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Genitourinary Cancer

Prognostic Value of Germline DNA Repair Gene Mutations in De Novo Metastatic and Castration-Sensitive Prostate Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. De novo metastatic prostate cancer • Germline mutations • DNA repair genes • *BRCA2* • Prognostic value

Abstract

Background. Germline DNA damage repair gene mutations (gDDRm) have been found in approximately 12% of patients with metastatic prostate cancer (mPCa). Previous studies of the clinical impact of gDDRm have mainly been in the setting of metastatic castration-resistant prostate cancer (mCRPC). This study aimed to determine the prognostic value of gDDRm in de novo metastatic and castration-sensitive prostate cancer (mCSPC).

Materials and Methods. We retrospectively collected the records of 139 consecutive men with de novo mCSPC who initially received systemic therapies following guidelines. This included 128 patients who underwent genetic testing at our center and 11 patients referred to our center after being identified as gDDRm carriers. Time to mCRPC was collected. Kaplan-Meier and log-rank analysis were used to analyze the association between gDDRm and clinical outcomes. Survival outcomes were adjusted using multivariable Cox regression models.

Results. Of the 139 patients with de novo mCSPC, 28 gDDRm carriers were identified. Median time progressing to mCRPC was significantly shorter in patients carrying gDDRm than in those without mutations (8.3 vs 13.2 months; hazard ratio [HR], 2.37; $p < .001$). Moreover, median progression time was almost halved in *BRCA2* carriers (6.3 vs. 13.2 months; HR, 3.73; $p < .001$). Subgroup analysis revealed that the presence of gDDRm indicated poor therapy response regardless of disease volume and prostate-specific antigen nadir within the first 7 months. Presence of gDDRm remained independently associated with increased risk of progression to mCRPC in multivariate analysis (adjusted HR, 1.98; $p = .006$).

Conclusion. Our study suggested that positive gDDRm status predicted rapid progression to castration resistance in patients with de novo mCSPC. We propose identifying gDDRm status at the time of diagnosis for mCSPC patients, considering it is the first step of tailoring individualized treatment. In addition, DNA repair genes were a good therapeutic target for poly (ADP-ribose) polymerase inhibitors, and our results call for more frontline targeted therapy trials in gDDRm carriers to prolong the progression time. ***The Oncologist*** 2020;25:e1042–e1050

Implications for Practice: Results of this study suggested that positive germline DNA damage repair gene mutation (gDDRm) status predicted earlier progression to castration resistance in patients with de novo metastatic and castration-sensitive prostate cancer (mCSPC). These findings indicated the importance of intense therapy for some subgroups of mCSPC, especially for mCSPC harboring gDDRm with low-volume disease. Moreover, gDDRm was a good therapeutic target for poly (ADP-ribose) polymerase inhibitors, and these findings call for more molecular marker driven trials moving to the mTNPC setting.

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Introduction

Germline mutations in several DNA repair genes (DRGs), especially *BRCA2* alterations, have been reported to be associated with increased risk of prostate cancer (PCa) [1, 2]. Recently, two landmark publications revealed that patients harboring germline DNA damage repair gene mutations (gDDRm) accounted for 8%–12% of men with metastatic prostate cancer (mPCa) [3, 4], which was significantly higher than that in localized PCa (5%) and the general population (3%) [3, 5]. Our previous study also confirmed a similar mutation prevalence in Chinese patients with PCa, although there is a large difference in risk of PCa between China and the West [6]. Moreover, gDDRm has been identified to be associated with aggressive disease and poor survival [7, 8], indicating that patients with DNA repair deficiency may have an inferior response to standard of care systemic therapies. To elucidate the role of gDDRm in response to systemic therapy, many case series have been reported [9–13]. However, most previous studies on the prognostic value of gDDRm have focused on patients with metastatic and castration-resistant prostate cancer (mCRPC), with few data reported in patients with metastatic castration-sensitive prostate cancer (mCSPC). Owing to insufficient data and conflicting results, the consensus on the prognostic value of gDDRm in response to systemic therapy in patients with mCSPC has not yet been reached.

De novo mPCa represents the more aggressive disease compared with recurrent mPCa and is associated with almost 50% of PCa-related death [14–16]. Most patients with de novo mPCa missed the opportunity to receive surgical treatment and were initially treated with androgen deprivation treatment (ADT), ADT plus abiraterone, or ADT plus docetaxel. Patients with mCSPC will inevitably progress to mCRPC, although the progression time varies. Moreover, few biomarkers estimating time to castration resistance makes it difficult for individual management. Recent studies indicated that the use of poly (ADP-ribose) polymerase (PARP) inhibitors or platinum-based chemotherapy might be of benefit for patients with gDDRm [17, 18]. Thus, there is an increasing interest in defining the role of gDDRm in de novo mCSPC cases to potentially guide therapy choices.

