Neoplasma 2023; 70(3): 476–484

doi:10.4149/neo_2023_221220N1190

Predictors of outcomes of docetaxel treatment in de novo metastatic hormone-sensitive prostate cancer: A single-center cohort study

Tomislav OMRČEN[1,*], Davor ETEROVIĆ[2], Tea JOZIĆ[3], Eduard VRDOLJAK[1]

[1]University Hospital Split, Department of Oncology and Radiotherapy, Spinčićeva 1, 21 000 Split, Croatia; 2University of Split, School of Medicine, Department of Medical Physics, Šoltanska 2, 21 000 Split, Croatia; 3General Practitioner Office Dr Krešimir Bago, Trg Hrvatske bratske zajednice 4, 21 000 Split, Croatia

**Correspondence: tomislavomrcen@yahoo.com*

Received December 20, 2022 / Accepted June 28, 2023

Six cycles of docetaxel in addition to androgen deprivation therapy (ADT) are currently one of the treatment options for patients with de novo metastatic hormone-sensitive prostate cancer (mHSPC). Since the outcomes in patients with high-volume (HV) disease remain modest, we aimed to identify patients for more intensified treatment. We report a cohort of 73 consecutive patients with de novo mHSPC treated with early docetaxel at the Department of Oncology and Radiotherapy, University Hospital of Split, Croatia, from October 2015 until March 2020. The outcomes analyzed were the occurrence of castration-resistant disease (CRPC) and death from any cause (OS). The median follow-up was 54 (50-73) months. Forty-six (63%) patients developed CRPC and 34 (47%) died during the follow-up. The median time to CRPC and median OS were 16.2 and 58.4 months, respectively. The risk of CRPC was higher for patients with high (above median) values of serum alkaline phosphatase (ALP) (HR=2.4; 95% CI [1.4–4.5]), lactate dehydrogenase (LDH) (HR=1.98; 95% CI [1.1–3.7]), prostate-specific antigen (PSA) (HR=1.8; 95% CI [1.1–3]), ECOG performance status >1 (HR=2; 95% CI [1.2–3.3]) and HV disease (HR=1.9; 95% CI [1.1–3.1]). The risk of any-cause death was higher in patients with high values of ALP, LDH, and ECOG performance status >1. The predictive value of LDH was independent of disease volume. A set of baseline characteristics could be used in conjunction with disease volume in deciding on the optimal treatment strategy for patients with de novo mHSPC.

Key words: hormone-sensitive; prostate cancer; docetaxel; predictors

Androgen deprivation therapy (ADT) has been the backbone of treatment for metastatic prostate cancer (PC) since the mid-twentieth century [1]. Despite attempts to improve the efficiency of ADT among men with metastatic PC by intermittent ADT or by the addition of first-generation antiandrogens, the duration of sensitivity to ADT is usually less than two years, and resistance to ADT occurs in most patients [2].

Within the past two decades, we have witnessed that the landscape of advanced PC is shifting, primarily based on the understanding of the role of the androgen receptor (AR) signaling pathway in disease progression. This shift translated into improvements in overall survival (OS), first for men with metastatic castration-resistant PC (mCRPC) and, a few years later, in men with metastatic hormone-sensitive PC (mHSPC) [3–18]. Despite proven advances in the treatment of mCRPC, the survival gain from chemotherapy (docetaxel, cabazitaxel), AR-targeted agents (ARTA) – abiraterone acetate plus prednisone (AAP) or enzalutamide (ENZ), radium-223, or immunotherapy (i.e. Sipuleucel-T) was rather limited and ranged from 2.5 to 4.5 months [4–11]. A significantly better outcome was achieved when docetaxel or ARTA, alone or combined, were administered at an earlier, hormone-sensitive stage, presumably to target the cancer cell clones resistant to ADT at the earliest opportunity and thus delay the castration resistance [12–18].

Given that the spectrum of patients receiving ADT for mHSPC is quite broad, clinicians need to know the pattern of the disease. Some patients present with synchronous metastatic disease (i.e., *de novo*), and others present with metachronous disease (e.g., after previous radical local treatment with curative intent). The largest proportion of patients who die from PC is from a pool of patients with synchronous mHSPC, and these patients have a shorter duration of hormone sensitivity, worse survival, and potentially different benefits from early intensification of treatment compared

with those with metachronous disease [19]. Some patients with mHSPC have a minimal disease, while others present with a widespread disease on conventional imaging modalities. This observation led to the stratification of patients according to 'disease volume', i.e., high-volume (HV) and low-volume (LV) disease [12]. Furthermore, some patients with mHSPC are fit and young, and others are old and frail.

ARTA plus ADT is currently the therapy of choice for the majority of patients with mHSPC, while docetaxel, alone or in combination with ARTA (i.e., triple therapy), is reserved for men with suspected more aggressive disease. Nevertheless, the choice between the use of docetaxel or ARTA in patients with mHSPC could be challenging. First, we lack trials that directly compare these treatment options or single-arm studies that identify the strong predictors of the outcome of either treatment aside from disease volume. Second, in a health-economically challenging environment, approved drugs in the treatment of advanced PC cannot be adequately sequenced.

