survival (C), and overall survival (D) in the cohort treated with docetaxel as the first-line therapy (without IDC-P vs. with IDC-P pattern 1 vs. with IDC-P pattern 2). IDC-P, intraductal carcinoma of the prostate [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In the present study, we first described the prognostic role and potential treatment-guiding value of IDC-P subtypes in mCRPC patients. Cases with IDC-P pattern 2 had more rapid disease progression and poorer response to either ABI or DOC treatment compared to those with IDC-P (–) and IDC-P pattern 1. For patients with IDC-P pattern 1, ABI showed superior clinical benefits than DOC as first-line therapy and might be considered as an optimal clinical choice for these patients. On the other hand, patients with IDC-P pattern 2 had unsatisfactory therapeutic efficacy for either ABI or DOC treatment. Thus, therapeutic strategies with novel mechanisms or targets are called for in the future. These findings lead to clinical implications that mCRPC patients with different IDC-P architectural patterns are likely to benefit from different therapeutic regimens.

DOC-based chemotherapy and androgen receptor (AR)-directed agents are both first-line therapies for mCRPC. The most prominent obstacle to personalized treatment is the lack of optimal biomarkers to guide first-line therapy. Several biomarkers have been identified to guide the treatment decision-making for mCRPC patients, for example, AR-V7, AKR1C3, neuroendocrine differentiation, and so on.[16–18] The positivity of these markers indicates poor prognosis in AR-targeting treatment. However, due to controversy over the testing techniques and the lack of validation with a large cohort,[19] the clinical availability of these markers is still limited. IDC-P as a pathological entity is easy to be detected by routine pathological testing. The presence of IDC-P has been identified to be associated with poor prognosis throughout the PCa disease stages,[3–9] whereas recent studies, including ours, uncovered its efficacy predictive value in mCRPC.[13,14] Data from this current study are consistent with our previous conclusion that the clinical efficacy of ABI as first-line therapy is superior to that of DOC for mCRPC patients with IDC-P, implying that ABI should be in the list of priorities in patients with IDC-P.

The architectural patterns of IDC-P have been proposed long before and defined in 2006.[10] Several studies explored the heterogeneity between different IDC-P subpatterns.[6,8,10,13,20] Recently, we found that mHSPC patients with different IDC-P architectural patterns had different prognosis under the ADT treatment.[12] Therefore, it is reasonable to speculate that, at the stage of mCRPC, distinct IDC-P subpatterns might be attributed to differential efficacy to the next-generation AR-targeting agent. According to our findings, ABI exhibited better efficacy than DOC in patients with IDC-P of either pattern. However, cases with IDC-P pattern 2 responded unsatisfactorily to either ABI or DOC compared to men with IDC-P pattern 1 or IDC-P (–). Taking together, IDC-P subpatterns could be considered as a prognostic

TABLE 3 Univariate and multivariate analyses of PSA-PFS and rPFS for patients with different IDC-P patterns