In this study, we focused on the association between gDDRm status and time to castration resistance to determine the prognostic value of gDDRm in mCSPC cases receiving standard ADT based therapies.

Subjects, Materials, and Methods

Patient Cohort

This study included 139 consecutive patients with de novo mPCa who received treatment at Fudan University Shanghai Cancer Center. All patients had been previously tested for gDDRm between January 2018 and March 2019. This cohort included 128 patients who underwent genetic testing at our center, which has been reported in our previous study [6], and 11 patients who were referred to our center after identified as gDDRm carriers. Importantly, patients were selected regardless of family history, age of diagnosis, or any other known genetic background.

Moreover, patients had to have histologically confirmed prostate adenocarcinoma and received ADT only or combination therapy (ADT plus abiraterone or docetaxel). Patients receiving additional concurrent anticancer therapies were excluded. The clinical characteristics of the study population were retrospectively reviewed via medical records and telephone interview. Baseline clinical information, including age at diagnosis, baseline prostate-specific antigen (PSA), Gleason score, disease volume, PSA nadir within the first 7 months of initial treatment, and family history of any cancer, was collected. High-volume disease (defined as the presence of visceral metastasis or four or more bone lesions with at least one outside of the vertebral column and pelvis according to the CHAARTED trial) was annotated [19]. For all the 139 patients, 100 (72%) patients were initially treated with ADT, with 18 (13%) patients and 21 (15%) patients receiving ADT plus abiraterone and ADT plus docetaxel, respectively. Finally, 99 (71%) patients have progressed to mCRPC at last follow-up. Median follow-up was 9.2 months. Written informed consents were obtained from all participants prior to enrollment.

Sequencing and Detection of gDDRm

For 128 patients who were included in the cohort we previously analyzed, sequencing and bioinformatics methodology have been reported in our previous study [6]. Different platforms were used as the sequencing platform evolved during the study. Next-generation sequencing panel, including 63 PCa-related genes for 58 patients, 508 genes for 1 patient, 618 genes for 11 patients, and whole-exome for 58 patients, was used to sequence the germline DNA extracted from patients' peripheral blood mononuclear cell. Annotations were defined with ANNOVAR (http://annovar.openbioinformatics.org/en/latest). Then, we retrieved information of variants from the Exome Aggregation Consortium ExAC Browser (http://exac.broadinstitute.org/), 1000 Genomes (www.1000genomes.org), the single-nucleotide polymorphism database of the National Center for Biotechnology Information (dbSNP) version 139 (www.ncbi.nlm.nih.gov/projects/SNP), and ClinVar. For this analysis, we focused on DNA repair genes: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *ERCC3*, *FAM175A*, *FANCA*, *GEN1*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51C*, and *RAD51D*. Based on the American College of Medical Genetics and Genomics criteria, the pathogenic and likely pathogenic mutations are defined as (a) all truncating mutations unless their allele frequency is 1% or higher in population databases or is identified as benign or likely benign in the ClinVar; (b) nonsynonymous mutations if their allele frequency is less than 1% and identified as pathogenic and likely pathogenic mutations in the ClinVar; and (c) in-frameshift mutations, which affect more than three amino acids.

Outcome Measures and Statistical Analysis

The primary endpoint was progression to mCRPC, which represented the time from initial treatment to castration resistance. Castration resistance was defined according to the European Association of Urology (EAU) guidelines (2019

edition): biochemical progression (three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA >2 ng/mL) or radiographic progression (the appearance of new lesions: 1 or ≥2 bone lesions on bone scan, or a soft tissue lesion as defined by the RECIST) and castrate serum testosterone <50 ng/dL or 1.7 nmol/L.

The study population was divided into two groups based on gDDRm status. Baseline characteristics, including Gleason score, PSA nadir within the first 7 months, disease volume, family history, and progression to mCRPC, were compared between two groups using Pearson's chi-squared test or Fisher's exact test. Continuous variable, such as age at diagnosis and baseline PSA, were compared using Student's *t* test. Then, we used Kaplan-Meier method to calculate survival (time to castration resistance) and used univariate and multivariate Cox proportional hazards model to analyze prognostic factors.

Finally, we assessed the prognostic value of germline *BRCA2* mutations, using the Kaplan-Meier method and Cox regression analysis. All *p* values were two-sided and $p < .05$ was defined as statistically significant. Statistical analysis was performed using SPSS 20.0 and R 3.3.0.