In this study, we evaluated the impact of several morphological, clinical, and biochemical baseline parameters on the outcomes of the first-line docetaxel treatment in patients with *de novo* mHSPC, aiming to help clinicians shape the optimal treatment approach for their patients.

Patients and methods

Study design and conduct. This work is a single-center cohort study. We analyzed the outcomes of 73 consecutive patients with synchronous mHSPC treated with docetaxel in addition to ADT at the Department of Oncology and Radiotherapy, University Hospital of Split, Croatia, from October 2015 until March 2020. We aimed to identify the characteristics of a patient or a disease that could predict the outcomes of the treatment. The research was approved by the Ethics Committee of the University Hospital of Split (Approval number: 500-03/22-01/140). Written informed consent was obtained from all individual participants included in the study. The recruitment of patients was stopped approximately 2 years before the end of the research in December 2019. The cutoff date was February 1st, 2022.

Therapy. In addition to ADT (LHRH agonist leuprolide, administered subcutaneously at 3- or 6-month intervals), the patients received docetaxel at a dose of 75 mg/m^2 intravenously dissolved in 250 cm^3 of saline. Premedication included 8 mg oral dexamethasone 12 hours, 3 hours, and 1 hour before the docetaxel infusion. Docetaxel was administered as a one-hour infusion every three weeks. The planned number of docetaxel cycles was 6. Eighty-eight percent of patients received 6 cycles of docetaxel. The time between the onset of ADT and docetaxel treatment was within 3 weeks in 58 (80 %) patients, median 0 (0–13 days; 95% confidence interval (CI)).

Data analyses. Median follow-up (and its 95% CI) was assessed from the Kaplan-Meier curve by reverse censoring on death, in which survival is considered the event and death censoring. The outcomes analyzed were the occurrence of castration-resistant disease (CRPC) and death from any cause (OS). The CRPC definition was based on biochemical and/or clinical progression according to the Prostate Cancer Working Group (PCWG) 2 and RECIST 1.1 criteria [20, 21]. Death was not used as a surrogate of progression. The potential predictors analyzed had to have less than 1/3 of the missing values and included 5 biochemical and 4 nonbiochemical baseline patient/tumor characteristics (Table 1). The patients were grouped according to disease volume, and assessed radiologically (i.e. by computed tomography scan of the lungs, abdomen, and pelvis) or scintigraphically. HV disease was assumed in the presence of at least four bone metastases, with at least one outside the pelvis and the vertebral column, or in the presence of at least one visceral metastatic lesion (or both).

The baseline characteristics were compared between the subgroups, dichotomized by the disease volume (HV vs. LV), or serum lactate dehydrogenase (LDH) (above or below the median) by the Mann-Whitney test. The distributions of the cumulative probabilities of time-to-event outcomes were assessed by the Kaplan-Meier method and compared across the subgroups by the log-rank test. The hazard ratios were assessed assuming the proportionality of hazards between the groups compared. The grouping was according to median values of the quantitative predictors, Gleason score (GS) >7 vs. GS ≤7, and ECOG performance status (PS) = 0 vs. ECOG PS 1 or 2. All analyses were run by MedCalc® Statistical Software version 20.118 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

Results

Baseline characteristics. The patient age (median 66 years; range 44–80 years) and ECOG PS (45% of patients had ECOG PS >0) were typical for patients with mHSPC. The sites of metastases were both bone and lymph nodes in 42 (57.5%) patients, bone only in 18 (24.7%) patients, and lymph nodes only in 7 (9.6%) patients, and the remaining 6 (8.2%) patients had visceral metastases in addition to bone or bone and lymph node metastases. The majority of patients (N=49) had HV disease. The disease volume did not discriminate the patients according to age, the baseline serum levels of LDH and the GS, while the differences in neutrophil/lymphocyte ratio (NLR) and hemoglobin (HGB) serum concentration were apparent but not significant. In contrast, the patients with HV disease had approximately 2 times higher serum levels of PSA and alkaline phosphatase (ALP) and were less fit than the patients with LV disease (Table 1).

Overall outcomes. The median follow-up was 54 (50–73) months. Forty-six (63%) patients developed CRPC and 34 (47%) died during the follow-up. The median time to CRPC and median OS were 16.2 and 58.4 months, respectively.

Outcomes according to biochemical predictors. A baseline PSA serum level above the median value of 151 ng/ml predicted a shorter time to the development of CRPC (HR=1.8; 95% CI [1.3–3], p=0.02) but was not predictive for OS. Baseline LDH and ALP were both highly predictive of both castrate resistance-free survival (HR=1.98; 95% CI [1–3.7]; p=0.036 and HR 2.4; 95% CI [1.4–4.5]; p=0.001, respectively) and OS (HR=3.2; 95% CI [1.2–7.9]; p=0.017 and HR 2.3; 95% CI [1.1–4.5]; p=0.021, respectively). In particular, the patients with a serum LDH level above the median of 178 U/l had an approximately 3 times higher hazard of dying than the patients with a serum LDH level less than 178 U/l (Table 2 and Figure 1).

