Prognostic factors of overall survival in patients with metastatic castration-resistant prostate cancer

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Introduction: *development of castration-resistant prostate cancer (CRPC) is traditionally associated with poor survival rates. However, the expansion of therapeutic opportunities of CRPC enabled to improve survival rates of this group of patients up to 2–3 years.*
Purpose: to evaluate overall survival (OS) in patients with metastatic CRPC (mCRPC) treated with modern therapeutic agents as well as to identify prognostic factors of OS.
Subjects and methods. *We conducted a retrospective study using data of 112 patients who»d been diagnosed with mCRPC and treated in N.N. Blokhin Russian Cancer Research Center in the period between 2005 and 2014. All patients underwent standard schemes of therapy based on docetaxel, cabazitaxel, abiraterone acetate in combination with prednisolone.*
Results. *Whatever the treatment option was, the 3-year OS rate was 32,0 ± 5,44 % with median OS – 24,3 months. We determined the following poor prognostic factors of OS: pain syndrome, ECOG performance status 2, the levels of prostate-specific antigen ≥ 288 ng/ml, lactate dehydrogenase ≥ 450 IU/l, alkaline phosphatase ≥ 250 IU/l, calcium < 2,28 mmol/l and hemoglobin < 11,5 g/dl, as well as duration of a response to hormonal therapy < 24 months.*
Conclusion. *The use of modern schemes of therapeutic treatment in patients with mCRPC enables to improve survival reaching the 3-year OS rate in this group of patients as well as to identify prognostic factors of OS which could be helpful in choosing the best possible approach for every patient.*

Key words: *castration-resistant prostate cancer, docetaxel, abiraterone acetate, cabazitaxel, overall survival, prognostic factors, alkaline phosphatase, prostate-specific antigen, hemoglobin, lactate dehydrogenase, calcium, ECOG scale, duration of response to hormonal therapy*

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Introduction

According to statistics, 10–20 % of prostate cancer (PC) patients develop castration-resistant form of the disease within approximately 5 years of the diagnosis [1]. Since 2014 criteria for diagnosis of castration-resistant prostate cancer (CRPC) has been reviewed. Nowadays CRPC is defined by disease progression despite second-line hormonal therapy (HT) and may present as one or any combination of a continuous rise in serum levels of prostate-specific antigen (PSA) and/or radiological examination during castration therapy. According to the European Association Urology guidelines 2015, the following criteria could indicate CRPC: castrate levels of testosterone (< 50 ng/dl or 1,7 nmol/l), 3 consecutive rises in PSA level with at least 1 week interval, with 2 rises in PSA level of more than 50 % above nadir (if PSA > 2 ng/ml) or radiological progression of the disease (appearance of 2 or more bone lesions or increase in the size of target lesions, based on RECIST) [2]. Disease progression without elevated levels of PSA or confirmed by radiological findings can»t be used for diagnosis of CRPC [3].

Development of CRPC is traditionally associated with poor survival rates. Median survival for patients with CRPC varies widely from 9 to 30 months and is highly dependent on the spread of the disease, initial patient performance status and a range of other factors [1]. The expansion of therapeutic opportunities for CRPC is highly connected with the emergence of such agents as docetaxel, cabazitaxel, abiraterone acetate and enzalutamide which enable to improve survival in this group of patients. According to Sridhar S. et al., median survival of patients with metastatic CRPC (mCRPC) increased up to 2–3 years due to the development and use of modern therapeutic agents [4].

Purpose – to evaluate overall survival (OS) in patients with mCRPC treated with modern therapeutic agents as well as to identify prognostic factors of OS.