Results

Patients' Characteristics and Germline DNA Repair Gene Mutation Status

There were 139 patients with de novo mPCa enrolled in this study. Deleterious gDDRm were identified in 28 patients. The distribution of pathogenic mutation genes was as follows: *BRCA2*, 17 patients; *ATM*, 2 patients; *MSH6*, 2 patients; *CHEK2*, 1 patient; *ERCC3*, 1 patient; *FANCA*, 1 patient; *GEN1*, 2 patients; *MSH2*, 1 patient; *PALB2*, 2 patients (1 patient had both *BRCA2* and *MSH6* mutations). The detailed gDDRm types and locations in this cohort were shown in Table 1.

Overall, patients with gDDRm had a younger age of onset than patients without mutations (median, 63 vs. 66 years, $p = .025$). The frequency of patients receiving ADT alone after diagnosis was similar between gDDRm carriers and noncarriers (71% vs. 72%). At the last follow-up, 71% of patients had progressed to mCRPC in our cohort. Eighty-six percent of gDDRm carriers progressed to castration resistance whereas 68% of gDDR wild-type cases progressed. Detailed clinical and pathological characteristics of patients were summarized in Table 2. Groups by gDDRm status appeared comparable with regard to clinical prognostic variables.

Germline DNA Repair Gene Mutations and Time to Castration Resistance

Analysis of progression to mCRPC included all 139 patients (Fig. 1). Patients with gDDRm had a median time to castration resistance of 8.3 versus 13.2 months in patients without gDDRm (hazard ratio [HR], 2.37; 95% confidence interval [CI], 1.48–3.80; $p < .001$; Fig. 2A). After adjusting treatment type, age of onset, baseline PSA, Gleason score, metastases volume, and PSA nadir within first 7 months, multivariate Cox regression model revealed that gDDRm was independently associated with higher risk of progression to mCRPC (adjusted HR, 1.98; 95% CI, 1.22–3.23; $p = .006$; Table 3). Moreover, high-volume disease (adjusted HR, 1.74; 95% CI; 1.07–2.82; $p = .024$; Table 3) and PSA nadir >4 ng/mL within the first 7 months (adjusted HR, 1.57; 95% CI, 1.02–2.41; $p = .042$; Table 3) were also significantly associated with higher risk of progression to mCRPC.

We stratified patients into two groups according to disease volume and PSA nadir within 7 months for further investigation, respectively. Interestingly, in both high- and low- volume metastatic disease groups, the shorter median time to mCRPC were observed in patients carrying gDDRm (8.2 vs. 11.3 months; $p = .032$; Fig. 3A; 10.2 vs. 24.2 months; $p = .004$; Fig. 3B). Furthermore, in group with PSA nadir ≤4 ng/mL within 7 months, the prognostic value of gDDRm remained significant and the median time to mCRPC was 9.7 versus 18.2 months for patients with and without gDDRm ($p < .001$; Fig. 3C). Besides, patients with the presence of gDDRm had a numerically shorter progression time than non-carriers for patients with PSA nadir >4 ng/mL, although no statistical difference was observed (6.5 vs. 11.3 months, $p = .15$; Fig. 3D).

BRCA2 Mutations and Time to Castration Resistance

Similar to the role of gDDRm, Kaplan-Meier analysis showed a shorter progression time in *BRCA2* mutation carriers compared with noncarriers (6.3 vs. 13.2 months; HR, 3.73; 95% CI, 2.12–6.58; $p < .001$; Fig. 2B). This association remained significant after adjusting for other potential prognostic variables in a multivariate Cox regression model (adjusted HR, 3.14; 95% CI, 1.76–5.60; $p < .001$; Table 3). Additional factor such as high-volume disease was also independently associated with higher hazard of progression to mCRPC in multivariate analysis (adjusted HR, 1.97; 95% CI, 1.21–3.22; $p = .007$; Table 3), whereas PSA nadir within first 7 months was nearly significantly associated with higher hazard of progression (adjusted HR, 1.55; 95% CI, 0.98–2.44; $p = .059$; Table 3).

Discussion

To shed a new light on the prognostic role of gDDRm in mCSPC, we retrospectively analyzed clinical outcome of patients with mCSPC by gDDRm status. Using a large number of patients and well-adjusted analysis, we confirmed that the presence of gDDRm was an independent prognostic factor for ADT-based therapies in patients with mCSPC. This finding is of great interest because not only prognostication improvement but also early identification of gDDRm may lead to precise application of targeted therapy such as PARP inhibitors or platinum-based chemotherapy in the setting of mCSPC [17, 20, 21]. Moreover, this strategy is gradually attracting attention because moving effective therapies earlier has produced great success in mCSPC [22, 23].