Outcomes according to nonbiochemical predictors. Compared with the patients with ECOG performance status 0, the patients with ECOG performance status >0 had a median time to castration resistance and OS approximately two times shorter (HR=2; 95% CI [1.2–3.3]; p=0.012 and HR=3.13; 95% CI [1.5–6.3]; p=0.0016, respectively). GS >7 was not predictive of either outcome, while HV disease predicted a shorter time to castration resistance but not OS (HR=1.9; 95% CI [1.1–3.1]; p=0.014 and HR=1.4; 95% CI [0.7–2.8]; p=0.355, respectively) (Table 3 and Figure 2).

The independent effects of LDH. Since LDH serum level proved to be the strongest predictor of the study outcomes (Figure 1) and independent of disease volume (Table 1), its independence from the other predictors was also assessed by comparing the respective medians (Cox regression could not be used due to sample size limitations). Patient age, serum prostate-specific antigen (PSA) and GS did not differ according to LDH. However, the patients with LDH levels above the median of 178 U/l also had significantly higher serum levels of ALP and NLR and were less fit than the patients with LDH levels below the median, while their serum HGB concentration was apparently but not significantly lower.

Subsequent treatment for CRPC. At the time of this analysis, 63 patients (86%) received treatment for CRPC, and most received either ENZ (33%) or AAP (26%), while eleven patients (15%) received chemotherapy (cabazitaxel) as first-line treatment for mCRPC. One patient received radium-223.

Study strength and limitations. We had a small cohort of patients with mHSPC, and the rather long median follow-up and the considerable number of outcomes investigated are relatively high for the single-center study. Consequently, we were able to demonstrate both clinically and statistically significant associations between the number of biochemical, radiological, and other characteristics of a patient and the disease with the outcomes of docetaxel treatment. However, some comparisons remained inconclusive, and the sample sizes were too small to run the multivariate analyses.

Discussion

Evidence has been presented in the last decade that has transformed the management of mHSPC. We now have clear

Table 1. Baseline patient and tumor characteristics and comparisons according to disease volume

	All patients	High-volume disease		p-value
	N=73	yes (N=49)	no (N=24)	
Quantitative; median(range)				
age at diagnosis (years)	66 (44–80)	66 (44–80)	66 (51–77)	0.87
prostate-specific antigen (ng/ml)	151 (3–5000)	185 (3–5000)	97 (4–1200)	0.013
lactate dehydrogenase (U/l); N = 46	179 (102–761)	180 (102–761)	177 (134–273)	0.38
alkaline phosphatase (U/l); N = 70	126 (52–5231)	238 (52–5231)	90 (55–189)	<0.0001
neutrophil/lymphocyte ratio	2.03 (0.75–7.5)	2.13 (0.75–7.5)	1.85 (0.84–3.8)	0.34
hemoglobin (g/dl)	138 (79–168)	137 (79–168)	142 (100–167)	0.20
Qualitative; N (%)				
Gleason score				
7	14 (19)	11 (22)	3 (12)	0.31
>7	59 (81)	38 (78)	21 (88)	
ECOG performance status				
0	40 (55)	21 (43)	19	0.012
1	31 (42)	26 (53)	5 (21)	
2	2 (3)	2 (4)	0	
Site of metastases				
lymph nodes only	7	0 (0)	7 (29)	
bone only	18	16 (33)	2 (8)	0.02
bone+lymph nodes	42	27 (55)	15 (63)	
bone+lymph nodes+visceral	6	6 (12)	0 (0)	

high-volume disease: the presence of ≥4 bone metastases, out of which at least one is out of the pelvis and the vertebral column, or the presence of at least one visceral metastatic lesion

