Urologic Oncology: Seminars and Original Investigations 39 (2021) 296.e11–296.e19

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

The prognostic value of serum MMP-7 levels in prostate cancer patients who received docetaxel, abiraterone, or enzalutamide therapy

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Received 22 July 2020; received in revised form 6 September 2020; accepted 12 September 2020

Abstract

Objectives: The rapidly changing treatment landscape in metastatic castration-resistant prostate cancer (mCRPC) calls for biomarkers to guide treatment decisions. We recently identified MMP-7 as a potential serum marker for the prediction of response and survival in mCRPC patients who received docetaxel (DOC) chemotherapy. Here, we aimed to test this finding in an independent patient cohort and in addition to explore the prognostic potential of serum MMP-7 in abiraterone (ABI) or enzalutamide (ENZA) treated patients.

Methods and Materials: MMP-7 levels were measured in 836 serum samples from 320 mCRPC patients collected before and during DOC ($n = 95$), ABI ($n = 140$), or ENZA ($n = 85$) treatment by using the ELISA method. Results were correlated with clinical and follow-up data.

Results: MMP-7 baseline levels were similar between the 3 treatment groups. In the ABI and ENZA cohorts, baseline MMP-7 levels were lower in patients with prior radical prostatectomy ($P = 0.058$ and $P = 0.041$, respectively). Baseline MMP-7 levels above the median were associated with shorter overall survival for the DOC ($P = 0.001$) and ENZA ($P = 0.006$) cohorts. Multivariable analyses in the DOC and ENZA cohorts revealed that high pretreatment MMP-7 level is an independent risk factor for patients' survival. In addition, in DOC-treated patients with high baseline MMP-7 level, marker decrease at the third DOC cycle was associated with improved survival. Patients with high baseline MMP-7 levels had better survival when treated with ABI compared to DOC or ENZA.

Conclusions: We confirmed the prognostic value of pretreatment MMP-7 serum level and its changes as independent predictors of survival in DOC-treated mCRPC patients. In addition, high MMP-7 was a negative predictor in ENZA-treated but not in ABI-treated patients. These results warrant further research to confirm the predictive value of serum MMP-7 and to explore the potential mechanistic involvement of MMP-7 in DOC and ENZA resistance of mCRPC patients.

Keywords: Prostate cancer; MMP-7; Docetaxel; Abiraterone; Enzalutamide

1. Introduction

Prostate cancer (CaP) accounts for over 350,000 deaths each year and is worldwide a leading cause of cancer-related

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https://doi.org/10.1016/j.urolonc.2020.09.005

deaths in men [1]. CaP shows a heterogeneous molecular and histological pattern, which is associated with its clinical heterogeneity. Metastatic castration-resistant prostate cancer (CRPC) represents an aggressive disease with a median survival of only 10 to 12 months when left untreated [2]. With approval of several new drugs, the therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has significantly changed in recent years. Currently, the most frequently used standard, first-line treatments for mCRPC are docetaxel (DOC) chemotherapy and next-generation antiandrogen therapies such as abiraterone (ABI) and enzalutamide (ENZA) [3]. Unfortunately, baseline and acquired resistance against all these therapies has been observed [4]. Therefore, serum biomarkers are urgently needed to guide the type, sequence and timing of therapeutic strategies.

Matrix metalloproteinases (MMP) are a family of zinc-containing endopeptidases that are involved in the degradation of the extracellular matrix and basement membrane [5,6]. MMP-7 is distinguished by its large substrate specificity and is shown to be involved in the regulation of cell adhesion, apoptosis, and angiogenesis [7]. Its elevated tissue and serum levels are associated with the presence of metastatic diseases and poor survival in patients with colorectal, urinary bladder, and renal cell cancer [8–11]. In CaP, MMP-7 has shown to be focally upregulated by the tumor cells [12]. Lynch et al. demonstrated that MMP-7 plays a key activator role in CaP-induced osteolysis and therefore critically involved in the formation of bone metastasis [13]. In accordance, we formerly found significantly elevated MMP-7 serum levels in CaP patients present with bone metastasis, while MMP-7 levels were not elevated in CaP patients with lymph node or visceral metastases [14]. Furthermore, enhanced tissue MMP-7 expression was associated with resistance to cisplatin chemotherapy in head and neck and lung cancer [15,16]. We recently demonstrated that elevated MMP-7 serum levels before chemotherapy were independently associated with resistance to DOC chemotherapy in CRPC patients [17]. These data, however, need to be validated in an independent patient cohort. In addition, the prognostic value of MMP-7 in ABI/ENZA treated patients has not been evaluated yet. Therefore, in the present study, we aimed to validate the prognostic value of serum MMP-7 in an independent cohort of DOC-treated CRPC patients. Furthermore, we assessed, for the first time, its prognostic value in ABI/ENZA-treated men. In addition to its pretreatment levels, we also assessed the MMP-7 concentrations in serum samples collected during DOC, ABI, and ENZA therapy.