Our data echoed the biological finding from a recent paper suggesting that patients with CSPC with gDDRm presented elevated genomic instability and a mutational profile closely resembling mCRPC [24]. For example, *MED12L*/*MED12*, a modulator of WNT/b-catenin signaling, is preferentially amplified in both *BRCA2*-driven primary tumors and sporadic mCRPC, which may help explain risk of early castration resistance for patients with germline *BRCA2* mutations [24].

Table 1. Pathogenic and likely pathogenic germline mutations in our cohort (*n* = 28)

ID	Gene	Chr	Start	End	Ref.	Alt.	NC change	AA change	Mutation type
1	BRCA2	13	32944609	32944610		AAAA	c.8402_8403insAAAA	p.F2801Lfs*	Frameshift ins
2	BRCA2	13	32914137	32914137	C	A	c.5645C>A	p.S1882*	nonsense
3	BRCA2	13	32971034	32971034	G	T	c.9502-1G>T	p.X3168_splice	Splice
4	BRCA2	13	32914174	32914174	C	G	c.5682C>G	p.Y1894*	nonsense
5	BRCA2	13	32900690	32900691		AT	c.571_572insAT	p.M192Ifs*	Frameshift ins
6	BRCA2	13	32914174	32914174	C	G	c.5682C>G	p.Y1894*	nonsense
7	BRCA2	13	32944692	32944692	C	T	c.8485C>T	p.Q2829*	nonsense
8	BRCA2	13	32912902	32912905	AAGA		c.4410_4413delAAGA	p. K1472Tfs*6	Frameshift del
9	BRCA2	13	32914066	32914069	AATT		c.5574_5577delAATT	p. I1859Kfs*3	Frameshift del
10	BRCA2	13	32911145	32911148	GACA		c.2653_2656delGACA	p. D885Mfs*9	Frameshift del
11	BRCA2	13	32911337	32911337	T		c.2845delT	p.Y949Mfs*11	Frameshift del
12	ATM	11	108236104	108236104	C	T	c.9040C>T	p.Q3014*	nonsense
13	ATM	11	108121756	108121756	G	T	c.1564G>T	p.E522*	nonsense
7	MSH6	2	48033792	48033795	TAAC		c.4001+2delTAAC	p.X1334_splice	Splice
14	MSH6	2	48033792	48033795	TAAC		c.4001+2delTAAC	p.X1334_splice	Splice
15	BRCA2	13	32930649	32930652	CAGG		c.7520_7523delCAGG	p.G2508Vfs*15	Frameshift del
16	BRCA2	13	32914356	32914356	C	G	c.C5864G	p.S1955*	nonsense
17	CHEK2	22	29130450	29130464	TCCTCAGG TTCTTGG		c.246_260delTCCT CAGGTTCTTGG	p.D82_E86del	Inframeshift del
18	ERCC3	2	128030510	128030511	CT		c.1757_1758delCT	p.Q586Rfs*17	Frameshift del
19	FANCA	16	89874714	89874715		CACAATGCCT TGCAGGCTAC	c.583_584insCACAAT GCCTTGCAGGCTAC	E195Gfs*57	Frameshift ins
20	GEN1	2	17955667	17955667	C	T	c.C1201T	p.R401*	nonsense
21	GEN1	2	17955667	17955667	C	T	c.C1201T	p.R401*	nonsense
22	MSH2	2	47702205	47702205	C	T	c.C1801T	p.Q601*	nonsense
23	BRCA2	13	32914174	32914174	C	G	c.5682C>G	p.Y1894*	nonsense
24	BRCA2	13	32914127	32914130	GAGA		c.5638_5641delGAGA	p.E1879Ifs*29	Frameshift del
25	BRCA2	13	32968969	32968969	G		c.9401delG	p.G3134Afs*29	Frameshift del
26	BRCA2	13	32911681	32911684	GTCA		c.3192_3195delGTCA	p.S1064Lfs*12	Frameshift del
27	PALB2	16	23646807	23646807	A		c.1059delA	p.S354Lfs*2	Frameshift del
28	PALB2	16	23652432	23652432	T		c.47delT	p.K16Sfs*2	Frameshift del

Abbreviations: AA, amino acid; Alt., alternative base(s); Chr, chromosome; ID, identifier; NC, nucleotide; Ref = reference base(s).