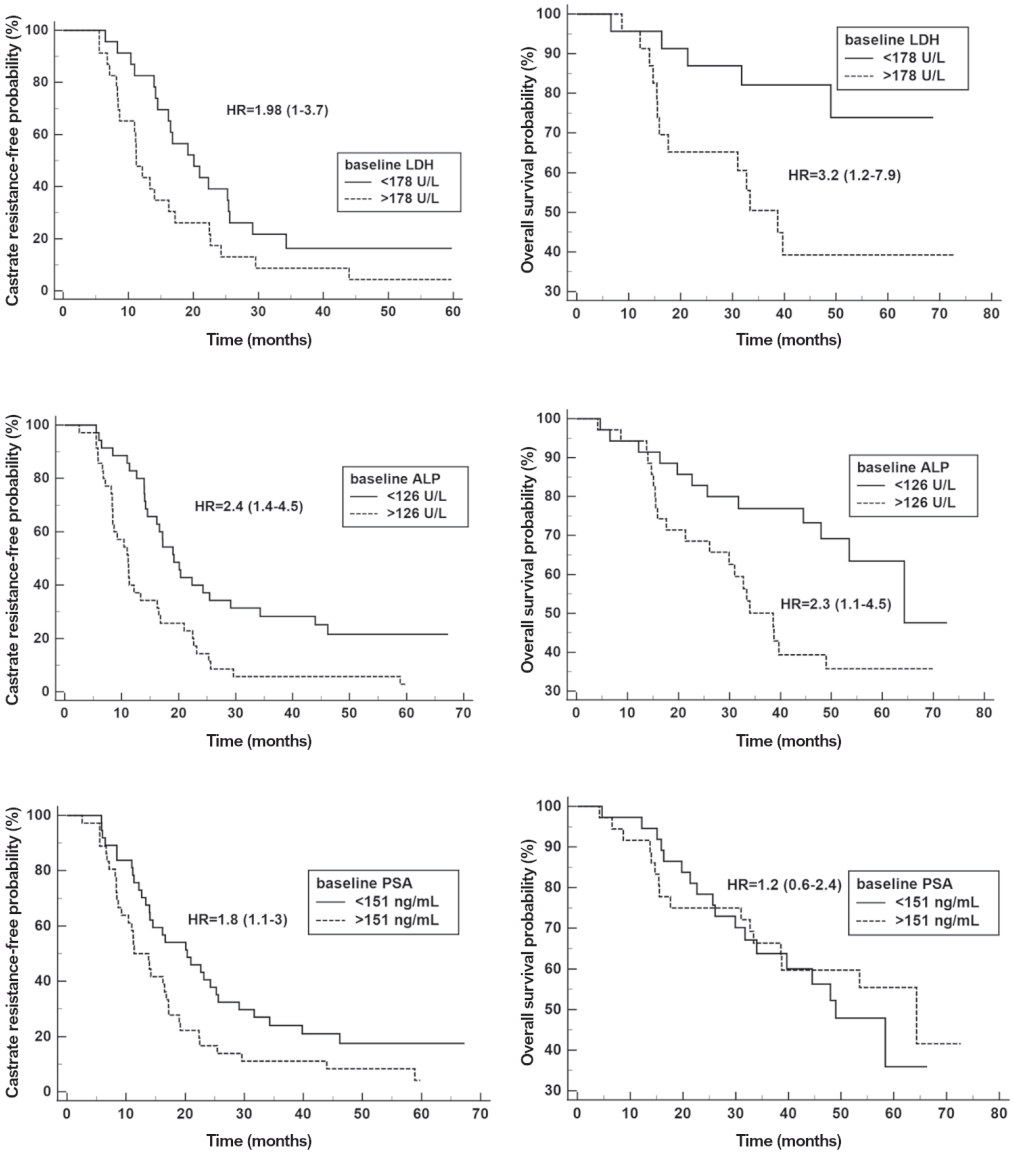

Figure 1. Kaplan-Meier survival estimates according to biochemical predictors

data for the OS benefit of double therapy when docetaxel or ARTA have been added to ADT in this setting [12–16]. Additional intensification of treatment, i.e., triplet therapy (combination of ADT, docetaxel, and an ARTA), could further improve the treatment outcome of a particular subset of patients with mHSPC [17, 18]. However, at some point, all patients will progress to CRPC.

Several prognostic and predictive factors have been proposed in mCRPC, whereas fewer data are available for mHSPC [22, 23]. Glass et al. reported four risk factors for mHSPC: the localization of bone disease, ECOG PS, PSA, and GS, while Gravis et al. reported that ALP, pain intensity, HGB, LDH, and bone metastases were independent risk factors for mHSPC [24, 25]. Currently, the prognosis of patients with mHSPC is mainly based on the disease volume criteria according to the CHAARTED trial and the time of onset of metastatic disease [12, 26]. The prognosis and selection of treatment for patients with mHSPC according to the criteria from the LATITUDE trial (i.e., low vs. high risk) is less often used [27]. Moreover, recommendations on the optimal treatment of these patients are derived from the prognostic model that stratifies these patients into good (i.e., LV and metachronous disease), intermediate (i.e., LV and synchronous or HV and metachronous disease), and poor (i.e., HV and synchronous disease) prognostic group [28]. However, the extent to which these prognostic factors are predictive of the outcome of a particular mHSPC treatment (i.e., chemotherapy, ART, or their combination) is questionable.