2. Materials and methods

2.1. Patients

We retrospectively assessed an overall number of 836 serum samples from 320 mCRPC patients divided in 3 cohorts (DOC, ABI, and ENZA).

The DOC cohort consisted of 95 mCRPC patients who received first-line DOC chemotherapy between 1/2013 and 11/2018. For this cohort, samples collected at the first, second, third, fourth, fifth, and sixth therapy cycles were available for 95, 73, 67, 56, 54, and 47 patients.

The ABI cohort included 140 mCRPC patients who underwent ABI therapy in first or second line between 01/2011 and 05/2015. For 137 patients serum samples at 3 months after therapy start were available for analysis.

The ENZA cohort consisted of 85 mCRPC men who received ENZA therapy in first or second line between 09/2013 and 03/2016. Serum samples at 3 months after therapy start were for 82 of 85 patients.

The study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by the ethical board of the hospitals (TUKEB 55/2014, ECS 1986/2017). Follow-up time for overall survival (OS) was calculated as the period between the date of start of systemic (DOC, ABI, ENZA) treatment and last databank check at the registry office by 01/2019. High volume was defined as presence of visceral metastases or having four or more bone metastases. PSA response was defined, according to the PCWG II Criteria, as at least 50% PSA decline from baseline during the first chemotherapy series [18].

2.2. Serum MMP-7 analysis

MMP-7 serum levels were quantified by using the Quantikine ELISA Kit (DMP700; R&D Systems Wiesbaden, Germany) according to the manufacturer's instructions. This research use only, sandwich ELISA kit includes precoated microplates (for more details please refer the freely available protocol on the manufacturer website). For the detection of color reaction we used the Multiskan FC microplate reader (Thermo Fisher).

2.3. Statistical analysis

We used the nonparametric 2-sided Wilcoxon rank sum test for independent group comparisons. Univariable survival analyses were done using both Kaplan-Meier curves with log-rank tests and univariable Cox regression analysis. For multivariable analysis, the Cox proportional hazards regression model was used. Statistical analyses were performed using the SPSS 26.0 (IBM, Chicago, IL) software.

3. Results

3.1. Patients' characteristics

The median age in the DOC-treated cohort was 71 years (range: 44–86) which was similar to those of 72 years (55–93) of the ABI and 73 years (56–89) of the ENZA cohorts (Table 1). Fifty-three (56%) of 95 DOC-treated patients died during a median follow-up time of 13 months. In the ABI cohort, 94 (67%) patients died during a median follow-up period which was comparable to the ENZA cohort with 56 deaths (66%).

Table 1
Patients' characteristics in the docetaxel (DOC) and abiraterone (ABI) and enzalutamide (ENZA) treated cohorts

Parameters	All patients	DOC	ABI	ENZA
Total nr. of patients	320	95	140	85
Median age (years - range)	72 (44–93)	71 (44–86)	72 (55–93)	73 (56–89)
Median PSA (ng/ml - range)		89 (1.5–6155)	71 (0.1–6785)	65 (0.2–8422)
ECOG ps.				
0	195	57	81	57
1	61	28	19	14
2	15	9	2	4
unknown	49	1	38	10
Metastases				
bone	286	89	123	74
LN (>2cm)	80	37	24	19
visceral mets.	37	15	15	7
Primary local therapy				
prostatectomy	110	18	59	33
radiation	56	12	26	18
Line of therapy				
1st	160	92	51	17
2nd	122	3	82	37
later	33	0	2	31
unknown	5	0	5	0
Nr. of patients died at last follow-up	203	53	94	56
Follow-up median, months	17	13	22	18

LN = lymph node; PS = performance status.