Although biologically reasonable, the evidence reported to data about the role of gDDRm in response to systemic therapies in PCa remained conflicting, and almost all prior studies focused on mCRPC [9–13]. A retrospective data of 319 patients, including 22 gDDRm carriers, reported a worse outcome from abiraterone plus enzalutamide treatment for patients with mCRPC with gDDRm (3.3 vs. 6.2 months) [11]. The data from the PROREPAIR-B trial showed that germline *BRCA2* mutations have a deleterious impact on mCRPC outcomes but not for non-*BRCA2* germline mutations [9]. Conversely, results from the NCI9012 trial (NCT01576172) of abiraterone and the PARP inhibitor veliparib suggested that patients with PCa with DNA damage repair defects (including somatic and germline mutations) appear to be benefiting from abiraterone treatment [13]. Similar results were observed in the data reported by Antonarakis et al., in which nine carriers of *BRCA*/*ATM* experienced a more prolonged progression-free survival (PFS) compared with noncarriers (15.2 vs. 10.8 months) [12]. Finally, in a retrospective series with 330 noncarriers and 60 gDDR carriers, there was no association between the presence of gDDRm and the response to abiraterone plus enzalutamide or docetaxel [10]. The contradictory conclusions from prior studies is multifactorial. Retrospective design and a relatively limited number of patients with gDDRm would introduce bias in analysis. Also, heterogeneity of disease burden and prior treatments could play a role in disparate results. Moreover, different variants in DNA repair genes, even in the same genes, may lead to different responsiveness to specific therapies, and all prior studies did not control for other potential prognostic factors such as genomic aberrations in *AR*, *TP53*, and *RB1* [25, 26], which could also contribute to explain the conflicting data.

However, in the setting of mCSPC, the data about impact of gDDRm remained sparse. A recent study exploring the genomic alterations in patients who developed mCRPC in a short amount of time (median time to mCRPC, 1.17 years) found that *BRCA2* and *CDK12* mutations were significantly more common than described in The Cancer Genome Atlas cohort, and patients with germline or somatic *BRCA2* alterations had the lower time to ADT progression compared with

Table 2. Baseline clinical and pathological characteristics, by germline mutation status

Characteristics	Patients with germline mutations (*n* = 28)	Patients without germline mutations (*n* = 111)	*p* value
Median age at diagnosis (IQR), yr	63 (58–67)	66 (60–71)	.025
Median baseline PSA (IQR), ng/mL	238 (98–407)	100 (47–252)	.9
Gleason grade group, *n* (%)			.99
1	0 (0)	0 (0)	
2	0 (0)	3 (2.7)	
3	3 (11)	9 (8.1)	
4	8 (29)	38 (34)	
5	17 (60)	59 (53)	
Unknown	0 (0)	2 (1.8)	
Metastases volume,[a] *n* (%)			.11
High volume	23 (82)	70 (63)	
Low volume	5 (18)	39 (35)	
Unknown	0 (0)	2 (1.8)	
PSA nadir within the first 7 mo of initial treatment, ng/mL			.7
<0.2	5 (18)	28 (25)	
0.2–4	13 (46)	47 (43)	
>4	10 (36)	36 (32)	
Initial therapy regimen after diagnosis, *n* (%)			.4
ADT only	20 (71)	80 (72)	
ADT + docetaxel	6 (21)	15 (14)	
ADT + abiraterone	2 (7.1)	16 (14)	
Family history of cancers, *n* (%)	10 (36)	31 (28)	.4
Progression to mCRPC at the last follow-up, *n* (%)	24 (86)	75 (68)	.058

[a]High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with at least one outside of the vertebral column and pelvis according to the CHAARTED trial.
Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; mCRPC, metastatic and castration-resistant prostate cancer; PSA, prostate-specific antigen.

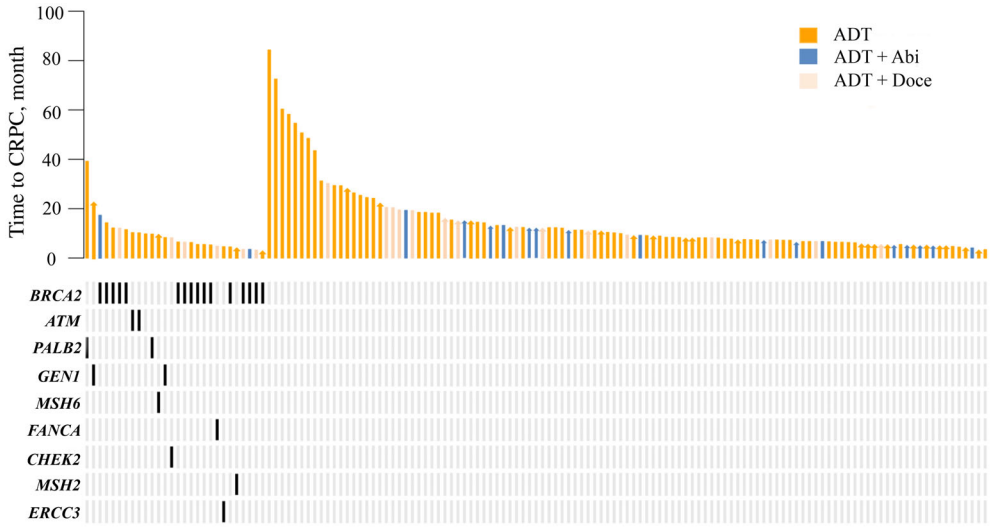

Figure 1. Swimmers plot of time to metastatic CRPC from initial treatment, stratified by germline DNA damage repair gene mutation status.
Abbreviations: Abi, abiraterone; ADT, androgen deprivation therapy; CRPC, castration resistance prostate cancer; Doce, docetaxel chemotherapy.

