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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Research

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Abstract

Background

To explore whether patients with distinct intraductal carcinoma of the prostate (IDC-P) subtypes respond differently to standard first-line therapy among patients with metastatic castration resistant prostate cancer (mCRPC).

Methods

We retrospectively analyzed data of 170 mCRPC patients receiving abiraterone (ABI) or docetaxel (DOC) as first-line therapy between 2014 and 2019. PSA response, PSA progression-free survival (PSA-PFS), radiographic progression-free survival (rPFS), and overall survival (OS) were analyzed and compared based on the presence of IDC-P and its sub-patterns.

Results

Totally, IDC-P was confirmed in 91/170 (53.5%) patients. Among them, 36/91 (39.6%) and 55/91 (60.4%) harbored IDC-P pattern 1 and pattern 2, respectively. The presence of IDC-P was confirmed to be associated with poor prognosis in the whole cohort. Patients with IDC-P pattern 1 shared similar clinical outcomes to those without IDC-P in both ABI and DOC treatment. However, compared to patients with IDC-P pattern 1 and without IDC-P, IDC-P pattern 2 had markedly poorer prognosis in either ABI (PSA-PFS: P<0.001; rPFS: P<0.001) or DOC (PSA-PFS: P<0.001; rPFS: P<0.001) treatment. For patients without IDC-P, DOC had comparable therapeutic efficacy with ABI. In contrast, the therapeutic efficacy of DOC in patients with either IDCP pattern 1 (PSA-PFS: P=0.021; rPFS: P=0.027) or pattern 2 (PSA-PFS: P=0.003; rPFS: P=0.007) was significantly inferior to ABI.

Conclusion

Compared to DOC, ABI exhibited better efficacy in patients with IDC-P of either pattern. However, IDC-P pattern 2 still responded unsatisfactorily to either ABI or DOC therapy. Novel therapeutic strategies appropriate for IDC-P pattern 2 need to be further investigated in the future.

Background

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 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). With its clinical value being studied, the presence of IDC-P has now been widely acknowledged to be associated with poor prognosis throughout almost all stages of PCa(3-9).

Tumoral heterogeneity also exists within IDC-P lesions. According to 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). Of note, our recent studies uncovered that IDC-P pattern 2 exhibited more aggressive characteristics compared with IDC-P pattern 1 in patients with not only locally advanced PCa but also mHSPC(5, 11). These findings prompt whether the prognostic value of IDC-P also differs between its two sub-patterns in mCRPC patients.

Previous studies have verified that IDC-P was independently associated with unfavorable response and poor prognosis in patients treated with classic androgen deprivation therapy (ADT)(6, 8, 9, 12). Further investigation from a Japanese research team and ours suggested that IDC-P was not only a prognostic factor but also a predictive biomarker for therapeutic decisions in mCRPC patients(13, 14). Specifically, the therapeutic efficacy of abiraterone (ABI) was superior to that of docetaxel (DOC) as first-line therapy in mCRPC patients with IDC-P component. Even so, the inconsistent tumor response to ABI among patients with IDC-P, again, makes us wondering whether IDC-P sub-patterns contribute to the differential response to standard of care for mCRPC and whether it is a valuable predictive parameter to guide personalized therapy for mCRPC patients.

Therefore, the main 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 a more elaborative decision in the treatment of mCRPC patients.

Methods

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 and CRPC. All patients were treated with maximal androgen blockade at the initial diagnosis of metastatic prostate cancer (medical or surgical castration plus bicalutamide 50 mg per day). The median time from the initial diagnosis to CRPC (CRPC-free survival, CFS) was 13.5 months. After mCRPC was confirmed, patients received ABI (Abiraterone acetate 1000 mg/day plus prednisone 10 mg/day) and DOC (Docetaxel 75 mg/m2 q3w, plus prednisone 10 mg/day, maximized with 10cycles) as first-line therapy, respectively. Owing to the socioeconomic burden, only 52/170 (30.6%) of our patients received one or more sequencing treatments after first-line therapy.

Clinicopathological data of these patients were collected with Institutional Review Board approval, including age, CFS, IDC-P status, visceral metastasis, ECOG score, baseline PSA (prostate-specific antigen) 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 PSA level and 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, Nie Ling) independently. The presence of IDC-P was based on repeated biopsy at the time of mCRPC diagnosis and strictly defined by the Epstein criteria(16). 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. Definition for proportion of IDC-P has been carefully described previously(11).

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 CT (Computer tomography), 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.

Statistics

Chi-square 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. All statistical analyses were performed by SPSS version 25.0. A P value <0.05 was considered statistically significant.

Results

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. Among them, 122 and 48 patients received ABI and DOC, 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 associated with younger age. Other baseline factors were well balanced among different groups. The median follow-up time was 34.4-mo for the whole cohort. 104/170 (61.2%) patients died during the follow-up. As shown in **table S2**, 40/122 (32.8%) 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

abiraterone (n=11), docetaxel (n=30), enzalutamide (n=7), olaparib (n=4), proxalutamide (n=2), pembrolizumab (n=1), pazopanib (n=1) and everolimus (n=1).