3.2. Correlations of clinicopathological parameters with MMP-7 levels

MMP-7 serum levels were not associated with patients' age, ECOG status and metastases in any of the cohorts (Table 2). MMP-7 serum levels were significantly lower in the ENZA cohort in patients who were formerly treated with radical prostatectomy ($P = 0.041$). A similar trend could be observed in the ABI cohort ($P = 0.058$). MMP-7 pretreatment levels were significantly lower in men who experienced a strong PSA-response (>90% decrease) to ABI treatment ($P = 0.017$). A similar, however insignificant trend could be observed for the ENZA-cohort ($P = 0.099$; Table 2). We performed Spearman rho test (ABI: $P = 0.927$, ENZA: $P = 0.266$ and DOC: $P = 0.204$) and Pearson's correlation analyses (ABI: $P = 0.827$, ENZA: $P = 0.998$ and DOC: $P = 0.625$) that revealed no significant correlation between MMP-7 and PSA levels in any of the assessed cohorts. In order to evaluate the correlation between, tumor volume and MMP-7 levels, we grouped patients based on the number of their bone metastases (≥10 bone mets.). In the ABI and ENZA cohort Mann-Whitney U test revealed no significant correlation between the number of bone metastases and MMP-7 serum levels ($P = 0.296$, $P = 0.265$), while the number of bone metastases was not available for the DOC-treated patients. Patients with vs. without bone metastases had similar MMP-7 levels ABI: $P = 0.878$, ENZA: $P = 0.655$ $P =$ DOC: $P = 0.464$) and similarly patients present with soft tissue lesions had similar MMP-7 levels to those without soft tissue metastases ABI: $P = 0.549$, ENZA: $P = 0.565$ DOC: $P = 0.715$).

3.3. Changes in MMP-7 levels during DOC, ABI, and ENZA treatment

In addition to pretreatment serum samples of the DOC cohort, we determined MMP-7 levels also in serum samples taken during therapy. The median values at each therapy cycles (second; 6.72 ng/ml, third; 7.27 ng/ml, fourth; 6.76 ng/ml, fifth; 6.56 ng/ml and sixth; 6.89 ng/ml) were similar to those of the pretreatment samples (7.39 ng/ml).

MMP-7 levels in the ABI and ENZA cohorts at 3 months after therapy begin showed no significant changes compared to baseline (Supplementary Fig. 1).

3.4. Associations of baseline MMP-7 levels with PSA response

PSA waterfall plots demonstrated a random distribution of cases regarding their MMP-7 levels in all three cohorts (Supplementary Fig. 2).

3.5. Survival analyses

Results of univariable survival analyses are shown in Table 3. Patients' age was associated with shorter OS in the ABI cohort ($P = 0.039$). Patients with poor ECOG

Table 2
Correlations of baseline MMP-7 levels with clinicopathological parameters