Table 2. Comparison of the baseline patient and tumor characteristics according to LDH

	LDH>178 U/l		p-value
	yes (N=23)	no (N=23)	
Quantitative; median months (range)			
age at diagnosis (years)	66 (53–77)	66 (51–73)	0.75
prostate-specific antigen (ng/ml)	277 (4–3199)	117 (15–5000)	0.14
hemoglobin (g/dl)	128 (79–167)	138 (84–163)	0.07
alkaline phosphatase (U/l)	237 (60–1768)	88 (52–1254)	0.006
neutrophil/lymphocyte ratio	2.8 (0.75–5.7)	1.75 (1–3.2)	0.01
Qualitative; N (%)			
Gleason score			
7	6 (26)	3 (13)	0.27
> 7	17 (74)	20 (87)	
ECOG performance status			
0	7 (30)	15 (65)	0.01
1	16 (70)	6 (26)	
2	0 (0)	2 (9)	
Site of metastases			
lymph nodes only	0 (0)	2 (9)	
bone only	5 (22)	7 (30)	0.37
bone+lymph nodes	16 (69)	12 (52)	
bone+lymph nodes+visceral	2 (9)	2 (9)	

LDH = lactate dehydrogenase

Table 3. Outcomes according to patient and tumor characteristics; median in months (95% CI)

	Time to CRPC	p-value	Survival	p-value
all patients (N=73)	16.2 (12–19)	/	58.4 (39–64)	/
age at diagnosis				
>66 years	16.6 (13–59)	0.61	64.3 (45–64)	0.11
<66 years	13.9 (11–20)		39.7 (21–49)	
prostate-specific antigen				
>151 ng/ml	11.4 (8.7–17)	0.02	49 (32–58)	0.60
<151 ng/ml	20.3 (14–26)		64.3 (33–64)	
lactate dehydrogenase				
>178 U/l	11.2 (8.4–16)	0.036	38.7 (16–40)	0.017
<178 U/l	20.1 (15–25)		not reached	
alkaline phosphatase				
>126 U/l	11.1 (8.4–13)	0.001	38.6 (26–49)	0.021
<126 U/l	19.2 (15–25)		64.3 (26–49)	
neutrophil/lymphocyte ratio				
>2.03	12.2 (9–23)	0.70	49 (33–49)	0.60
<2.03	16.6 (14–20)		58.4 (34–64)	
disease volume				
high	13.8 (11–17)	0.014	44.5 (33–64)	0.355
low	20.3 (14–44)		58.4 (49–58)	
hemoglobin				
<138 g/dl	14 (11–19)	0.79	49 (33–53)	0.41
>138 g/dl	16.2 (12–22)		64.3 (33–64)	
Gleason score				
>7	11.2 (8–24)	0.35	53.5 (39–64)	0.61
7	16.5 (14–20)		not reached	
ECOG performance status				
>0	11.2 (9–17)	0.012	32.7 (16–40)	0.0016
=0	19 (14–25)		64.3 (54–64)	