The clinical outcomes of mCRPC in the whole cohort

For the total 170 patients, the median PSA-PFS , rPFS and OS were 7.9-mo, 13.7-mo and 24.8-mo, 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-mo vs. 10.6-mo, *P*=0.001; mrPFS: 11.2-mo vs 18.0-mo, *P*<0.001; mOS: 21.9-mo vs. 30.0-mo, *P*=0.076). Among patients treated with ABI (n=122), PSA response was achieved in 71/122 (58.2%) cases, the median PSA-PFS, rPFS and OS was 9.1-mo, 14.8-mo and 27.4-mo 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-mo, 8.9-mo and 21.5-mo, respectively **(Table 2)**.

The prognostic value of IDC-P architectural patterns in patients treated with abiraterone

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 S1A**). However, IDC-P was associated with shorter median PSA-PFS (7.9-mo vs. 11.9-mo, *P* =0.012), rPFS (11.9-mo vs 18.9-mo, *P* =0.003), and OS (25.4-mo vs. 31.1-mo, *P*=0.031) (**Figure S1 B-D**). Multivariate Cox regression further confirmed that IDC-P, together with GS and ALP level, was one of the independent prognosticators predicting worse clinical outcomes in the first-line ABI treatment of mCRPC. (**Table 3**).

The therapeutic efficacy of ABI treatment in patients with different IDC-P sub-patterns 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-mo, *P*=0.001; mrPFS: 9.6 vs. 19.4-mo, *P*<0.001; mOS: 23.1 vs. 27.0-mo, *P*=0.596) or those without IDC-P (mPSA-PFS: 6.1 vs. 11.9-mo, *P*<0.001; mrPFS: 9.6 vs.18.9-mo, *P*<0.001; mOS: 23.1 vs. 31.1-mo, *P*=0.037) (**Figure 2 B-D**). Multivariate COX regression after adjusting other prognosticators further strengthened these findings (**Table 3**). In addition, the proportion of IDC-P was not found to be related to the efficacy of ABI.

The prognostic value of different IDC-P architectural patterns in patients treated with docetaxel

Among patients treated with DOC, IDC-P was also a predictor of poor prognosis (**Figure S2 and Table S1**). IDC-P-carriers had shorter median PSA-PFS (5.1-mo vs. 6.2-mo, *P*=0.038), rPFS (15.1-mo vs 6.8-mo, *P*=0.011) against the non-carriers **(Figure S2 B-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-mo vs. 22.3-mo, *P*=0.569) (**Figure S2 A, D**). Multivariate Cox regression further confirmed that the presence of IDC-P was an independent factor predicting worse PSA-PFS and rPFS in DOC treatment (**Table S1**). Similarly, the proportion of IDC-P was not found to be related to the efficacy of DOC.

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 (**Figure 3**). Multivariate COX regression after adjusting other prognosticators also confirmed this finding (**Table S1**).

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) (**Figure S3 A**), median PSA-PFS (11.9-mo vs. 6.23-mo, *P*=0.158), rPFS (18.9-mo vs. 15.1-mo, *P*=0.213) and OS (31.1-mo vs. 22.33-mo, *P*=0.188) was found between ABI and DOC treatment (**Figure 4 and Figure S4 A-C**).

Notably, among patients with IDC-P pattern 1 (n=36), ABI brought significantly longer PSA-PFS (11.1-mo vs. 6.6-mo, *P*=0.022) and rPFS (19.4-mo vs. 12.6-mo, *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-mo vs. 14.4-mo, *P*=0.535) (**Figure 4 and Figure S4 D-F**). The PSA response rate was similar between ABI and DOC treatment (14/23 [60.9%] vs. 5/13 [38.5%], *P*=0.299) (**Figure S3B**) in IDC-P pattern 1 carriers. Additionally, COX regression suggested ABI was superior to DOC in prolonging PSA-PFS (HR=2.24, 95% CI: 1.01-4.96, *P*=0.047) and rPFS (HR=3.37, 95% CI: 1.49-7.63, *P*=0.004) among patients with IDC-P pattern 1 (**Table 4**).

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 was found in patients treated with ABI versus DOC (PSA response: 47.5% vs. 26.7%, *P*=0.163; mPSA-PFS: 6.0 vs. 3.1-mo, *P*=0.003; mrPFS: 9.6 vs. 5.5-mo, *P*=0.007; mOS: 23.1 vs. 17.8-mo, *P*=0.890) (**Figure S3B, Figure 4 and Figure S4 G-I**). 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. 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.