Subjects and methods

We conducted a retrospective study using data of 112 patients who»d been diagnosed with mCRPC and treated in N.N. Blokhin Russian Cancer Research Center in the

period between 2005 and 2014. We included only those patients who had distant metastases. The main baseline characteristics of patients with mCRPC are depicted in table 1. All patients (100 %) had morphologically verified PC. High-grade (poorly differentiated) PC (Gleason score ≥ 8) was indicated in 37 (33,1 %) patients. All patients underwent castration therapy through surgical castration (orchiectomy) or medical castration. Median duration of response to castration therapy was 20,4 ± 1,7 (3,7–55,5) months. Patients developed castration-resistant form of the disease within approximately 3,25 ± 0,28 years of the diagnosis which varied from 4,5 months to 20 years. Patients» age at the time of indication of castration-resistant form of the disease ranged from 44 to 86 years. The median age at the time of diagnosis of mCRPC was 66,1 ± 0,7 (44,5–85,8) years. Bones were the most common location of distant metastases – 96 (85,7 %) patients with mCRPC; 11 (9,8 %) patients had visceral metastases with liver and lung involvement. At the time of mCRPC diagnosis, 63 (56,3 %) patients had clinical signs of the disease. Among the main symptoms were fatigue and bone pain. Due to the presence and severity of the symptoms, we decided to divide all patients into following groups: 1) absence of symptoms or mild symptoms (fatigue) – 48 (42,9 %); 2) moderate symptoms – 49 (43,8 %); 3) severe symptoms – 13 (11,6 %). Moderate symptoms were characterized by the presence of the pain syndrome. Patients who needed to take opioid-drugs as pain relievers were directed to the group of severe symptoms.

In the treatment of patients with mCRPC we used standard schemes of therapy based on docetaxel (75 mg/m^2 every 3 weeks), cabazitaxel (25 mg/m^2 every 3 weeks), abiraterone acetate (1000 mg/daily) in combination with prednisolone (10 mg/daily). Among 112 patients 35 underwent only 1 line of therapy, 54–2 lines of therapy and 23–3 lines of therapy. The distribution of patients as per the type of treatment and line of chemotherapy is depicted in table 2. Docetaxel has been primarily used in the 1-st line therapy. However, only 10 (9,2 %) out of 109 patients received docetaxel in the 2-nd line therapy. Abiraterone acetate has been used as a starting treatment in the 1-st line therapy in 13 patients. Abiraterone acetate and cabazitaxel were the main medicines used in the 2-nd and 3-rd lines of therapy.

We defined OS as the time from treatment initiation to the date of death, due to any cause, or last follow-up. We used the Kaplan-Meier method to describe OS and the log-rank test for comparing two survival curves. The time to the event measure was done by using a two-sided 95 % confidence interval (CI). At the time of analysis 71 (63,4 %) out of 112 patients suffering from mCRPC died. Among them 65 (91,6 %) patients had disease progression and 6 (8,5 %) patients died from reasons not associated with PC. Cox proportional hazard models were used to build prognostic models for OS.

Table 1. *Baseline characteristics of patients with mCRPC (n =112)*

Characteristic	Meaning
Median age (range), years	66,1 ± 0,7 (44,5–85,8)
Median time of developing castration-resistant form of the disease within the diagnosis of PC, years	3,2 (0,4–20)
ECOG performance status, *n* (%):	
0	27 (24,1)
1	75 (67,0)
2	10 (8,9)
Gleason score, *n* (%):	
< 8	75 (66,9)
≥ 8	37 (33,1)
Median PSA level, ng/ml	288,9 ± 51,9 (5,2–3197)
Median hemoglobin level, g/dl	12,6 ± 0,16 (9,1–15,8)
Median LDH level, IU/l	478,6 ± 51,3 (168–1493)
Median ALP level, IU/l	521,9 ± 91,6 (242–4385)
Median calcium level, mmol/l	2,3 ± 0,02 (1,8–2,6)
Sites of distant metastases, *n* (%):	
bone metastases	96 (85,7)
retroperitoneal LN	23 (20,5)
liver	5 (4,5)
lung	7 (6,3)
mediastinal LN	8 (7,1)
Prior HT, *n* (%):	
surgical castration	36 (32,1)
medical castration:	76 (67,9)
a) intermittent HT by LHRH analogues	12 (15,8)
b) continuous HT by LHRH analogues	64 (84,2)
Clinical signs of the disease, *n* (%):	
yes	63 (56,3)
no	49 (43,8)

Abbreviations. *LDH — lactate dehydrogenase, ALP — alkaline phosphatase, LN— lymph node, HT — hormonal therapy, LHRH — luteinizing hormone-releasing hormone.*

Results

The 3-year OS rate was 32,0 ± 5,44 % and wasn't influenced by the type of therapeutic drug. The median OS was 24,3 months. We evaluated the influence of such clinical laboratory parameters as age, spread of the disease, Gleason score, ECOG performance status, pain syndrome, severity of the symptoms, levels of hemoglobin, ALP, LDH and serum calcium on OS of patients with mCRPC (type of medication wasn't taken into consideration). We didn't find statistically significant difference with OS rates in patients of different age groups as well as the tumors of various grades ($p > 0,05$). Median OS in patients with Gleason score < 8 and ≥ 8 was 25,3 and 20,6 months accordingly ($p > 0,05$).