CRPC = castration-resistant prostate cancer

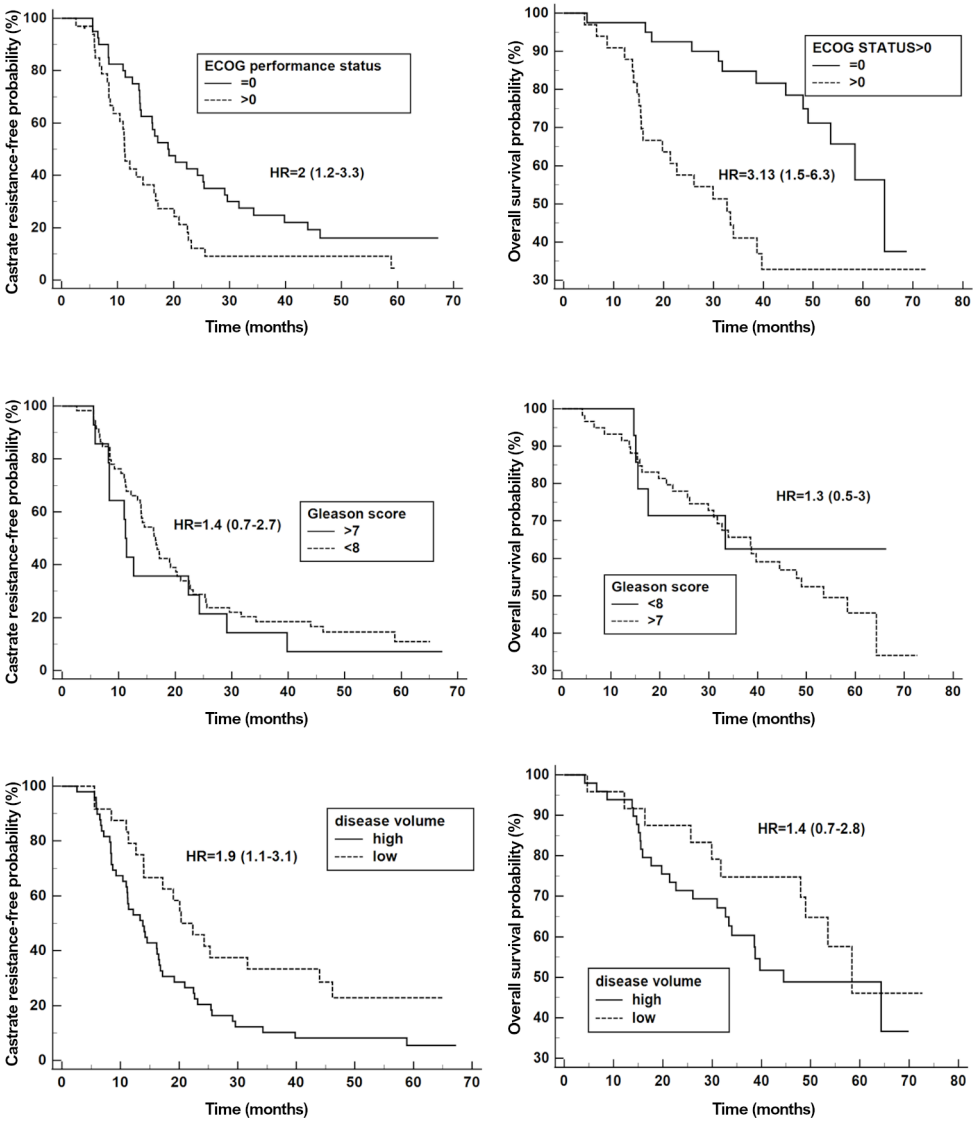

Figure 2. Kaplan-Meier survival estimates according to non-biochemical predictors

Overall, the effectiveness of docetaxel in our cohort was in line with results from the CHAARTED and STAMPEDE trials, with median times to CRPC and OS of 16.2 and 58.4 months, respectively, but varied markedly according to the patient profile [12, 14]. We demonstrated the predictive value of the number of baseline biochemical, radiological, and patient characteristics for both the development of castration resistance and the OS of mHSPC patients treated with docetaxel. The presence of HV disease predicted faster progression to CRPC and shorter OS. In particular, patients with HV disease at initial diagnosis developed the castration-resistant disease after a median of 13.8 months, which indicated that the efficacy of docetaxel was less pronounced in this population. Nevertheless, our finding of a median time to CRPC in the HV population is similar to data from the CHAARTED trial (i.e., 14.9 months) and from another real-world study of patients who received upfront chemotherapy in this setting [29, 30]. Time to castration resistance reflects the efficacy of first-line mHSPC treatment and predicts survival and overall tumor behavior [31]. The median survival in HV patients of our cohort was more than triple the median time to CRPC, demonstrating that castration resistance and the associated deterioration of quality of life constitute the majority of the remaining survival time in this patient subgroup. Furthermore, these findings show the importance of prolonging the time to castration resistance by adding other treatments at the time of ADT initiation. Given the lack of data on the median time to CRPC for HV

patients in ARTA trials in this setting, we can rightly raise the question of whether these patients should receive more than docetaxel added to ADT.

The LV disease patients in our cohort had a median time to CRPC and OS of 20.3 and 58.4 months, respectively, which is consistent with the results of the CHAARTED study (31.0 months for the whole LV population and 58.0 months for the *de novo* LV population, respectively) and confirms the better outcomes for these patients in daily clinical practice [12]. However, in light of the results of studies in this indication with ARTA, docetaxel is not the optimal choice of treatment for LV patients in this setting. Compared to LV patients, HV patients had significantly higher baseline levels of PSA and ALP and worse ECOG PS, which confirms the aggressive nature of HV mHSPC and can guide us in selecting the optimal treatment.

To our knowledge, data on the predictive value of pretreatment PSA are lacking in the context of docetaxel therapy for mHSPC. In the overall study cohort, we observed that patients with a pretreatment PSA above the median level (i.e., >151 ng/ml) had a significantly shorter time to CRPC (11.3 vs. 20.4 months, p=0.02) and numerically but not significantly worse OS (49 vs. 64.3 months, p=0.6) than patients with a pretreatment PSA below the median level. This finding suggests that pretreatment PSA after docetaxel therapy in mHSPC patients has predictive value, although further evaluation of its association with OS is necessary.

ALP is an enzyme primarily found in the bone and liver and has been associated with bone turnover markers. The prognostic value of ALP has been shown in various solid malignancies with bone metastases [32, 33]. It has also been used to evaluate treatment efficacy in bone mCRPC. The dynamic changes in ALP during treatment were associated with better OS in the castration-resistant setting [34]. Evidence associated with ALP as a predictor of outcomes after docetaxel treatment for mHSPC is lacking. In our study, pretreatment ALP ≥126 U/l (above median) was significantly associated with HV disease (p<0.0001), suggesting that ALP is an indirect sensitive measure of metastatic tumor burden. Moreover, patients with a high level of ALP had both a significantly shorter time to CRPC (11.1 vs. 19.2 months, p=0.001) and worse OS (38.6 vs. 64.3 months, p=0.021), suggesting its pretreatment predictive value after docetaxel treatment in mHSPC.