Discussion

In the present study, we firstly 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 should 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, e.g. AR-V7, ARK1C3, neuroendocrine differentiation and etc(17-19). 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(20), 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 prostate cancer disease stages(3-9), while recent studies including ours, uncovered its efficacy predictive value in mCRPC(13, 14). Data from this current study is 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(16). Several studies explored the heterogeneity between different IDC-P sub-patterns(6, 8, 13, 16, 21). Recently, we found that mHSPC patients with different IDC-P architectural patterns had different prognosis under the ADT treatment (11). Therefore, it is reasonable to speculate that, at the stage of mCRPC, distinct IDC-P sub-patterns 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, IDC-P pattern 2 still responded unsatisfactorily to either ABI or DOC compared to IDC-P pattern 1 and IDC-P (-). Therefore, ABI should be considered as an optimal clinical choice for mCRPC patients with IDC-P pattern 1. As for patients with IDC-P pattern 2, new therapeutic strategies need to be further investigated. Based on these results, IDC-P sub-patterns could be considered as a predictive pathological parameter to guide personalized therapy for mCRPC patients. Besides, routine reporting the architectural patterns of IDC-P for patients with mCRPC could be of great importance and necessity. Notably, although our previous study suggested that a 10% or greater proportion of IDC-P was an unfavorable prognosticator in mHSPC(11), unlike the value of arichitectural pattern of IDC-P, data from this study showed the proportion of IDC-Pcould not predict efficacy of standard of cares among patients with mCRPC.

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 clinical trials (22, 23). We suppose the lower proportion for subsequential therapy (only 30.6%) 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 9-10, and 81.7% of patients belonged to intermediate/high risk group according to West China Hospital (WCH) nomograms for mPCa patients(24). At last, the higher proprotion of IDCP-2 (60.4%) could contribute to the shorter OS as well.

In the process of accurate IDC-P diagnosi, 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, while the diagnosis of IDC-P pattern 2 requires the presence of a solid or dense cribriform pattern(10). Epstein diagnostic criteria can reliably distinguish IDC-P and cribriform HGPIN in most cases: the architectural and cytological atypia of IDC-P are always more pronounced(16). Besides, we also performed immunohistochemical staining with a triple antibody cocktail (AMACR/P63/HCK) in all biopsy specimens to precisely identify IDC-P. 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(25).

Our studies have several limitations. Selection bias caused by small-size and single medical center cannot be ruled out. Especially, the sample size of patients with IDC-P pattern 1 was relatively small, although this seems the case in epidemiology and data from our other unpublished work suggests the same. Bias related to the randomness of biopsy is also an inevitable problem.

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 should be considered as an optimal clinical choice for mCRPC patients with IDC-P pattern 1, and novel therapeutic strategies appropriate for IDC-P pattern 2 need to be further investigated in the future.

Abbreviations

mCRPC, metastatic castration-resistant prostate cancer**;** IDC-P, intraductal carcinoma of the prostate; ABI, abiraterone; DOC, docetaxel; PSA, prostate-specific antigen; PSA-PFS, PSA progression-free survival; rPFS: radiographic progression-free survival; OS: overall survival; CFS, CRPC-free survival; HGB: hemoglobin; LDH: lactate dehydrogenase; ALP: alkaline phosphatase.

Declarations

Ethics approval and consent to participate

Our study was approved by The Biomedical Ethics Committee of West China Hospital, Sichuan University (approval no. 2012 (15)). All patients provided written informed consent prior to enrollment in the study.

Consent for publication

This manuscript is approved by all authors for publication.

Availability of data and material

Data are available upon reasonable request. Please contact the corresponding author for more information.

Competing interests

None of the contributing authors have any conflicts of interest.

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Authors' contributions

Zhipeng Wang, Sha Zhu, Jinge Zhao and Hao Zeng: conception and design. Zhipeng Wang, Sha Zhu, Ling Nie, Xueqin Chen, Mengni Zhang and Ni Chen: data collection and assembly. Guangxi Sun, Junru Chen, Yuchao Ni, Jingdong Dai, Zhenhua Liu and Ronggui Tao: manuscript preparations. Zhipeng Wang, Xingming Zhang, Xudong Zhu, Haoran Zhang, Jiayu Liang, Zilin Wang and Ben He: data analysis and interpretation. P Shen and H Zeng: principal investigator.

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Tables

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 (y)					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 (mo)					0.340
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)	
≥10	109 (64.1%)	54 (68.4%)	24 (66.7%)	31 (56.4%)	
<10	61 (35.9%)	25 (31.6%)	12 (33.3%)	24 (43.6%)	
GS, no					0.626
<8	14 (8.2%)	8 (10.1%)	3 (8.3%)	3 (5.5%)	
8-10	156 (91.8%)	71 (89.9%)	33 (91.7%)	52 (94.5%)	
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)					0.325
Median (IQR)	13.1 (4.4-66.9)	13.2 (4.8-94.2)	11.0 (5.1-27.4)	13.6 (4.10-46.6)	
≥50, no (%)	48 (28.2%)	26 (32.9%)	7 (19.4%)	15 (27.3%)	
<50, no (%)	122 (71.8%)	53 (67.1%)	29 (80.6%)	40 (72.7%)	
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%)	
Prognostic model from WCH[a]					
Favorable risk	31 (18.2%)	26 (32.9%)	3 (8.3%)	2 (3.6%)	
Median risk	73 (42.9%)	31 (39.2%)	17 (47.2%)	25 (45.5%)	
High risk	66 (38.8%)	22 (27.8%)	16 (44.4%)	28 (50.9%)	
Proportional ratio of Sequential therapy					0.442
	52 (30.6%)	25 (31.6%)	8 (22.2%)	19 (34.5%)	

IQR = interquartile range; CRPC = castration-resistant prostate cancer; CFS = CRPC free survival; IDC-P = intraductal carcinoma of the prostate; ECOG = Eastern Cooperative Oncology Group; PSA = prostate specific antigen; HGB = hemoglobin; LDH = lactate dehydrogenase; ALP = alkaline phosphatase; a: WCH = west China hospital.