	IDC-P pattern 1				IDC-P pattern 2			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
PSA-PFS								
Age (years), ≥70 vs. <70	0.89 (0.42–1.87)	0.754			1.20 (0.69–2.06)	0.520		
CFS (months), ≥14 vs. <14	0.42 (0.20–0.90)	0.024	0.38 (0.14–1.02)	0.056	0.94 (0.55–1.61)	0.812		
GS, 9–10 vs. <9	1.18 (0.48–2.92)	0.719			2.49 (0.76–8.12)	0.131		
Visceral metastasis, with vs. without	0.75 (0.23–2.51)	0.645			1.00 (0.36–2.82)	0.997		
ECOG score, ≥2 vs. 0–1	2.37 (0.70–7.98)	0.165			0.89 (0.32–2.48)	0.821		
PSA (ng/ml), ≥13 vs. <13	1.01 (0.48–2.10)	0.990			0.99 (0.58–1.70)	0.970		
HGB (g/L), ≥120 vs. <120	0.33 (0.15–0.75)	0.008	0.32 (0.13–0.76)	0.010	0.46 (0.24–0.87)	0.016	0.43 (0.22–0.82)	0.010
LDH (IU/L), ≥250 vs. <250	2.09 (0.90–4.82)	0.085	2.00 (0.69-5.74)	0.200	2.13 (1.01–4.51)	0.047	1.99 (0.93–4.24)	0.076
ALP (IU/L), ≥160 vs. <160	4.78 (1.99–11.50)	<0.001	2.79 (0.91–8.53)	0.072	1.45 (0.79–2.66)	0.234		
DOC vs. ABI	2.37 (1.11–5.06)	0.027	2.90 (1.22–6.90)	0.016	2.50 (1.34–4.65)	0.004	2.61 (1.39–4.88)	0.003
rPFS								
Age (years), ≥70 vs. <70	0.83 (0.39–1.75)	0.622			1.22 (0.69–2.17)	0.495		
CFS (months), ≥14 vs. <14	0.45 (0.21–0.96)	0.038	0.44 (0.16–1.19)	0.106	0.96 (0.54–1.72)	0.895		
GS, 9–10 vs. <9	0.83 (0.33–2.08)	0.683			4.32 (1.02–18.27)	0.047	3.27 (0.75–14.27)	
Visceral metastasis, with vs. without	0.83 (0.25–2.78)	0.764			0.56 (0.17–1.83)	0.333		
ECOG score, ≥2 vs. 0–1	2.64 (0.77–9.05)	0.122			1.20 (0.43–3.37)	0.731		
PSA (ng/ml), ≥13 vs. <13	0.79 (0.37–1.67)	0.534			1.02 (0.57–1.84)	0.945		
HGB (g/L), ≥120 vs. <120	0.48 (0.22–1.07)	0.073	0.57 (0.25–1.30)	0.181	0.34 (0.17–0.69)	0.003	0.35 (0.17–0.72)	0.004
LDH (IU/L), ≥250 vs. <250	1.88 (0.82–4.31)	0.137			1.67 (0.74–3.78)	0.218		
ALP (IU/L), ≥160 vs. <160	3.84 (1.62–9.11)	0.002	3.16 (1.12–8.93)	0.030	2.09 (1.08–4.03)	0.028	1.47 (0.75–2.88)	0.261
DOC vs. ABI	2.28 (1.08–4.82)	0.031	3.61 (1.50–8.65)	0.004	2.41 (1.25–4.66)	0.009	2.32 (1.17–4.59)	0.016

Abbreviations: ABI, abiraterone; ALP, alkaline phosphatase; CFS, CRPC-free survival; CI, confidence interval; DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group; GS, Gleason score; HGB, hemoglobin; HR, hazard ratio; IDC-P, intraductal carcinoma of the prostate; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; PSA-PFS, PSA-progression-free survival; rPFS, radiographic progression-free survival.

pathological parameter to guide personalized prognostic evaluation for mCRPC patients. Besides, routine reporting the architectural patterns of IDC-P for patients with mCRPC could be of great importance and necessity.

In our study, the exact efficacy of DOC and ABI among patients with IDC-P is not as satisfied as we expect. The total median OS, either with ABI or with DOC is relatively shorter than the data from phase III clinical trials.[21,22] We suppose the lower proportion for subsequential therapy (only 35.9%) might explain the shorter survival outcome in the present cohort. Another possible explanation is that patients in this study harbored generally more aggressive tumor. Ninety-two percentage of patients had a GS score 8–10, and 90.0% of patients belonged to intermediate/high-risk group according to West China Hospital-BJU I (WCH-BJUI) nomograms for mPCa patients.[23] At last, the higher proportion of IDC-P pattern 2 (60.4%) could contribute to the shorter OS as well.

In the process of accurate IDC-P diagnosis, differential diagnosis with other special pathological types of PCa is of great importance. In addition to malignant epithelial cells filling large acini and prostatic ducts with preservation of basal cells, the diagnosis of IDC-P pattern 1 requires a loose cribriform or micropapillary pattern with either marked nuclear atypia or comedonecrosis, whereas the diagnosis of IDC-P pattern 2 requires the presence of a solid or dense cribriform pattern.[10,11] Epstein diagnostic criteria can reliably distinguish IDC-P and cribriform high grade prostatic intraepithelial neoplasia in most cases: the architectural and cytological atypia of IDC-P is always more pronounced.[10] The distinction between cribriform PCa and IDC-P was not difficult by labeling basal cells as cribriform PCa lacks a basal cell lining and IDC-P is usually associated with high-grade and high-volume overtly invasive PCa.[24]