Many studies have shown that LDH plays an important role in tumor proliferation, invasion, and metastasis and has prognostic value for various solid tumors, including prostate cancer [35]. A recent meta-analysis of 38 studies (most of them were CRPC trials) and 9,813 patients with mPC included showed that higher levels of LDH in patients with mPC were significantly associated with poorer OS and PFS. The subgroup analyses indicated that the negative prognostic impact of higher levels of LDH on the oncologic outcomes of mPC was significant regardless of ethnicity, treatment type, age, and disease state [36]. However, according to our knowledge, this study is the first to examine the predictive value of pretreatment LDH in patients treated with docetaxel for mHSPC. The pretreatment level of LDH above the median of 178 U/l predicted both shorter median times to CRPC and OS. Notably, the predictive value of LDH was independent of disease volume; the medians of LDH were virtually the same in the HV and LV patients and the distribution of metastases did not differ significantly between low LDH and high LDH patients. This suggests that, along with disease volume, LDH should be considered when deciding on intensified treatment approaches for mHSPC patients. Most other predictors are associated with disease volume and are thus of less value, not adding much to the disease volume stratification paradigm. A larger study is, however, required to delineate the effect of variables that appeared associated with both the disease volume and LDH, like ALP and patient fitness.

In conclusion, the treatment of mHSPC is challenging – prolonging time to CRPC and OS are the main aims. In our cohort of *de novo* patients with mHSPC treated with docetaxel, PSA, LDH, ALP, disease volume, and ECOG PS at the start of chemotherapy were predictive of the treatment outcomes.

Taking the disease volume as the accepted landmark in mHSPC, increased serum LDH is the most useful adjunct, conferring independent information. We believe this study can help in making decisions about the proper treatment of patients with mHSPC and for the promotion of biochemical parameters, including clinical trials for stratified randomization.

References

[1] HUGGINS C, HODGES CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972; 22: 232–240. https://doi.org/10.3322/canjclin.22.4.232

[2] KLOTZ L. Maximal androgen blockade for advanced prostate cancer. Best Pract Res Clin Endocrinol Metab 2008; 22: 331–340. https://doi.org/10.1016/j.beem.2008.01.004

[3] LONERGAN PE, TINDALL DJ. Androgen receptor signaling in prostate cancer development and progression. J Carcinog 2011; 10: 20. https://doi.org/10.4103/1477-3163.83937

[4] TANNOCK IF, DE WIT R, BERRY WR, HORTI J, PLUZANSKA A et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502–1512. https://doi.org/10.1056/NEJMoa040720

[5] DE BONO JS, OUDARD S, OZGUROGLU M, HANSEN S, MACHIELS JP et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147–1154. https://doi.org/10.1016/S0140-6736(10)61389-X

[6] KANTOFF PW, HIGANO CS, SHORE ND, BERGER ER, SMALL EJ et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. N Engl J Med 2010; 363: 411–422. https://doi.org/10.1056/NEJMoa1001294

[7] DE BONO JS, LOGOTHETIS CJ, MOLINA A, FIZAZI K, NORTH S et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995–2005. https://doi.org/10.1056/NEJMoa1014618

[8] SCHER HI, FIZAZI K, SAAD F, TAPLIN ME, STERNBERG CN, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187–1197. https://doi.org/10.1056/NEJMoa1207506

[9] PARKER C, NILSSON S, HEINRICH D, HELLE SI, O'SULLIVAN JM et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213–223. https://doi.org/10.1056/NEJMoa1213755

[10] RYAN CJ, SMITH MR, FIZAZI K, SAAD F, MULDERS PF et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015; 16: 152–160. https://doi.org/10.1016/S1470-2045(14)71205-7

[11] BEER TM, ARMSTRONG AJ, RATHKOPF DE, LORIOT Y, STERNBERG CN et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–433. https://doi.org/10.1056/NEJMoa1405095

[12] SWEENEY CJ, CHEN YH, CARDUCCI M, LIU G, JARRARD DF, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; 373: 737–746. https://doi.org/10.1056/NEJMoa1503747

[13] FIZAZI K, TRAN N, FEIN L, MATSUBARA N, RODRIGUEZ-ANTOLIN A et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; 377: 352–360. https://doi.org/10.1056/NEJMoa1704174

[14] JAMES ND, SYDES MR, CLARKE NW, MASON MD, DEARNALEY DP et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016; 387: 1163–1177. https://doi.org/10.1016/S0140-6736(15)01037-5

[15] CHI KN, AGARWAL N, BJARTELL A, CHUNG BH, PEREIRA DE SANTANA GOMES AJ et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019; 381: 13–24. https://doi.org/10.1056/NEJMoa1903307

[16] ARMSTRONG AJ, SZMULEWITZ RZ, PETRYLAK DP, HOLZBEIERLEIN J, VILLERS A et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019; 37: 2974–2986. https://doi.org/10.1200/JCO.19.00799

[17] FIZAZI K, GALCERAN JC, FOULON S, ROUBAUD G, McDERMOTT R, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: overall survival with abiraterone acetate plus prednisone in PEACE-1. Ann Oncol 2021; 32(suppl_5): S1283–S1346. https://doi.org/10.1016/annonc/annonc741

[18] SMITH MR, HUSSAIN M, SAAD F, FIZAZI K, STERNBERG CN, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 2022; 386: 1132–1142. https://doi.org/10.1056/NEJMoa2119115

[19] PATRIKIDOU A, LORIOT Y, EYMARD JC, ALBIGES L, MASSARD C et al. Who dies from prostate cancer? Prost Cancer Prost Dis 2014; 17: 348–352. https://doi.org/10.1038/pcan.2014.35

[20] SCHER HI, HALABI S, TANNOCK I, MORRIS M, STERNBERG CN et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26: 1148–1159. https://doi.org/10.1200/JCO.2007.12.4487

[21] EISENHAUER EA, THERASSE P, BOGAERTS J, SCHWARTZ LH, SARGENT D et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228–247. https://doi.org/10.1016/j.ejca.2008.10.026.