Table 2. Clinical outcomes among patients with mCRPC				
	PSA response	mPSA-PFS (m)	mrPFS (m)	mOS (m)
The whole cohort(n=170)				
Total	92/170 (54.1%)	7.9 (6.6-9.2)	13.7 (11.6-15.9)	24.8 (21.6-28.1)
IDC-P (-)	50/79 (63.3%)	10.6 (7.7-13.5)	18.0 (15.7-20.2)	30.0 (24.0-36.0)
IDC-P (+)	42/91 (46.2%)	6.6 (5.1-8.2)	11.2 (8.9-13.5)	21.9 (18.5-25.3)
Pattern 1	19/36 (52.8%)	8.6 (5.8-11.4)	15.4 (8.6-22.2)	23.4 (16.9-29.9)
Pattern 2	23/55 (41.8%)	5.3 (4.3-6.3)	8.9 (6.5-11.2)	21.8 (18.2-25.3)
Abiraterone-treated group(n=122)				
Total	71/122 (58.2%)	9.1 (7.7-10.5)	14.8 (12.5-17.1)	27.4 (23.0-31.7)
IDC-P (-)	38/59 (64.4%)	11.9 (8.3-15.5)	18.9 (16.1-21.7)	31.1 (28.8-33.4)
IDC-P (+)	33/63 (52.4%)	7.9 (6.3-9.5)	11.9 (10.2-13.6)	25.4 (20.5-30.4)
Pattern 1	14/23 (60.9%)	11.1 (6.1-16.2)	19.4 (11.3-27.5)	27.0 (22.4-31.6)
Pattern 2	19/40 (47.5%)	6.1 (3.0-9.2)	9.6 (7.3-11.8)	23.1 (18.3-27.9)
Docetaxel-treated group(n=48)				
Total	21/48 (43.8%)	5.6 (4.8-6.4)	8.9 (5.6-12.2)	21.5 (16.8-26.2)
IDC-P (-)	12/20 (60.0%)	6.2 (5.3-7.1)	15.1 (1.6-28.6)	22.3 (19.4-25.2)
IDC-P (+)	9/28 (32.1%)	5.1 (3.4-6.9)	6.8 (5.1-8.5)	17.8 (11.6-23.9)
Pattern 1	5/13 (38.5%)	6.6 (4.8-8.5)	12.6 (5.4-19.8)	14.4 (3.3-25.5)
Pattern 2	4/15 (26.7%)	3.0 (2.0-4.0)	5.5 (3.9-7.1)	17.8 (12.2-23.3)

mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate specific antigen; mPSA-PFS = median PSA-progression free survival; mrPFS = median radiographic progression free survival; mOS = median overall survival.

Table 3. 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 (y), ≥70 vs. <70	0.98 (0.65-1.48)	0.918		
CFS (mo), ≥10 vs. <10	0.62 (0.41-0.94)	0.023	0.71 (0.46-1.09)	0.113[a]
GS, ≥8 vs. <8	3.04 (1.23-7.52)	0.016	3.06 (1.22-7.65)	0.017[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), ≥50 vs. <50	0.98 (0.62-1.54)	0.926		
HGB (g/L), ≥120 vs. <120	0.60 (0.40-0.91)	0.017	0.54 (0.35-0.85)	0.008[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	1.72 (1.08-2.76)	0.024[a]
IDC-P (+) vs. IDC-P (-)	1.66 (1.11-2.48)	0.013	1.94 (1.26-2.97)	0.003[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	3.04 (1.88-4.93)	<0.001[A]
Pattern 2 vs. 1	3.22 (1.74-5.95)	<0.001	2.82 (1.53-5.24)	0.001[A]
	rPFS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (y), ≥70 vs. <70	0.78 (0.51-1.20)	0.265		
CFS (mo), ≥10 vs. <10	0.48 (0.31-0.75)	0.001	0.47 (0.29-0.75)	0.001[b]
GS, ≥8 vs. <8	3.32 (1.22-9.07)	0.019	3.91 (1.41-10.86)	0.009[b]
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), ≥50 vs. <50	1.13 (0.71-1.79)	0.601		
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	1.81 (1.13-2.90)	0.014[b]
IDC-P (+) vs. IDC-P (-)	1.86 (1.23-2.81)	0.003	1.96 (1.28-3.01)	0.002[b]
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	3.62 (2.18-6.02)	<0.001[B]
Pattern 2 vs. 1	3.33 (1.81-6.17)	<0.001	3.37 (1.80-6.29)	<0.001[B]
	OS			
	Univariate analysis		**Multivariate analysis**	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Age (y), ≥70 vs. <70	1.04 (0.63-1.70)	0.888		
CFS (mo), ≥10 vs. <10	0.53 (0.33-0.86)	0.010	0.56 (0.34-0.93)	0.024[b]
GS, ≥8 vs. <8	8.35 (1.16-60.25)	0.035	8.43 (1.16-61.05)	0.035[b]
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), ≥50 vs. <50	1.15 (0.69-1.91)	0.597		
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	2.10 (1.26-3.51)	0.004[b]
IDC-P (+) vs. IDC-P (-)	1.68 (1.04-2.72)	0.033	1.70 (1.05-2.78)	0.033[b]
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	1.78 (1.03-3.08)	0.040[B]
Pattern 2 vs. 1	1.15 (0.60-2.23)	0.673	1.12 (0.57-2.19)	0.746[B]

