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APPROACH TO THE TREATMENT OF METASTATIC CASTRATION-SENSITIVE PROSTATE CARCINOMA: A SINGLE CENTER EXPERIENCE

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ABSTRACT

Objevtive: Prostate cancer is the the second common cancer in men in Turkey. We aimed to share our single center experience on the characteristics of patients with metastatic castration sensitive prostate cancer (mCSPC) and the factors affecting survival.

Material and Methods: In this retrospective cross-sectional study, 280 patients (aged 18 years and older men) who applied with the diagnosis of metastatic prostate carcinoma were screened between January 2007 and December 2020. Sociodemographic and clinicopathological characteristics of the patients were obtained retrospectively from the hospital database. The study variables of the research were included descriptive characteristics of the patients, metastasis sites, treatment approachs, comorbidities of the patients and overall survival (OS) were evaluated. The descriptive statistics, Chi-Square Test, Fisher Exact Test, Kaplan Meier, and Cox Regression models were used as appropriate for the statistical analysis.

Results: A total of 201 patient who applied with the diagnosis of mCSPC were included in this study. The median age of the patients at the time of diagnosis was 68.67 years (43,97-90,48), 43.56% (n=88) of the patients were ≥ 70 years old and 56.43% (n=114) were under 70 years of age. The median follow-up time was 55.5 months, and the median OS was found to be 34.93 months (27.90-41.96). 34.7% of the patients were still alive at the time of date cut-off. The median OS of the patients was found to be significantly lower in individuals ≥70 years old than under 70 years of age (p=0.032). According to the LATITUDE study the median OS of the high-risk group (26.56 months) was statistically significantly lower than in the low-risk group (44.83 months). When the patients were evaluated in terms of disease volume according to CHAARTED, it was found that the median OS of the patient group with high-volume disease (29.03 months) was statistically significantly lower than the group with low-volume disease (46.80 months) (p=0.001).

Conclusion: In this study, it was shown that being over 70 years old, a low BMI, high volume disease defined as in the CHAARTED trial, and high risk disease defined as in the LATITUDE trial had a negative impact on survival of patients with mCSPC.

Keywords: prostat cancer, survival, castration, elderly

INTRODUCTION

Prostate cancer is the most common cancer in men worldwide, with an estimated 1,600,000 cases and 366,000 deaths annually (1). Affects 11% of men in the United States, and the risk of developing it increases with age (2). According to GLOBOCAN

2020 data, prostate cancer is the second common cancer (%14,6) and the second leading cause of death from cancer among men in Turkey (3). Males over the age of 65 account for around 6 out of every 10 cases, whereas men under the age of 40 are extremely rare. Men are diagnosed at an average age of 66. When all stages are included, the five-year survival rate is 98%, while the five-year survival rate is 30% in case of distant metastasis (4). Surgery, radiotherapy and testosterone suppressive treatments, also known as androgen deprivation therapy (ADT), are used in the treatment of localized prostate carcinoma. Unfortunately, despite all these treatments, the transition of some of the patients to the metastatic stage cannot be prevented. Patients who relapse after radical treatments are defined as castration sensitive prostate cancer (CSPC). Patients who progress while receiving adjuvant "adrogen deprivation therapy" are defined as "castration resistant prostate cancer (CRPC)". In the castration-sensitive non-metastatic stage, observation or androgen deprivation therapy can be recommended, while in the metastatic stage, ADT alone for patients who can not tolerete combined systemic therapies, abiraterone asetate (AA), enzalutamide (E), docetaxel (T), apalutamide (APA) can be recommended. EBRT for the primary tumor in low-volume disease can be recommended. Treatment options in CRPC include anti-androgen therapies (AA, oteronel, seviteronel, galaterone), androgen receptor blockers (E, APA, darolutamide), taxanes (T, cabazitaxel), radionuclide therapies (Lu-177, Ra-223). immunotherapies (Spilucel T, pembrolizumab, durvalumab, ipilimumab), PARP inhibitors (olaparib) and multikinase inhibitors (cabozantinib). Bisphosphonate and denosumab can be used as bone-sparing treatment in patients with bone metastases (5). Among the factors affecting the treatment decision; parameters such as the patient's age, comorbidities, ECOG performance score, tumor burden, natural history of the disease in the patient, and Gleason score (GS). Aim of this study is to determine the demographic, clinicopathological and treatment characteristics of prostate cancer patients, as well as to reveal the effects of these characteristics on survival as a single center experience.