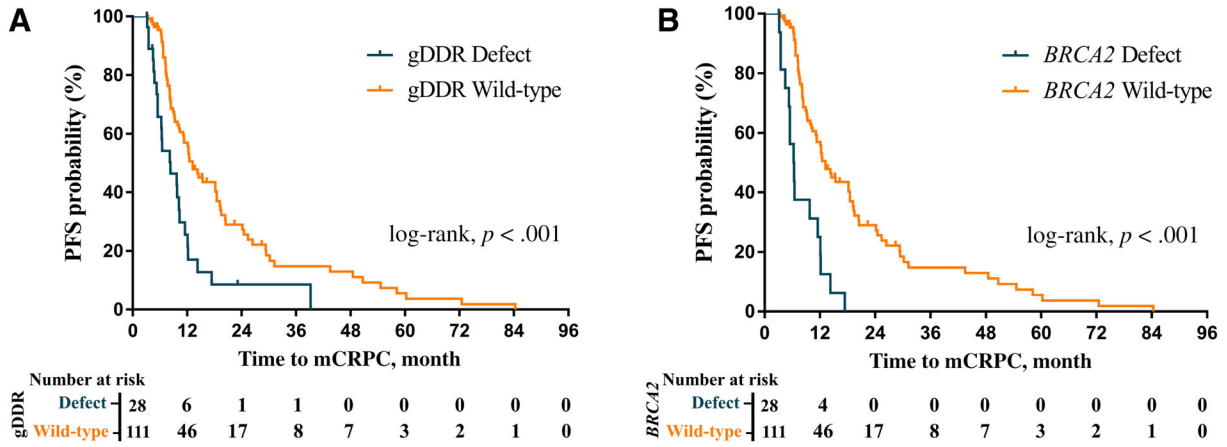

Figure 2. Kaplan-Meier plots of time to mCRPC from initial treatment in patients. **(A):** Time to mCRPC from initial treatment in patients by gDDR gene mutation. (**B):** Time to mCRPC from initial treatment in patients with and without BRCA2 mutation.
Abbreviations: gDDR, germline DNA damage repair; mCRPC, metastatic castration resistance prostate cancer

Table 3. Cox regression analyses of time to mCRPC

	Univariate analysis		Multivariate analysis	
Time to mCRPC	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
Model 1				
Any gDDRm	2.37 (1.48–3.80)	<.001	1.98 (1.22–3.23)	.006
Treatment (combination therapy vs. ADT alone)	1.00 (0.62–1.63)	.9	0.86 (0.51–1.43)	.6
Age of onset, yr	0.99 (0.96–1.01)	.4	0.99 (0.97–1.02)	.5
Baseline PSA (log), ng/mL	1.38 (0.99–1.91)	.058	1.14 (0.79–1.64)	.5
Gleason grade group (4–5 vs. 1–3)	1.63 (0.84–3.16)	.15	1.85 (0.95–3.61)	.070
High-volume disease (present vs. absent)	1.86 (1.17–2.94)	.008	1.74 (1.07–2.82)	.024
PSA nadir within the first 7 mo (>4 vs. ≤4), ng/mL	1.36 (0.91–2.04)	.13	1.57 (1.02–2.41)	.042
Model 2				
mBRCA2 mutation	3.73 (2.12–6.58)	<.001	3.14 (1.76–5.60)	<.001
Treatment (combination therapy vs. ADT alone)	0.94 (0.57–1.55)	.8	0.67 (0.39–1.14)	.14
Age of onset, yr	0.99 (0.97–1.01)	.4	0.99 (0.97–1.02)	.8
Baseline PSA (log), ng/mL	1.32 (0.94–1.86)	.11	1.05 (0.72–1.53)	.8
Gleason grade group (4–5 vs. 1–3)	1.48 (0.74–2.98)	.3	1.25 (0.61–2.55)	.5
High-volume disease (present vs absent)	1.93 (1.20–3.11)	.007	1.97 (1.21–3.22)	.007
PSA nadir within the first 7 mo (>4 vs ≤4), ng/mL	1.42 (0.93–2.16)	.10	1.55 (0.98–2.44)	.059