[a]: Adjusted for: CFS, GS, HGB, ALP and IDC-P (+) vs IDC-P (-). [A]: Adjusted for: CFS, GS, HGB, ALP and IDC-P pattern 2 vs. pattern 1 vs. IDC-P (-). [b]: Adjusted for: CFS, GS, ALP and IDC-P (+) vs IDC-P (-). [B]: Adjusted for: CFS, GS, ALP and IDC-P pattern 2 vs. pattern 1 vs. IDC-P (-). PSA-PFS = PSA-progression free survival; rPFS = radiographic progression free survival; OS = overall survival from 1-st line therapy to death; HR = hazard ratio; CI = confidence interval; ABI = abiraterone; CFS = CRPC free survival; GS:

Gleason Score; IDC-P = intraductal carcinoma of the prostate; ECOG = Eastern Cooperative Oncology Group; PSA = prostate specific antigen; HGB = hemoglobin; LDH = lactate dehydrogenase; ALP = alkaline phosphatase.

Table 4 Univariate and multivariate analyses of PSA-PFS and rPFS for patients with different IDCP patterns.

PSA-PFS	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
Age(y), ≥70 vs <70	0.89 (0.42-1.87)	0.754			1.20 (0.69-2.06)	0.520		
CFS (mo), ≥10 vs <10	0.48 (0.22-1.04)	0.063	0.53 (0.21-1.36)	0.186	0.96 (0.56-1.67)	0.897		
GS, ≥8 vs <8	1.53 (0.36-6.51)	0.564			1.06 (0.33-3.43)	0.922		
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), ≥50 vs <50	0.81 (0.31-2.16)	0.677			0.80 (0.43-1.50)	0.490		
HGB (g/L), ≥120 vs <120	0.33 (0.15-0.75)	0.008	0.31 (0.13-0.75)	0.009	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	1.70 (0.61-4.76)	0.312	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	3.80 (1.27-11.35)	0.017	1.45 (0.79-2.66)	0.234		
DOC vs ABI	2.37 (1.11-5.06)	0.027	2.24 (1.01-4.96)	0.047	2.50 (1.34-4.65)	0.004	2.61 (1.39-4.88)	0.003
rPFS	**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%**	**P**	**HR (95%**	**P**

					CI)		CI)	
Age(y), ≥70 vs <70	0.83 (0.39-1.75)	0.622			1.22 (0.69-2.17)	0.495		
CFS (mo), ≥10 vs <10	0.25 (0.11-0.59)	0.001	0.19 (0.06-0.55)	0.002	0.96 (0.54-1.72)	0.898		
GS, ≥8 vs <8	0.87 (0.20-3.74)	0.855			0.38 (0.09-1.61)	0.190		
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), ≥50 vs <50	1.03 (0.38-2.77)	0.954			1.17 (0.62-2.20)	0.622		
HGB (g/L), ≥120 vs <120	0.48 (0.22-1.07)	0.073	0.39 (0.16-0.91)	0.030	0.34 (0.17-0.69)	0.003	0.33 (0.16-0.67)	0.002
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	2.80 (0.97-8.08)	0.058	2.09 (1.08-4.03)	0.028	1.59 (0.81-3.10)	0.178
DOC vs ABI	2.28 (1.08-4.82)	0.031	3.37 (1.49-7.63)	0.004	2.41 (1.25-4.66)	0.009	2.44 (1.23-4.82)	0.011