MATERIAL AND METHODS

This retrospective cross-sectional study was conducted to 280 male patients (aged 18 years and older) who applied with the diagnosis of metastatic prostate carcinoma, between January 2007 and December 2020. After excluding 79 patients with missing data and the presence of a second primary malignancy, a total of 201 patients were included in the study.

Inclusion criteria were being a male patient aged 18 years and over and diagnosis of prostate carcinoma at stage IV as well as patients who have received at least one line of therapy for prostate carcinoma, including ADT. Exclusion criteria were inability to access patient data from the hospital database, having a histology other than prostate adenocarcinoma, castration resistant patients and presence of synchronous malignancy (except carcinomas in situ, bladder noninvasive carcinomas, non-melanoma skin cancers).

The dependent variables of the research were progression-free survival, time to castration resistance, time to skeleton related events and overall survival (OS). The independent variables of the research were descriptive and clinicopathologic characteristics of the patients, site of metastasis, GS, disease volume, chemohormonal agents, age and comorbidities. Sociodemographic and clinicopathological characteristics of the patients were obtained retrospectively from the hospital database.

For the statistical analysis, descriptive statistics (mean ± standard deviation, percent (%)), the Chi-Square Test and Fisher Exact test were used as appropriate. Survival analysis was evaluated with Kaplan Meier. The level of statistical significance was set as $p < 0.05$. All data analysis was performed using the Statistical Package for Social Science (SPSS) version 24.0. Ethical approval for this study was obtained from the Tepecik Training and Research Hospital Ethics Committee (Date of approval: 23.12.2020; Decision number 2020/14- 59).

RESULTS

A total of 201 patients who applied to our oncology clinic with the diagnosis of metastatic castration sensitive prostate carcinoma were included in this study. The descriptive and clinicopathologic characteristics of the study (age, comorbidity, body mass index (BMI), stage, disease volume/risk status and histopathological features of the patient population) were presented in Table 1 and Table 2, respectively. The factors affecting the OS of the patients were evaluated according to clinical, histopathological, volume/risk, and treatment given.

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Table 1. Sociodemographic and Clinicopathologic Caracteristics of Patients

Characteristics	n (%)
Comorbidity	
None	95 (47%)
One	65 (32,2%)
Two or more	42 (20,8%)
Age Distribution	
< 70 years	114 (56,4%)
≥ 70 years	88 (43,6%)
BMI	
<18,5	2 (1%)
18,5-24,9	62 (30,7%)
25-29,9	103 (51%)
>30	35 (17,3%)
ISUP Grade	
1	4 (2%)
2	21 (10,4%)
3	34 (16,8%)
4	41 (20,3%)
5	92 (45,5%)
Unknown	10 (5%)
Stage	
M0	2 (1%)
M1a	20 (9,9%)
M1b	138 (68,3%)
M1c	28 (13,9%)
Mx	5 (0,5%)
Unknown	13 (6,4%)
CHAARTED Volume	
Low Volume	59 (29,2%)
High Volume	141 (69,8%)
Unknown	2 (1%)
LATITUDE Rısk	
Low Risk	97 (48%)
High Risk	103 (51%)
Unknown	1 (1%)
Skeleton Related Events	
No	152 (75,2%)
Yes	50 (24,8%)

The median age of the patients at the time of diagnosis was 68.67 years (43,97-90,48), 43.56% (n=88) of the patients were ≥ 70 years old and 56.43% (n=114) were under 70 years of age. The median follow-up time was 55.5 months, and the median OS was found to be 34.93 months (27.90-41.96) (Figure 1). 34.7% of the patients were still alive at the time of date cut-off. At the time of data cut-off, castration resistance developed in 151 patients (75.1%) and not yet developed in 50 patients (24.9%). The median time to develop castration resistance was 19 months (0-124 months).