Model 1 evaluated the effect of any gDDRm versus wild-type. Model 2 evaluated the effect of *BRCA2* mutation versus wild-type.
High-volume disease was defined as the presence of visceral metastases or ≥ 4 bone lesions with at least one outside of the vertebral column and pelvis according to the CHAARTED trial.
Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; gDDRm, germline DNA repair gene mutations; PSA, prostate-specific antigen.

noncarriers, but the difference was not statistically significant, possibly owing to a limited number of patients carrying mutations and only two patients with germline mutations [27]. To overcome these disadvantages, we enrolled 139 patients with mCSPC with full adjustment of well-known risk factors. In addition to confirming that independent of other clinical prognostic factors, gDDRm indicated earlier progression to castration resistance in mCSPC, our subgroup analysis also revealed that gDDRm was associated with poor therapy response, regardless of disease volume. Currently, with multiple treatment options available for patients with mCSPC [28–30], treatment selection to optimize patients outcome has become increasingly difficult. Only disease volume has been validated as a reliable prognostic factor to guide treatment decisions [16], which impede the implement of individualized treatment. Our study provided another usable genomic biomarker to help identify patients who may benefit from intensified therapy and highlighted the necessity of intensified treatment in low-volume mPCa carrying gDDRm. Besides, National Comprehensive Cancer Network Asia Consensus still recommends ADT alone as first-line therapy for patients with mCSPC [31], and some patients preferred to receive ADT because of economic cost or intolerable adverse effect induced by combination therapy. Thus, patients receiving ADT constituted a considerable proportion of entire group in Asia, which also emphasizes the value of our study.