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

Figures

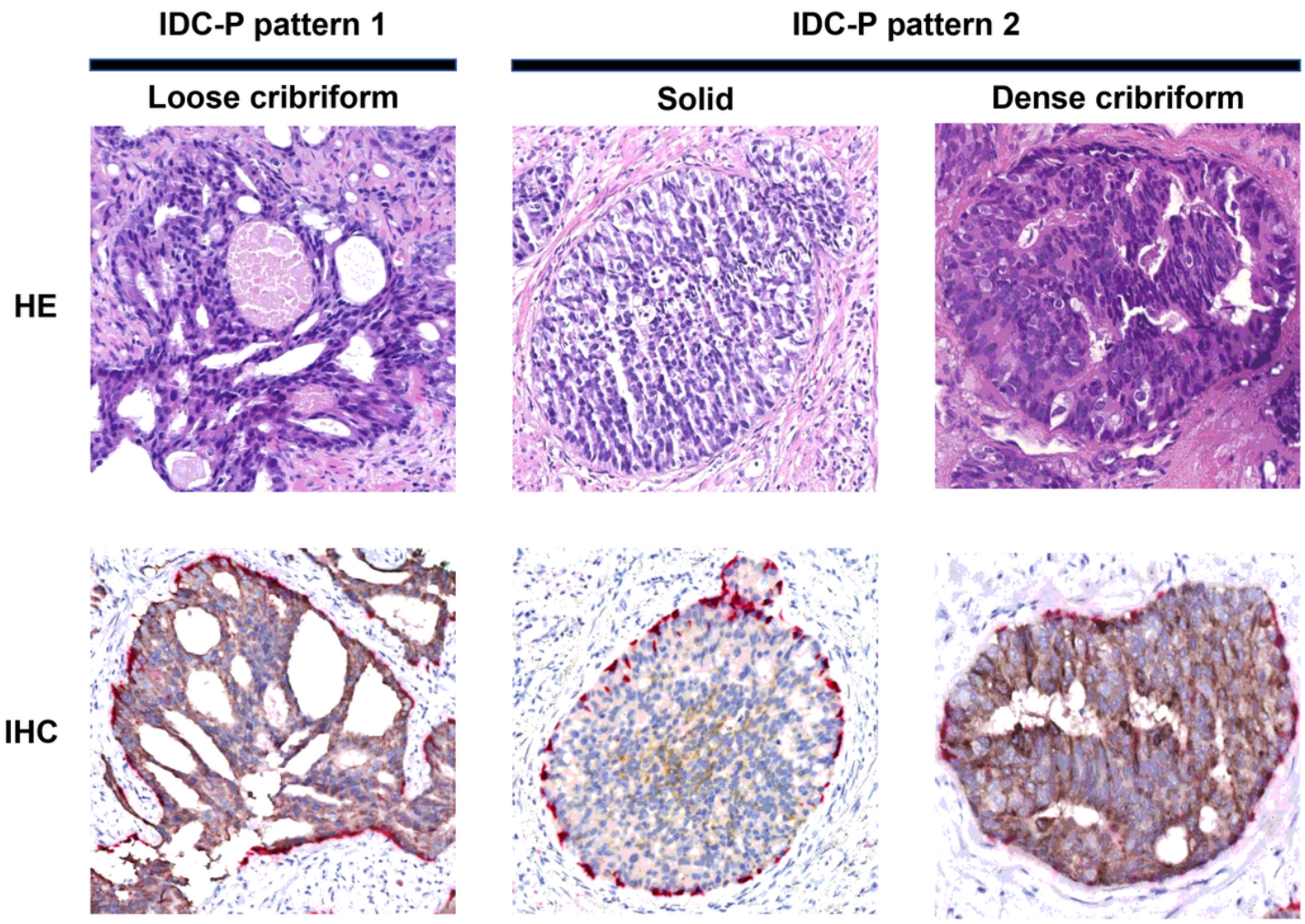

Figure 1

Histopathological features of IDC-P architectural patterns (A: hematoxylin-eosin staining; B: Immunohistochemistry).