	DOC cohort			ABI cohort			ENZA cohort		
	n	MMP-7 ng/ml median (range)	*P*	*n*	MMP-7 ng/ml median (range)	*P*	*n*	MMP-7 ng/ml median (range)	*P*
Whole cohort	95	7.39 (1.83–34.97)		140	6.84 (3.01–36.10)		85	6.53 (3.05–28.17)	
Age (years)									
≤ 72	55	7.19 (3.76–34.97)	0.864	76	6.67 (3.01–23.84)	0.405	41	6.48 (3.05–18.25)	0.190
>72	40	7.51 (1.83–24.32)		64	7.21 (3.28–36.10)		44	6.94 (3.15–28.17)	
Primary RPE or RAD									
no	65	7.53 (1.83–24.32)	0.983	57	7.55 (3.01–36.109	0.131	36	7.54 (3.30–28.17)	**0.041**
yes	30	6.99 (2.70–61.55)		83	6.68 (3.04–33.75)		49	6.04 (3.05–16.56)	
Primary RPE									
no	77	7.45 (1.83–34.97)	0.968	60	7.53 (3.01–36.10)	0.058	52	7.37 (3.30–28.17)	**0.041**
yes	18	7.17 (2.70–32.33)		80	6.17 (3.04–33.75)		33	5.88 (3.05–15.00)	
Primary RAD									
no	83	7.51 (1.83–32.33)	0.986	114	6.80 (3.01–36.10)	0.510	67	6.48 (3.05–28.17)	0.554
yes	12	6.68 (3.05–34.97)		26	7.53 (4.05–23.84)		18	7.07 (4.06–22.67)	
Line of above therapy									
1st line	92	7.08 (1.83–34.97)	0.058	51	7.91 (3.28–36.10)	0.099	17	6.76 (3.05–28.17)	0.621
2nd or later	3	16.95 (7.55–32.33)		84	6.65 (3.01–33.75)		68	6.51 (3.15–15.00)	
unknown	0			5			0		
ECOG PS									
0	85	6.39 (2.70–32.33)	0.201	81	6.88 (3.01–33.75)	0.801	57	6.36 (3.15–28.17)	0.184
1–2	9	7.61 (1.83–34.97)		21	6.65 (3.04–36.10)		18	7.93 (3.05–22.67)	
Unknown	1			38			10		
LN status									
N -	58	7.17 (1.83–34.97)	0.720	114	6.84 (3.01–36.10)	0.987	66	6.45 (3.05–28.17)	0.513
N +	37	7.60 (2.82–32.33)		24	6.84 (3.04–24.63)		19	9.16 (3.30–22.67)	
Unknown	0			2			0		
Visceral mets.									
no	80	7.28 (2.70–34.97)	0.715	122	6.79 (3.01–36.10)	0.549	78	6.62 (3.15–28.17)	0.565
yes	15	8.03 (1.83–15.95)		15	7.47 (3.23–33.75)		7	6.04 (3.05–12.26)	
Unknown	0			3			0		
Bone mets.									
No	5	6.36 (2.82–10.73)	0.464	7	7.50 (3.28–36.10)	0.873	7	6.51 (3.68–25.06)	0.643
Yes	90	7.45 (1.83–34.97)		131	6.80 (3.01–33.75)		78	6.62 (3.05–28.17)	
Unknown	0			2			0		
Tumor volume									
Low	22	7.58 (2.82–32.33)	0.437	21	7.23 (3.28–36.10)	0.767		6.45 (3.18–25.06)	0.393
high	73	6.99 (1.83–34.97)		112	6.84 (3.01–33.75)			6.78 (3.05–28.17)	
unknown	0			7					
PSA response									
Response	66	6.95 (1.83–32.33)	0.682	119	6.65 (3.01–36.10)	0.218	69	6.48 (3.05–28.17)	0.473
No response	14	8.35 (3.98–14.37)		19	8.41 (3.51–19.63)		12	7.80 (3.30–15.00)	
Unknown	15			2			4		
PSA response									
>30%	49	6.80 (1.83–32.33)	0.634	101	6.65 (3.01–36.10)	0.141	56	6.49 (3.05–28.17)	0.996
<30%	33	7.58 (3.98–24.32)		29	8.26 (3.51–24.16)		23	6.53 (3.30–15.00)	
unknown	13			10			6		
PSA response									
> 50%	42	6.65 (1.83–21.43)	0.197	87	6.80 (3.01–36.10)	0.622	53	6.36 (3.05–28.17)	0.407
< 50%	40	7.61 (3.98–32.33)		43	7.23 (3.28–24.63)		26	7.76 (3.30–15.00)	
unknown	13			10			6		
PSA response									
>90%	24	6.10 (2.70–19.79)	0.196	43	6.20 (3.01–25.34)	**0.017**	49	5.60 (3.05–28.17)	0.099
<90%	58	7.51 (1.83–32.33)		87	7.75 (3.28–36.10)		30	7.54 (3.15–25.06)	
unknown	13			10			6		

LN = lymph node; PS = performance status; RAD = radiation; RPE = radical prostatectomy.