Clinical signs of the disease at the time of mCRPC diagnosis. We defined significant OS association with the pres-

Table 2. *Distribution of patients as per the type of treatment and line of chemotherapy*

Therapeutic drug	1-st line, *n* (%)	2-nd line, *n* (%)	3-rd line, *n* (%)	Total, *n* (%)
Docetaxel	99 (90,8)	10 (9,2)	–	109 (100)
Abiraterone acetate	13 (25,0)	29 (55,8)	10 (19,2)	52 (100)
Cabazitaxel	–	38 (74,5)	13 (25,5)	51 (100)
Total	*112*	*77*	*23*	—

ence and severity of clinical symptoms of the disease. Absence of all the symptoms was a favorable prognostic factor of OS in patients with mCRPC. Presence of the severe symptoms was found to be associated with poor OS compared with OS in patients who didn»t have any symptoms or whose symptoms were moderate (p = 0,005) (fig. 1). Presence of pain syndrome was found to be associated with poor OS in patients with mCRPC (p = 0,01).

Spread of the disease. Presence of visceral metastases (p = 0,006) as well as mediastinal LN metastases (p = 0,06) was found to be associated with poor OS in comparison to OS in patients who had only bone metastases. Median OS of patients according to the site of distant metastases is depicted in fig. 2.

ECOG performance status. We defined significant OS association with the patient's initial performance status (fig. 3). Our results were statistically significant (p = 0,005). Median OS in patients with mCRPC of EGOG 0, 1, 2 were 51,9; 21,1 and 9,2 months accordingly.

Laboratory findings. We identified prognostic value of such laboratory parameters as PSA, LDH, ALP, hemoglobin and serum calcium for OS in patients with mCRPC. Levels of PSA greater than the average meaning (288 ng/ml) was associated with poor OS: median OS for patients with PSA > 288 ng/ml was 15,3 months and for those who had PSA < 288 ng/ml – 25,9 months (p = 0,05). Those patients who had LDH and ALP levels greater than the upper reference value (URV) (> 450 IU/l and > 250 IU/l accordingly), had shown statistically significant lower OS rate, comparing to the patients whose levels of LDH and ALP were in their reference value – 11,9 and 30,9 months (p = 0,01) and 21,1 and 41,8 months (p = 0,014) accordingly. Level of hemoglobin < 11,5 g/dl was associated with poorer OS after 2 years of follow-up. Median OS in patients with mCRPC whose baseline levels of hemoglobin was > 11,5 g/dl found out to be 21,0 months, in comparison to those whose level was < 11,5 g/dl – 15,1 months (p = 0,05). We also identified the difference in median OS depending on the median serum calcium, levels: median OS for patients with calcium > 2,28 mmol/l was 23,4 months, whereas with calcium level < 2,28 mmol/l – 15,8 months (p = 0,05).

Duration of response to castration therapy. Duration of response to castration therapy longer than 24 months was a favorable prognostic factor of OS in patients with mCRPC (fig. 4). Median OS for those patients whose duration of response to castration therapy was longer than 24 months found out to be of two times higher than OS for those pa-

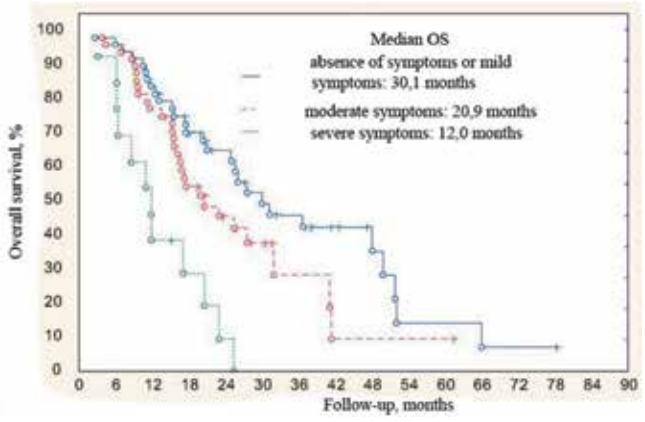

Рис. 1. *ОВ больных мКРРПЖ в зависимости от наличия и выраженности симптомов заболевания*