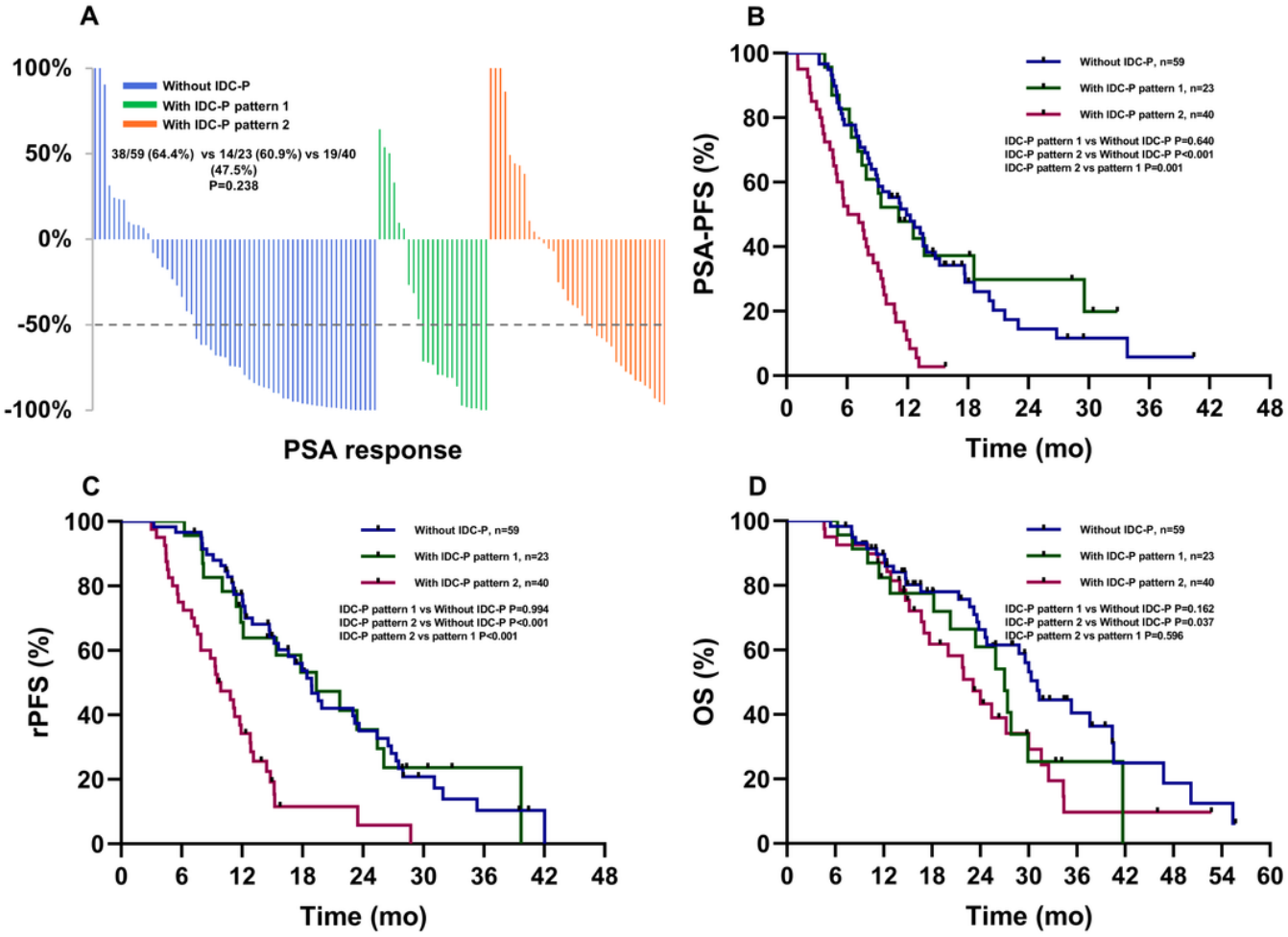

Figure 2

Waterfall chart of PSA response (A) and Kaplan-Meier curves of PSA-PFS (B), rPFS (C) and OS(D) in the cohort treated with abiraterone as the first-line therapy (without IDC-P vs. with IDCP pattern 1 vs. with IDC-P pattern 2).