Table 3
Univariable analysis of overall survival in patients who received docetaxel (DOC), abiraterone (ABI), and enzalutamide (ENZA) treatment

		DOC			ABI			ENZA		
Variables		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age	>72 y.	1.374	0.774–2.441	0.278	1.549	1.024–2.345	**0.039**	1.138	0.674–1.924	0.628
ECOG	2	1.713	1.057–2.776	**0.029**	3.996	2.270–7.034	**<0.001**	1.583	0.824–3.038	0.168
Visceral mets.	pos.	1.213	0.587–2.505	0.603	1.180	0.610–2.284	0.623	1.511	0.644–3.543	0.343
LN mets.	pos.	0.964	0.547–1.698	0.899	1.455	0.848–2.499	0.174	0.625	0.306–1.276	0.197
Bone mets.	pos.	0.861	0.208–3.561	0.836	2.388	1.040–5.483	**0.040**	5.870	1.810–19.037	**0.003**
Primary RPE	pos.	0.950	0.485–1.860	0.881	0.643	0.425–0.974	**0.037**	1.029	0.601–1.762	0.917
Primary RAD	pos.	1.473	0.573–3.785	0.421	0.833	0.486–1.428	0.506	0.690	0.356–1.335	0.270
Tumor volume	high	1.109	0.693–1.371	0.292	1.742	0.943–3.219	0.076	3.232	1.366–7.650	0.008
PSA median	*	1.739	0.982–3.080	0.058	2.545	1.665–3.890	**<0.001**	3.405	1959–5.919	**<0.001**
PSA response	present	0.291	0.144–0.590	**0.001**	0.820	0.446–1.507	0.523	0.562	0.280–1.130	0.106
PSA response	>30%	0.490	0.263–0.913	**0.025**	0.490	0.295–0.813	**0.006**	0.635	0.343–1.174	0.147
PSA response	>50%	0.422	0.222–0.805	**0.009**	0.512	0.325–0.807	**0.004**	0.645	0.357–1.167	0.147
PSA response	>90%	0.434	0.182–1.035	0.060	0.545	0.345–0.859	**0.009**	0.453	0.253–0.812	**0.008**
MMP-7 median	a	2.875	1.559–5.301	**0.001**	1.503	0.997–2.268	0.052	2.127	1.238–3.653	**0.006**

LN = lymph node; RAD = radiation; RPE = radical prostatectomy.
[a]DOC cohort: median PSA: 88.8 ng/ml, median MMP-7: 7.39 ng/ml.
[a]ABI cohort: median PSA: 71 ng/ml, median MMP-7: 6.84 ng/ml.
[a]ENZA cohort: median PSA: 65 ng/ml, median MMP-7: 6.53 ng/ml.
For all cohorts: MMP-7 BJU cut-off: 4.40 ng/ml.

performance status (>1) had a shorter survival in the DOC ($P = 0.029$) and ABI ($P < 0.001$) cohorts. Presence of bone metastases were associated with poor survival in the ABI ($P = 0.040$) and ENZA ($P = 0.003$) but not in the DOC ($P = 0.836$) cohort. High tumor volume was associated with shorter OS in the ENZA cohort ($P = 0.008$). High PSA and MMP-7 pretreatment levels were significantly associated with shorter OS in all 3 cohorts (Table 3).

Kaplan-Meier OS curves demonstrate that combining pretreatment MMP-7 and PSA serum levels increase prognostic stratification in all 3 cohorts (Fig. 1A).

In addition, we performed OS analysis by stratifying patients according to their received treatments (DOC/ABI/ENZA) in the subgroups of high baseline MMP-7 vs. low baseline MMP-7 levels (Fig. 1B). We found no difference in OS between the treatment groups in the low baseline MMP-7 subgroup ($P = 0.557$). In contrast, in the high baseline MMP-7 group, patients treated with ABI had the most favorable and DOC-treated patients the worst OS ($P = 0.048$; Fig. 1B).

Multivariable analyses in the DOC cohort revealed pretreatment MMP-7 levels and ECOG status as independent predictive factors for OS (Table 4). In the ABI cohort only ECOG performance status (>1) and pretreatment serum PSA level proved to be independent predictors for OS. In the ENZA cohort, the presence of bone metastases and high serum PSA and MMP-7 levels were associated with poor OS (Table 4).