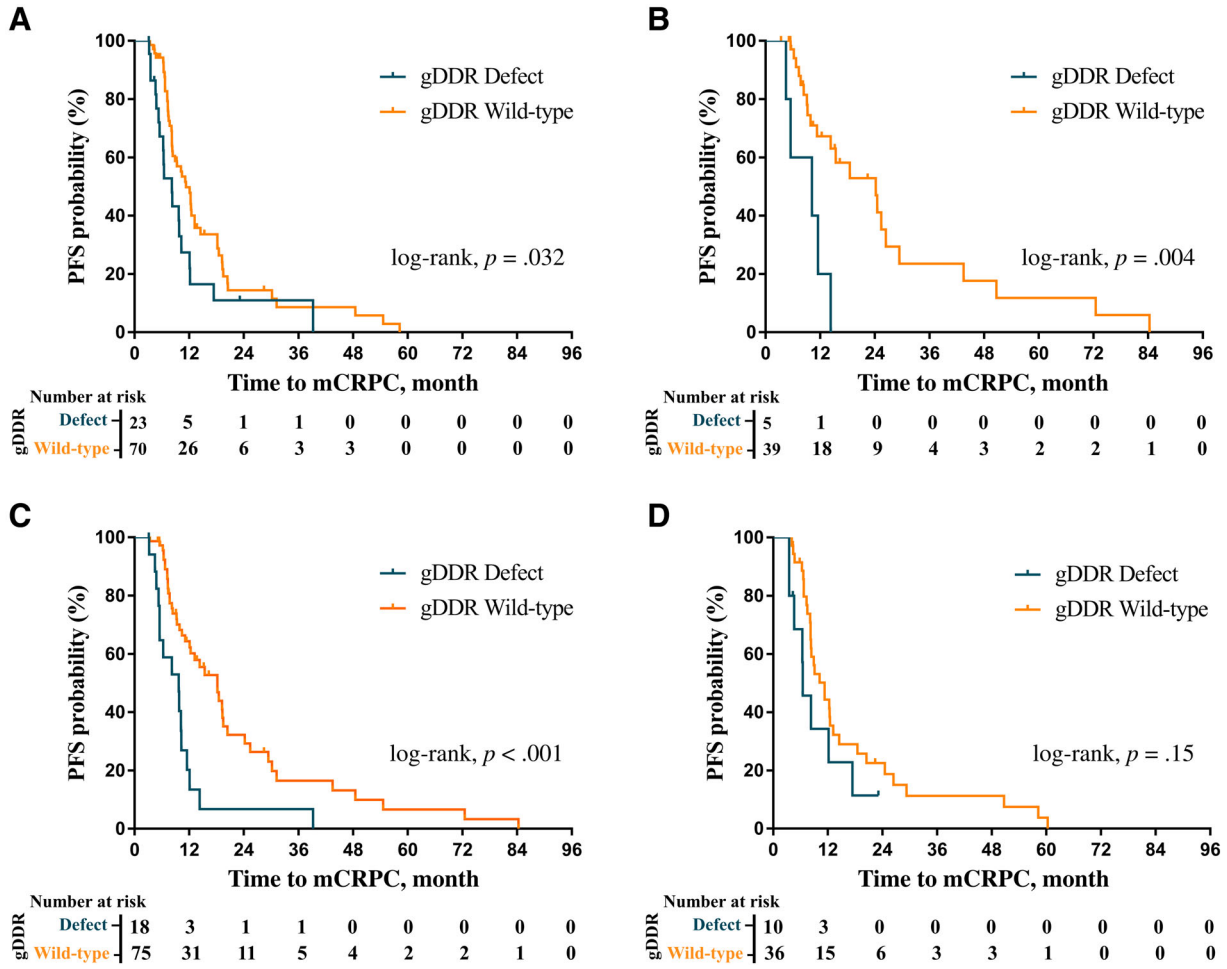

Figure 3. Kaplan-Meier plots of time to mCRPC in patient subgroups. **(A):** Kaplan-Meier plot of time to mCRPC from initial treatment in high-volume disease patient subgroup by gDDR gene mutation (gDDRm). **(B):** Kaplan-Meier plot of time to mCRPC from initial treatment in low-volume disease patient subgroup by gDDRm. **(C):** Kaplan-Meier plot of time to mCRPC from initial treatment in patient subgroup with prostate-specific antigen nadir ≤4 ng/mL by gDDRm. **(D):** Kaplan-Meier plot of time to mCRPC from initial treatment in patient subgroup with PSA nadir >4 ng/mL by gDDRm

Abbreviations: gDDR, germline DNA damage repair; mCRPC, metastatic and castration resistance prostate cancer; PFS, progression-free survival.

In addition to pinpointing individuals progressing rapidly to mCRPC, the presence of gDDRm is also a druggable biomarker indicating the benefit of PARP inhibitors or platinum-based chemotherapy [17, 18]. The National Comprehensive Cancer Network Prostate Cancer guideline now recommends germline genetic testing for all patients with mPCa, regardless of family history. Thus, increasingly more gDDRm carriers have been identified in the stage of mCSPC. However, the recommendation of use of PARP inhibitors remained confined to patients with mCRPC who have failed multiple lines of therapy, based on the evidence from PROfound study. Identifying the germline mutation status did not translate into clinical benefit for patients with mCSPC with gDDRm. Results from the SOLO1 trial revealed that median PFS was significantly longer when olaparib was used as a first-line maintenance therapy in ovarian cancer (~50 vs. 13.8 months) [32]. The outstanding results achieved in ovarian cancer suggested that early engagement of PARP inhibitors for patients with gDDRm could also be considered in mPC, and more prospective trials were warranted to confirm this treatment strategy.

Our study is still relevant in the treatment of recurrent mPCa. In this subgroup, the benefit of intensified therapy is less convincing and even more debatable in the era of new imaging. Thus, ADT alone was the preferred treatment for recurrent mPCa. Our results suggested that patients with gDDRm were prone to resistant to conventional ADT. Thus, there is an unmet need to prospectively test the hypothesis that patients with recurrent mPCa with gDDRm have worse outcome to ADT and therefore might benefit more from intensified therapy.

Considering that *BRCA2* was identified as the core functional components in homologous recombination repair pathway and the most commonly mutated DNA repair gene in our cohort [33], we further separately examined the effect of *BRCA2* and found median progression time was almost halved in *BRCA2*-mutant cases compared with those without mutations (6.3 vs 13.2 months). The rapid progression to castration resistance were further enhanced when considering *BRCA2* alone. Our data indicated discerning the different prognostic role in the full spectrum of DRGs is needed.

There are several limitations in our study. Although we achieved standard of care following guidelines in a single center, retrospective design remained a significant limitation. Second, we incorporated clinical prognostic factors such as high-volume disease and PSA nadir after initial treatment, which were recommended in the EAU guidelines to perform a multivariate analysis. However, emerging evidence showed genomic alterations in *TP53*, *PTEN*, *RB1*, and Wnt-pathway may also impact response to systemic therapy [25, 34, 35], which were not adjusted in our Cox regression model. Finally, that 72% of patients in our cohort were treated with ADT alone is also a limitation. Therefore, our conclusions were mainly based on the fact that gDDRm was associated with poor response to ADT in mPCa. Further studies were needed to compare the outcome of intensified therapy in patients with mCSPC carrying gDDRm with those without mutations, giving the era of combination therapy is coming.

Conclusion

Our results confirmed that the presence of gDDRm indicated earlier progression to castration resistance in mCSPC. We propose identifying gDDRm status at the diagnosis for patients with mCSPC, considering it is the first step of tailoring individualized treatment. In addition, gDDRm was a good therapeutic target for PARP inhibitors. Our results call for more frontline targeted therapy trials for patients with mCSPC with gDDRm to prolong the progression time.

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Disclosures

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