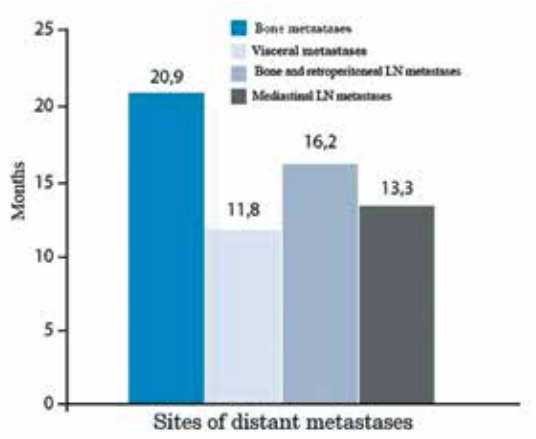

Fig. 2. *Median OS of patients with mCRPC according to the site of distant metastases, months*

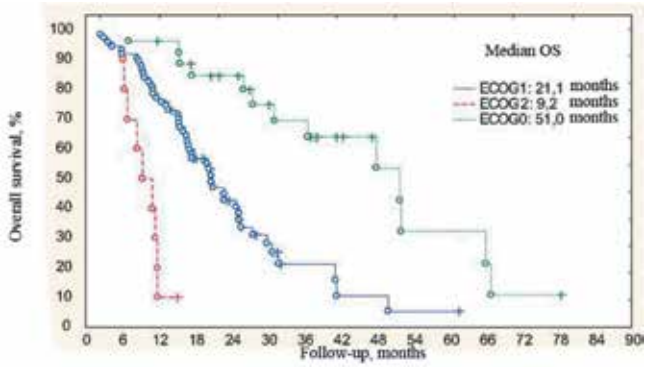

Fig. 3. *Median OS of patients with mCRPC according to ECOG performance status, months*

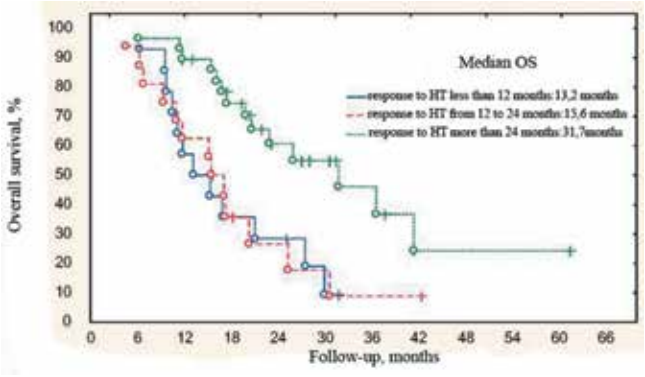

Fig. 4. *Median OS of patients with mCRPC according to the duration of response to prior HT, months*

tients whose duration of response was from 12 to 24 months and < 12 months – 31,7 months vs 15,6 months ($p = 0,004$) and 13,2 months ($p = 0,002$) accordingly.

In general, univariate analysis revealed the following prognostic factors associated with poor OS in patients with mCRPC: pain syndrome, ECOG performance status 2, PSA level ≥ 288 ng/ml, LDH ≥ 450 IU/l, ALP ≥ 250 IU/l, serum calcium < 2,28 mmol/l and hemoglobin < 11,5 g/dl, as well as duration of response to HT < 24 months. Multivariate analysis revealed that ECOG performance status 2 was the most important prognostic factor. Among laboratory findings ALP level exceeding the URV was the most significant factor with the highest hazard ration, HR (table 3).