We then merged all 3 treatment cohorts and divided into low vs. high baseline MMP-7 groups and stratified patients according to the received treatment (DOC/ABI/ENZA). In the low MMP-7 group, we did not see any difference in patients' survival between the 3 treatment groups. In contrast, patients with high MMP-7 levels benefited significantly better from ABI treatment compared to DOC and ENZA (Supplementary Fig. 3). We performed a similar analysis on our currently published results on CGA and NSE, which have been measured in partly overlapping patient cohorts [19]. For patients with low CGA and NSE levels ABI and ENZA treatment provided significant better survival compared to DOC. In contrast, in CGA/NSE high group DOC-treated patients had significant better survival compared to those who received ABI or ENZA [19] (Supplementary Fig. 3).

3.6. Prognostic value of changes in marker levels during therapy

In the DOC cohort, we calculated marker level changes at second, third, and sixth cycles of treatment compared to baseline and assessed their correlations with OS in the whole cohort and also in the subgroups of patients with high MMP-7 baseline levels (>8 ng/ml). For these analyses, marker level changes were dichotomized in 3 different ways; as (1) any increase, (2) at least 20%, and (3) at least 50% increase. We could not detect any correlations between MMP-7 level changes and OS in the whole DOC cohort (Supplementary Table 1). However, in the subgroup of patients with high MMP-7 baseline levels, decrease of MMP-7 levels at the third and sixth therapy cycles of DOC treatment were significantly associated with more favorable survival. This observation gives the rationale to construct an MMP-7-based prognostic stratification as follows: (1) low MMP-7 baseline levels, (2) high MMP-7 baseline levels but MMP-7 decrease at the third cycle of treatment, and (3) high