The OS of the patients was evaluated according to age and presented in Figure 2. The median time to castration resistance development was statistically significantly longer in patients younger than 70 years compared to patients 70 years of age and over (24.7 vs 20 months, p=0.046). The median OS of the patients under 70 years and ≥70 years old were 39.40 (95% CI; 31.07-47.72) and 27.86 (95% CI; 19.50 - 36.22), respectively. The median OS of the patients was found to be significantly lower in patients ≥70 years old than under 70 years of age (p=0.032). When the median OS was evaluated according to BMI, it was interestingly found that patients with higher BMI had longer survival than patients with lower BMI (p<0.001) (Figure 3). Patients were separated into two risk groups (high-risk group and low risk group) according to the LATITUDE study. The median OS of the high-risk group (26.56 months), which was 51% of all patients, was statistically significantly lower than in the low-risk group (44.83 months) (p<0.001) (Figure 4). When the patients were evaluated in terms of disease volume according to CHAARTED (high volume and low-volume disease), it was found that the median OS of the patient group with high-volume disease (29.03 months), which constitutes 69.8% of the research group, was statistically significantly lower than the group with low-volume disease (46.80 months) (p=0.001) (Figure 5). In addition, the effects of chemotherapy, orchiectomy, bicalutamide use, comorbidity and ISUP grade on OS in CSPC were evaluated and summarized in Table 3. It was observed that these parameters did not have a statistically significant effect on survival.

Patients at the CSPC stage were separated into low-risk and high-risk groups according to the risk classification defined in the LATITUDE study and low-volume and high-volume groups according to the disease volume criteria defined in the CHAARTED study. The effects of systemic treatments (chemotherapy, new generation hormonal agents) on these groups were examined and presented in Table 4. When the median OS of the patients in the low-risk group were compared, altough the median OS of those who received chemotherapy (n=68 (70.8%)) were longer than who not received chemotherapy (n=28 (29.1%)), it was no statistically significant (p>0.05). When we examined our patients according to the LATITUDE study, there was no statistically significant difference in terms of OS in the high-risk group who received chemohormonal therapy (n: 65 [65.6%]) and who did not receive chemohormonal therapy (35.7 months). When we examined our

Table 2. Treatment Characteristics

Surgery Status	
No	**175 (86,6%)**
Radical Prostatectomy	**27 (13,4%)**
Radiotherapy	
No radiotherapy	98 (48,5%)
Adjuvant	4 (2%)
Definitive	19 (9,4%)
Palliative	75 (37,1%)
Definitive +Palliative	3 (1,5%)
Adjuvant + Palliative	1 (0,5%)
Salvage	2 (1%)
Orchiectomy	
Yes	36 (17,8%)
No	166 (82,2%)
Bicalutamid	
No or only to avoid flare	110 (54,5%)
Present	92 (45,5%)
Bone sparing therapy in the CSPC stage	
No	94 (46,5%)
Zoledronic acid	107 (53%)
Unknown	1 (0,5%)
Chemohormonal therapy in CSPC	
No	135 (%68,5)
Docetaxel (q3w)	56 (%27,2)
Docetaxel (q2w)	3 (%1,5)
Enzalutamide	2 (%1)
Abiraterone	1 (%0,5)

patients according to the CHAARTED study, the rate of patients who received chemotherapy was 64.96% versus 75.89% in high-volume and low-volume disease. However, there was no statistically significant effect on survival of chemohormonal therapy regardless of volume status (p>0.05).

Disease volume and risk discordance were evaluated according to the CHAARTED and LATITUDE studies and presented in Table 5. According to the CHAARTED criteria, 27.7% of our patients in the high-volume disease group were in the low-risk group according to the LATITUDE criteria. On the other hand, 1.7% of our patients in the high-risk group according to the LATITUDE criteria were in the low-volume disease group according to the CHAARTED criteria (p<0.001).