Discussion

According to our study the 3-year OS rate was 32,0 ± 5,44 % with median OS 24,3 months which were quite independent on the number of therapeutic lines as well as the sequence of drug administration. The median age of patients with mCRPC was 66,1 ± 0,7 (44,5–85,8) years. Patients developed castration-resistant form of the disease within approximately 3,25 ± 0,28 years of the diagnosis which varied from 4,5 months to 20 years. However, more than 90 % of patients had a locally advanced or metastatic PC at the time of diagnosis. The median duration of response to castration therapy in our study was 20,4 ± 1,7 (3,7–55,5) months which is similar to other reported studies [5–7]. Medical castration with LHRH analogues (67,9 %) was used primarily constant (84,2 %) and approximately 2 times more often than bilateral orchiectomy (32,1 %). Patients suffering from mCRPC had rare vis-

Table 3. *Influence of different clinical laboratory parameters on OS in patients with mCRPC (univariate and multivariate Cox regression analyses)*

Risk factors	Univariate analysis		Multivariate analysis		*p*-value
	OP	95 % ДИ	OP	95 % ДИ	
ECOG performance status: 0 1 2	 0,45 1,19 5,01	 0,40–0,49 1,11–1,25 5,12–5,32	 0,40 1,11 4,53	 0,29–0,62 1,01–1,24 4,01–5,12	$p < 0,05$
ALP level: < 250 IU/l ≥ 250 IU/l	 0,69 1,40	 0,59–0,74 1,29–1,49	 0,88 1,81	 0,61–0,95 1,51–2,01	$p < 0,05$
Calcium level: < 2,28 mmol/l ≥ 2,28 mmol/l	 1,38 0,76	 1,29–1,43 0,69–0,79	 1,77 0,82	 1,43–1,95 0,57–1,29	$p < 0,05$
PSA level: < 288 ng/ml ≥ 288 ng/ml	 0,89 1.52	 0,81–0,95 1,46–1,61	 0,78 1,59	 0,63–0,91 1,39–1,69	$p < 0,05$
Hemoglobin level: < 11,5 g/dl ≥ 11,5 g/dl	 1,28 0,95	 1,18–1,32 0,87–0,99	 1,52 0,93	 1,29–1,75 0,70–0,17	$p < 0,05$
Duration of response: < 24 months ≥ 24 months	 1,21 0,56	 1,09–1,32 0,48–0,67	 1,25 0,61	 1,01–1,37 0,42–0,79	$p < 0,05$
LDH level: < 450 IU/l__ ≥ 450 IU/l	 0,78 1,34	 0,70–0,84 1,29–1,44	 0,67 1,18	 0,53–0,80 1,01–1,39	$p < 0,05$
Pain: yes no	 1,42 0,78	 1,38–1,48 0,61–0,82	 1,05 0,60	 0,98–1,18 0,50–0,73	$p < 0,05$

ceral metastases (9,8 %), while bones were the most common site of distant metastases – 96 (85,7 %). Such distribution explains the most common complaints on fatigue and/or bone pain which suffered about half (56,3 %) of the patients at the moment of diagnosis.

When assessing the prognostic impact, we revealed that OS has been strongly influenced by such factors as the presence of pain syndrome, ECOG performance status 2, PSA level ≥ 288 ng/ml, LDH ≥ 450 IU/l, ALP ≥ 250 IU/l, serum calcium < 2,28 mmol/l and hemoglobin < 11,5 g/dl, as well as duration of response to HT < 24 months. The results we»ve got are similar to other reported studies [8–12]. It should be noted that such parameter as the existence of visceral metastases is also important from a clinical point of view. However, it wasn»t included in the multivariate analysis due to a small number of patients with visceral metastases at the beginning of mCRPC treatment. It should be said that the mentioned factors appear to be poor prognostic factors for OS but not for tumor response.

According to our results OS of patients with mCRPC hasn»t been influenced by the patient»s age and Gleason score ($p > 0,05$). By the way, absence of influence of the age on OS in patients with mCRPC is well reported in other studies [10, 13, 14]. Leibowitz-Amit R. et al. conducted a study (2015) in a unique age group of patients – older than 80 years old. According to their study treatment outcome on abiraterone and docetaxel did not differ in patients over and under the age of 80. However, febrile neutropenia was more common in patients over 80 years old treated with docetaxel, in comparison to the younger men ($p = 0,048$) [15]. In TROPIC trial it was shown that the risk of neutropenia and its complications is already higher in patients over 65 years old treated with cabazitaxel [16]. Overall, all patients, regardless of their age, would have survival benefit from treatment with docetaxel, cabazitaxel and abiraterone acetate. Nevertheless, patients of the older age group, especially of elderly and senile age, treated with taxanes are in risk of developing neutropenia and its complications. The last one has to be taken into consideration in choosing the optimal treatment.