[22] TERADA N, AKAMATSU S, KOBAYASHI T, INOUE T, OGAWA O et al. Prognostic and predictive biomarkers in prostate cancer: Latest evidence and clinical implications. Ther Adv Med Oncol 2017; 9: 565–573. https://doi.org/10.1177/1758834017719215

[23] OMRČEN T, ETEREOVIĆ D, VRDOLJAK E. Predictors of resistance to abiraterone acetate or enzalutamide in patients with metastatic castration-resistant prostate cancer in post-docetaxel setting: a single-center cohort study. Anticancer Drugs 2020; 31: 742–746. https://doi.org/10.1097/CAD.0000000000000945

[24] GLASS TR, TANGEN CM, CRAWFORD ED, THOMPSON I. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol 2003; 169: 164–169. https://doi.org/10.1016/S0022-5347(05)64059-1

[25] GRAVIS G, BOHER JM, FIZAZI K, JOLY F, PRIOU F et al. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the Glass model and development of a novel simplified prognostic model. Eur Urol 2015; 68: 196–204. https://doi.org/10.1016/j.eururo.2014.09.022

[26] FINIANOS A, GUPTA K, CLARK B, SIMMENS SJ, ARAGON-CHING JB. Characterization of differences between prostate cancer patients presenting with de novo versus primary progressive metastatic disease. Clin Genitourin Cancer 2017; 16: S1558–7673. https://doi.org/10.1016/j.clgc.2017.08.006

[27] FIZAZI K, TRAN N, FEIN L, MATSUBARA N, RODRIGUEZ-ANTOLIN A et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; 377: 352–360. https://doi.org/10.1056/NEJMoa1704174

[28] GILLESSEN S, BOSSI A, DAVIS IA, DE BONO J , FIZAZI K et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. Eur J Cancer 2023; 185:178–215. https://doi.org/10.1016/j.ejca.2023.02.018

[29] KYRIAKOPOULOS CE, CHEN YH, CARDUCCI MA, LIU G, JARRARD DF et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED Trial. J Clin Oncol 2018; 36: 1080–1087. https://doi.org/10.1200/JCO.2017.75.3657

[30] LAVOIE JM, ZOU K, KHALAF D, EIGL BJ, KOLLMANNSBERGER CK et al. Clinical effectiveness of docetaxel for castration-sensitive prostate cancer in a real-world population-based analysis. Prostate 2019; 79: 281–287. https://doi.org/10.1002/pros.23733

[31] WENZEL M, PREISSER F, HOEH B, SCHROEDER M, WURNSCHIMMEL C, et al. Impact of time to castration resistance on survival in metastatic hormone sensitive prostate cancer patients in the era of combination therapies. Front Oncol 2021; 11: 659135. https://doi.org/10.3389/fonc.2021.659135

[32] LIM SM, KIM YN, PARK KH, KANG B, CHON HJ et al. Bone alkaline phosphatase as a surrogate marker of bone metastasis in gastric cancer patients. BMC Cancer 2016; 16: 385. https://doi.org/10.1186/s12885-016-2415-x

[33] BROWN JE, COOK RJ, MAJOR P, LIPTON A, SAAD F et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J Natl Cancer Inst 2005; 97: 59–69. https://doi.org/10.1093/jnci/dji002

[34] ARMSTRONG AJ, FEBBO PG. Using surrogate biomarkers to predict clinical benefit in men with castration-resistant prostate cancer: an update and review of the literature. Oncologist 2009; 14: 816–827. https://doi.org/10.1634/theoncologist.2009-0043

[35] KOUKOURAKIS MI, GIATROMANOLAKI A, SIVRIDIS E, GATTER KC, HARRIS AL. Lactate dehydrogenase 5 expression in operable colorectal cancer: strong association with survival and activated vascular endothelial growth factor pathway – a report of the Tumour Angiogenesis Research Group. J Clin Oncol 2006; 24: 4301-4308. https://doi.org/10.1200/JCO.2006.05.9501

[36] LI F, XIANG H, PANG Z, CHEN Z, DAI J et al. Association between lactate dehydrogenase levels and oncologic outcomes in metastatic prostate cancer: A meta-analysis. Cancer Med 2020; 9: 7341–7351. https://doi.org/10.1002/cam4.3108