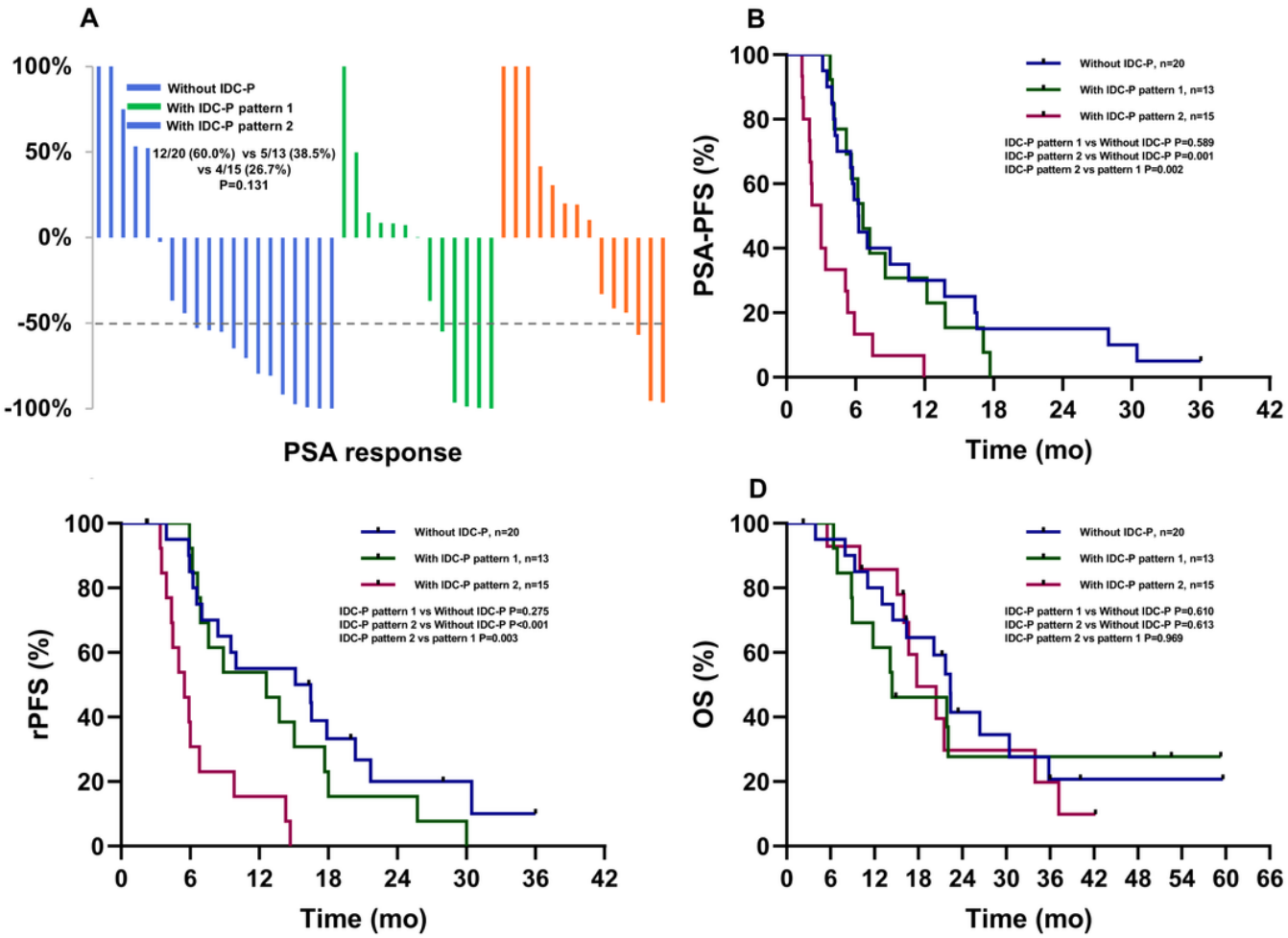

Figure 3

Waterfall chart of PSA response (A) and Kaplan-Meier curves of PSA-PFS (B), rPFS (C) and OS(D) in the cohort treated with docetaxel as the first-line therapy (without IDC-P vs. with IDCP pattern 1 vs. with IDC-P pattern 2).

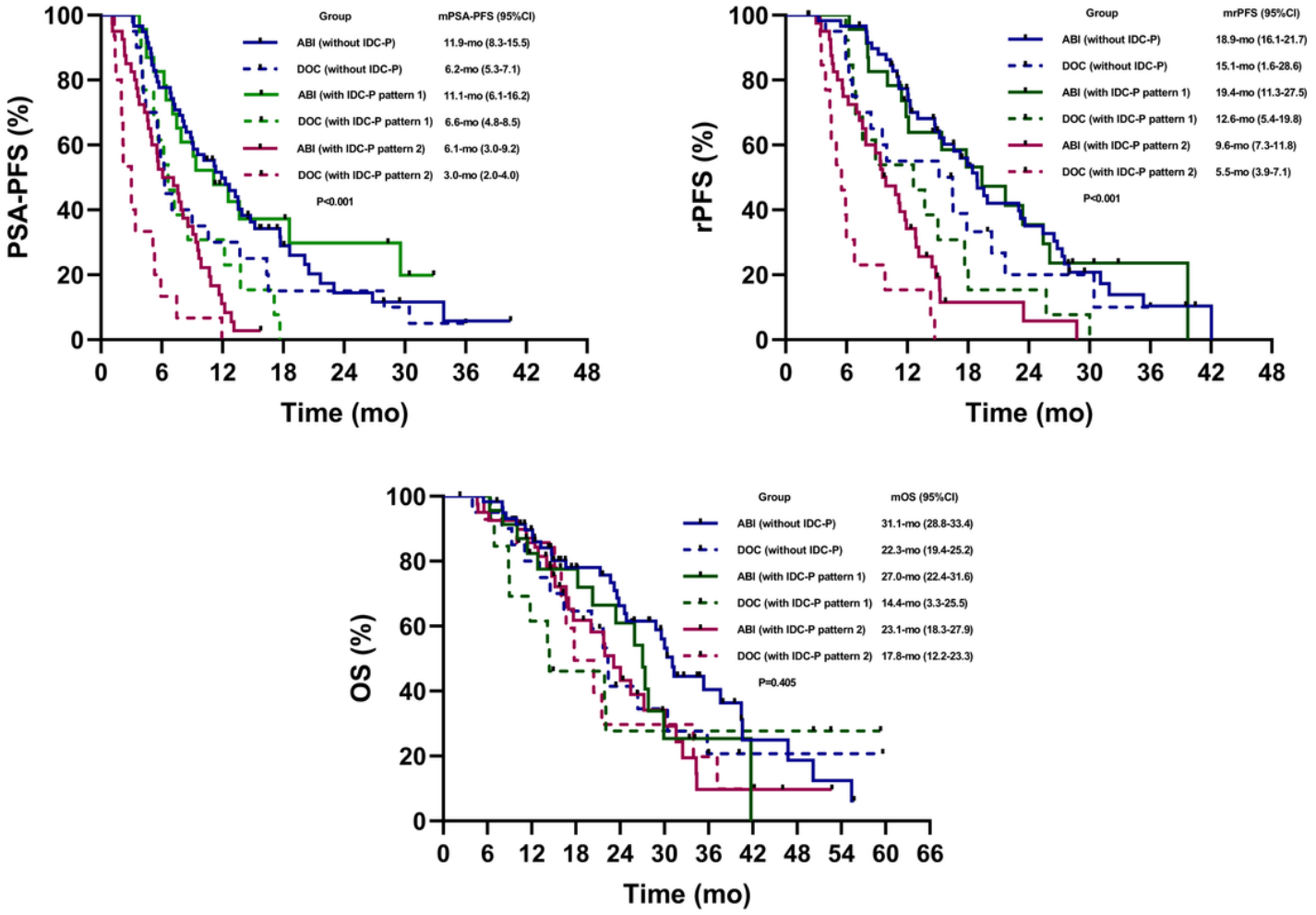

Figure 4

Kaplan-Meier curves of PSA-PFS (A), rPFS (B) and OS (C3) in the comparison between patients treated with abiraterone and docetaxel.

Supplementary Files

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