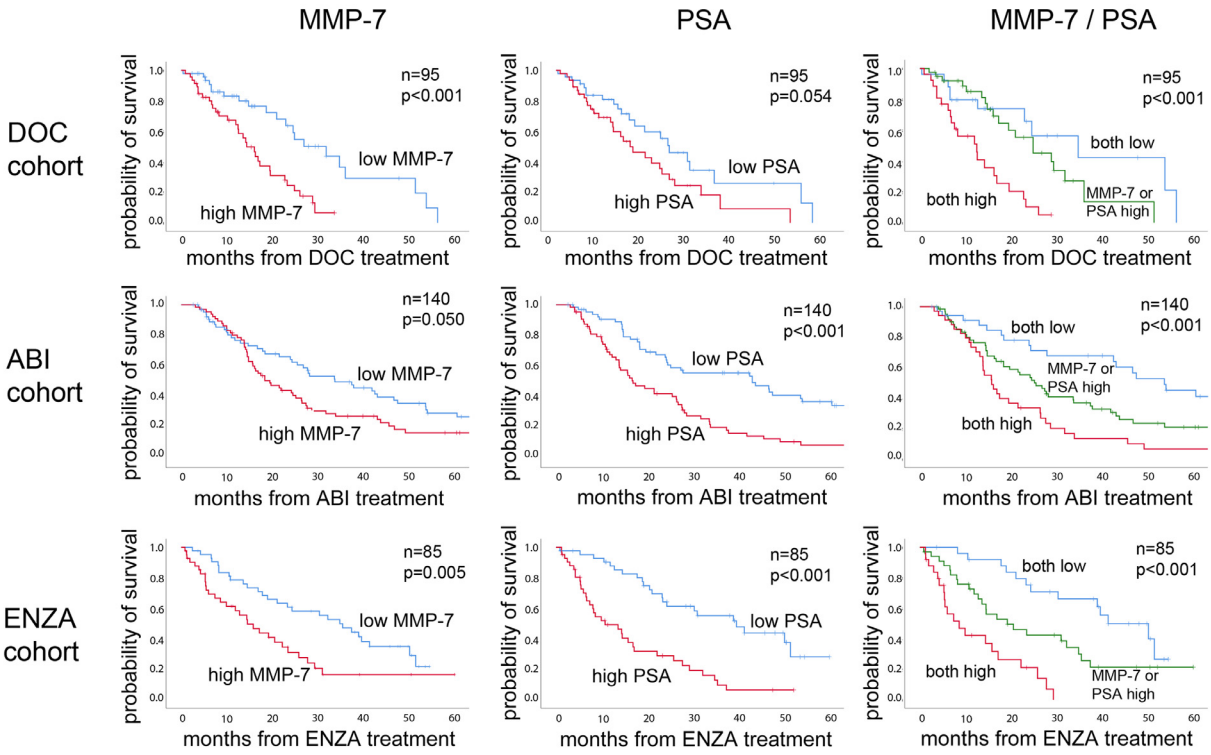

Fig. 1. Kaplan-Meier OS curves in the DOC, ABI, and ENZA cohorts stratified by MMP-7 and PSA as well as their combinations. In all cases median values were used as cut-offs for dichotomization as follows: DOC cohort: median PSA: 88.8 ng/ml, median MMP-7: 7.39 ng/ml. ABI cohort: median PSA: 71 ng/ml, median MMP-7: 6.84 ng/ml. ENZA cohort: median PSA: 65 ng/ml, median MMP-7: 6.53 ng/ml. Combination of MMP-7 with PSA improved the prognostic stratification in all 3 treatment cohorts.

MMP-7 baseline levels and MMP-7 serum level increase at third therapy cycle (Supplementary Fig. 3). This model provided an excellent prediction of OS; after 24 months of DOC therapy start, survival rates in the 3 risk groups were 70%, 30%, and 0% (Supplementary Fig. 4).

In ABI and ENZA treated patients, changes of MMP-7 levels after three months of treatment did not show any correlation with OS neither in the whole groups nor in the subgroups with elevated baseline MMP-7 concentrations (Supplementary Table 1).

Table 4
Multivariable analysis in patients who received docetaxel (DOC), abiraterone (ABI), and enzalutamide (ENZA) treatment

	Overall survival		
DOC cohort	HR	95% CI	*P*
ECOG (2)	1.657	1.020–2.693	**0.042**
PSA (median) >88.00 ng/ml	1.672	0.935–2.990	0.083
MMP-7 (median) >7.39 ng/ml	3.039	1.592–5.801	**0.001**
ABI cohort	*HR*	*95% CI*	*P*
Age	1.381	0.805–2.370	0.242
ECOG (2)	10.296	1.116–95.015	**0.040**
Bone mets.	2.435	0.716–8.287	0.154
Primary RPE	0.749	0.445–1.260	0.275
PSA (median) >71.00 ng/ml	2.187	1.279–3.740	**0.004**
MMP-7 (median) >6.84 ng/ml	1.348	0.807–2.254	0.254
ENZA cohort	*HR*	*95% CI*	*P*
PSA (median) >65.00 ng/ml	2.180	1.022–4.650	**0.044**
Bone mets.	12.987	1.431–117.840	**0.023**
Tumor volume (high)	0.895	0.311–2.573	0.836
MMP-7 (median) >6.53 ng/ml	3.870	1.646–9.098	**0.002**

4. Discussion

In this study, we assessed the value of serum MMP-7 levels alone and in combination with PSA for the prediction of OS in mCRPC patients who underwent various therapies (DOC, ABI, and ENZA). We were able to validate our recently reported findings that both pretreatment serum MMP-7 levels and its changes during DOC therapy are independently associated with poor OS. In addition, we analyzed the prognostic effect of pretreatment MMP-7 levels and their changes in ENZA and ABI treated mCRPC patients and found pretreatment MMP-7 to be independently associated with shorter OS in ENZA-treated but not in ABI-treated men.

An increasing body of evidence demonstrates the involvement of MMP-7 in chemotherapy resistance of different cancers [15–17]. Additionally, MMP-7 was shown to downregulate the Fas/FasL apoptotic pathway, which was accompanied with reduced chemosensitivity of tumor cells [20,21]. Overall, MMP-7 mediated Fas/FasL degradation may provide an escape mechanism from chemotherapy-induced apoptosis leading to increased therapy resistance of tumor cells. In accordance, enhanced tissue MMP-7 levels were detected in cisplatin-resistant lung cancer patients [16]. In CRPC, we currently demonstrated that elevated pre-treatment MMP-7 and FasL serum levels are associated with baseline resistance to DOC chemotherapy [17]. In the present study, we could confirm the independent association of high baseline MMP-7 with significant shorter survival under DOC chemotherapy.