Our studies have several limitations. First, our study is based on a cohort from a single medical center. Hence, selection bias cannot be

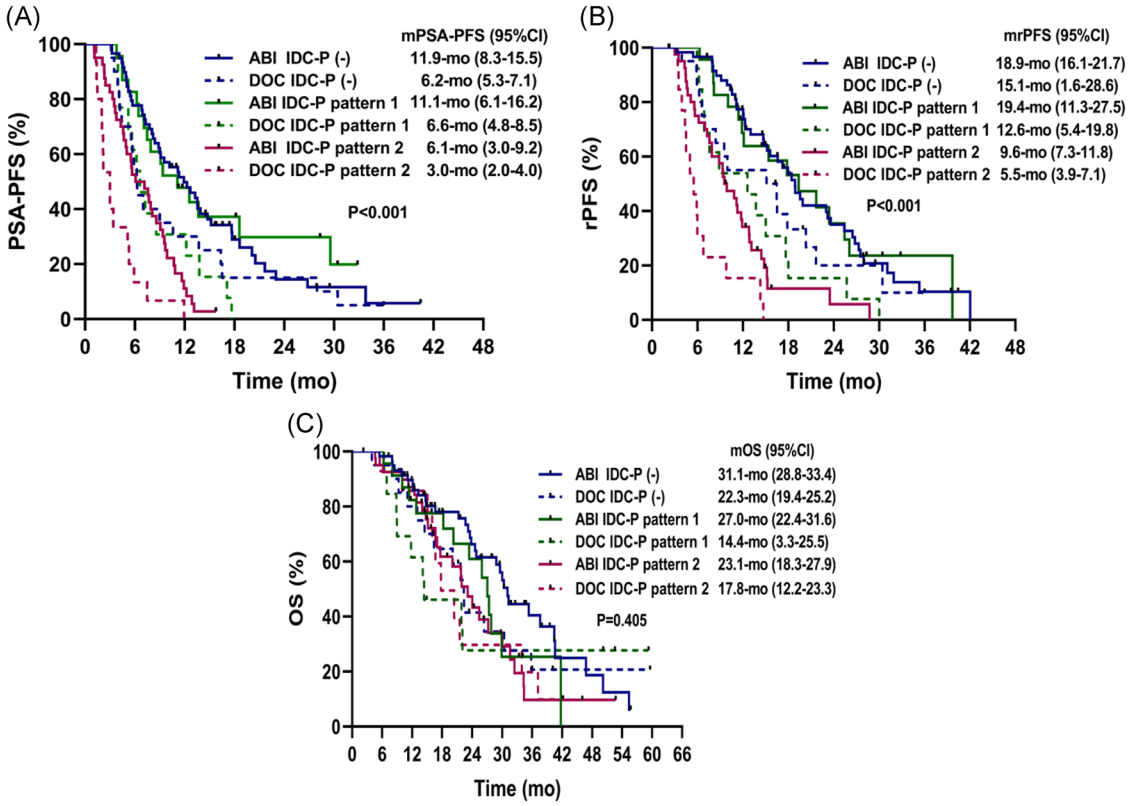

FIGURE 4 Kaplan–Meier curves of prostate-specific antigen-progression-free survival (A), radiographic progression-free survival (B), and overall survival (C) in the comparison between patients treated with abiraterone and docetaxel [Color figure can be viewed at wileyonlinelibrary.com]

ruled out. Second, it is a retrospective study with medium sample size. Especially the sample size of patients with IDC-P pattern 1 was relatively small. Finally, though standard 12-core biopsy was performed in each patient for both initial and repeat prostate biopsy, bias related to the randomness of biopsy is still an inevitable problem.

5 | CONCLUSION

The present study provided evidence that mCRPC patients with distinct architectural patterns of IDC-P had different therapeutic efficacy in ABI and DOC treatment. Compared to DOC, ABI did show superior clinical benefits as the first-line therapy in patients with IDC-P of either pattern. Even so, IDC-P pattern 2 still responded unsatisfactorily to either ABI or DOC therapy. Therefore, ABI might be considered as an optimal clinical choice for mCRPC patients with IDC-P pattern 1, while novel therapeutic strategies appropriate for IDC-P pattern 2 need to be further investigated in the future.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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