Suggestion that the patients suffering from high-grade PC with high Gleason scores have poorer OS rates wasn»t confirmed in our study ($p > 0,05$). However, median OS of patients with Gleason score ≥ 8 was lower in comparison to those patients with Gleason score < 8 (20,6 vs 25,3 months accordingly). It should be noted that the use of Gleason score in retrospective studies has its own limitations, primarily connected with the possible shift of the sum towards more aggressive parameters with time and the difference in how pathologists interpret prostate biopsy specimens [17]. As radical prostatectomy (RP) had been performed only in 19 (17 %) out of 112 patients, we primarily used the results of Gleason score written in histological conclusions which were made on biopsy specimens. According to the literature, concordance between Gleason scores of needle biopsies and RP specimens is only in 30–60 % of cases [18, 19]. Perhaps a larger sample size as well as a long-term follow-up would enable to receive more significant difference according to the Gleason score interpretation. According to the results of other studies, Gleason score didn»t predict the efficacy of therapy with abiraterone acetate, docetaxel and cabazitaxel but was considered to be a poor prognostic factor for OS [16, 20, 21].

Analysis of influence of the site of distant metastases on OS of patients with mCRPC revealed that the presence of visceral metastases ($p = 0,006$) as well as mediastinal LN metastases ($p = 0,06$) was associated with poorer OS in comparison to OS of patients who had only bone metastases. However, it wasn»t possible to compare OS of patients with liver and lung metastases in our study due to a small number of patients in these groups. Despite this visceral metastases have always been regarded as the significant poor prognostic factor. According to the results of TAX 327 trial, patients with liver metastases with or without other metastases had worse OS (median OS 10,0 months; 95 % CI 5,4–11,5) than those with lung metastases with or without bone or LN metastases (median OS 14,4 months; 95 % CI 11,5–22,4). Men with LN-only disease had the best OS (median OS 26,7 months; 95 % CI 22,3–34,2). Patients with bone-only metastases had median OS 19,0 months (95 % CI 18,2–20,7), whereas patients with bone-plus-LN disease had median OS 15,7 months (95 % CI 14,4–17,2) [22]. According to our data, patients with bone-only metastases had the best OS than those with bone-plus-retroperitoneal LN disease (median OS was 20,9 vs 16,2 months accordingly).

Our results regarding the prognostic significance of the mean value of PSA level (288 ng/ml) are justifiable for this sample. Nevertheless, the role of PSA level in OS of patients with mCRPC and moreover, its use as an individual prognostic factor, are highly debatable in literature. According to the results of MSKCC trial, higher level of PSA before initiation of the treatment of patients with mCRPC is associated with poor survival rates, but the confidence interval wasn»t significant. Analysis of the 25 % and 75 % quartile ranges didn»t reveal significant difference [12]. Analysis of the data of 143 patients from Dana-Farber Cancer Institute, Boston, revealed that higher PSA level predicted improved OS in patients who had bone metastases and ALP level not exceeding the URV [23]. Overall, higher PSA level could be a result of 2 competitive processes. On the one hand, its higher level is associated with disease progression, large tumor size and ultimately poor prognosis and is often combined with such significant risk factors as poor ECOG performance status, LDH level exceeding the URV, low hemoglobin level. On the other hand, higher PSA level could be identified in well differentiated tumors with a high number of androgen-dependent cells. Conjugation between PSA level with other clinically important factors as well as the broad reference range of this marker made it

being potentially used as a prognostic factor only in combination with other prognostic factors.

To sum up, the use of modern schemes of therapeutic treatment in patients with mCRPC enables to improve survival reaching the 3-year OS rate in this group of patients as well as to identify prognostic factors of OS which could be helpful in choosing the best possible approach for every patient.

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