Not only baseline MMP-7 levels but also its changes during DOC therapy were associated with survival as our data demonstrated that any increase in MMP-7 levels in patients with high baseline MMP-7 are associated with inferior prognosis. These results suggest that only a part of the CRPCs expressing higher levels of MMP-7 and these tumors could be serum monitored during DOC treatment. Based on these, we suggest a risk stratification for DOC-treated patients based on the combination of their MMP-7 levels at baseline and at the third treatment cycle as follows: low baseline MMP-7 (low-risk group), high baseline MMP-7 and decrease at the third cycle (intermediate-risk group) and high baseline MMP-7 and further increase at the third DOC cycle (high-risk group).

In the last years, next-generation antiandrogen agents such as ABI and ENZA became available for mCRPC patients, however also for these therapies baseline or acquired resistance has been observed. Underlying resistance mechanisms and respective biomarkers attracted significant interest. Genetic mutations, amplifications, or splice variants of androgen receptor were associated with ENZA and ABI resistance [22–24]. In addition, alterations in DNA repair-pathway genes (*BRCA2* or *ATM*) and therapy induced neuroendocrine transdifferentiation were also associated with ABI/ENZA resistance [25]. In accordance, we and others recently found that higher neuroendocrine serum markers (chromogranin A and neuron-specific enolase) are associated with survival of ABI/ENZA treated patients [19,26]. However, none of these factors has been incorporated in the daily clinical decision-making.

MMP-7 was shown to be modulated by endocrine therapy and vice versa, MMP-7 is able to influence endocrine signaling. A recent study suggested that MMP-7 may activate androgen signaling by destruction of Sema3A/perlecan pathway which may help circumvent the effect of androgen-targeting therapies [27]. Against this background, we assessed, for the first time, the possible correlation between serum MMP-7 levels and survival in ABI/ENZA-treated patients. Our results showed that patients with strong (>90%) PSA response to ABI and ENZA therapy have lower baseline MMP-7 levels, while MMP-7 levels were not associated with PSA level, tumor volume and metastatic site in any of the cohorts. In the multivariable OS analysis baseline MMP-7 levels above the median were independently associated with shorter OS only in the ENZA but not in the ABI cohort. In contrast to our findings in DOC-treated patients, changes of MMP-7 levels in the ABI and ENZA cohort were not associated with patients' survival.

In mCRPC patients with low pretreatment MMP-7 levels, no significant difference in OS could be observed between the 3 (DOC/ABI/ENZA) treatment groups. In contrast, in patients with high baseline serum MMP-7, ABI-treated men had a superior OS compared to those who received DOC or ENZA. These suggest the potential of serum MMP-7 in helping decision between ABI vs. DOC/ENZA treatment. A similar re-evaluation of our former results on 2 neuroendocrine serum markers CGA and NSE in an overlapping cohort revealed that patients with low pretreatment CGA/NSE levels benefit from ABI/ENZA therapy compared to DOC, while in contrast in the CGA/NSE high group DOC therapy provided significantly better OS [19]. These results suggest that serum CGA/NSE as well as MMP-7 levels may help therapeutic decision between DOC/ABI/ENZA treatments. These findings, however should be tested in an independent prospective study.

5. Conclusions

Overall our results showed the strongest prognostic value in DOC-treated patients (HR: 2.875) followed by ENZA- (HR: 2.127) and ABI-treated men (HR: 1.503). In accordance, among patients with high baseline MMP-7 concentrations, ABI-treated men had a significant better OS compared to those who received DOC therapy, while such a correlation could not be observed in patients with low MMP-7 baseline concentration. This may suggest that patients with high MMP-7 levels benefit from ABI rather than DOC treatment. Furthermore, in DOC and ENZA-treated patients baseline MMP-7 level proved to be an independent predictor of survival, while in the DOC cohort also changes of MMP-7 levels were associated with survival. Based on these, MMP-7 in combination with other serum protein markers such as PSA

and CGA/NSA may help to improve therapeutic decision-making on type and timing of systemic therapy.

Conflicts of interest

B·R·A·H·M·S GmbH (Thermo Fisher Scientific) covered all costs of the presented analyses.

Acknowledgments

This work was supported by the National Research, Development and Innovation Office–NKFIH/FK_12443 and NVKP_16-1-2016-004. Tibor Szarvas was supported by a János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.09.005.

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