DISCUSSION

In this study, we determined the demographic, clinicopathologic and treatment characteristics of prostate cancer patients and the effects of these characteristics on survival. In a trial conducted by Zorlu F et al the median age at the time of diagnosis was 68 years in patients with prostate cancer who living in Turkey (6). In our study, the median age was 68.67 years, which was consistent with our country's data. In our study, the number of patients over the age of 70 was 43.6%. After a median follow-up period of 55,5 months, 34.7% of the metastatic patients were still alive. Prostate cancer is the cancer of the geriatric age group, and the number of comorbidities increases with age. In a study conducted by Jefferson et al, in patients with prostate cancer, 51 % of the patients had at least 1 comorbidity (7). 53% of the patients in our study had at least 1 comorbidity, which was consistent with the literature. Clinical stage according to American Joint Committee on Cancer (AJCC), GS/grade group according to biopsy result, serum PSA value, imaging and genomic profile form the basis of initial treatment decisions in a patient diagnosed with prostate cancer (8). "The Gleason grades for the two most prevalent differentiation patterns are combined to create the GS, and GS is now incorporated into the newly adopted grade group system (9). In the grade group system, tumors are separated into five categories based upon the primary and secondary Gleason pattern: Grade group 1 (GS 3+3), Grade group 2 (GS 3+4), Grade group 3 (GS 4+3), Grade group 4 (GS 4+4, 3+5, or 5+3), Grade group 5 (GS 4+5, 5+4, or 5+5)." As the GS increases, the prognosis of the disease worsens. In our study grade group 4 and 5 was 65,8 % of patient populations. Therefore, it can be said that the patients included in our study represent a poor prognostic group. In a study that included 5100 patients diagnosed with prostate cancer between the ages of 70 and 80, 17.5% of the patients had a GS of 8 or higher. However, non-metastatic patients were also included in this study, and therefore, patients with a high GS were found to be less than in our study. Indirectly, it can be concluded that the GS is higher in metastatic patients (10). Bone metastasis is the most common metastasis in prostate cancer, and in a large population-based study where the incidence of bone metastasis in cancer patients was investigated (11), the rate of bone metastasis in patients with prostate cancer was found to be 84.7%. In our study, the rate of bone metastasis was 68.3%, although it was less common than this study. The mainstay of treatment for mPC has been to achieve castrate levels of testosterone in patients through medical ADT (LHRH agonists or antagonists) or surgical ADT (bilateral orchiectomy). In a retrospective study conducted on national cancer registries, that investigating castration methods in patients with prostate cancer, it

Table 3. Characteristics Evaluated as an Effect on Survival

Characteristics	n (%)	Median OS (mo)	% 95 CI	P Value
Age				
< 70 years	114 (56,4%)	39,40	31,07-47,72	
≥ 70 years	88 (43,6%)	27,86	19,50-36,22	**P=0,032**
BMI				
<18,5	2 (1%)	Not reached		
18,5-24,9	62 (30,7%)	26,56	21,57– 31,56	
25-29,9	103 (51%)	43,96	34,54 -53,38	**P=<0,001**
>30	35 (17,3%)	38,70	30,28-47,11	
Chemohormonal therapy				
Yes	62 (31,5%)	36,23	26,34-46,12	P=0,770
No	135 (68,5%)	35,96	26,53-45,39	
Orchiectomy				
Yes	36 (17,8%)	31,93	19,74-44,12	P=0,949
No	166 (82,2%)	35,70	27,70 -43,69	
Bicalutamid				
No	110 (54,5%)	32,30	24,21-40,38	P=0,220
Yes	92 (45,5%)	35,96	22,69-49,24	
Comorbidity				
None	95 (47%)	29,13	20,59-37,66	
One	65 (32,2%)	42,36	36,80-47,92	P=0,746
Two or more	42 (20,8%)	32,30	23,91-40,68	
ISUP Grade				
1	4 (2%)	Not reached	42,51-65,88	
2	21 (10,4%)	54,20	17,85- 54,34	
3	34 (16,8%)	35,96	32,09-45,30	
4	41 (20,3,%)	38,70	20,62-37,44	P=0,089
5	92 (45,5%)	29,03		
LATITUDE Rısk Status				
Low Risk	97 (48%)	44,83	33,94-55,72	**P=<0,001**
High Risk	103 (51%)	26,56	23,18-29,94	
CHAARTED Volume Status				
Low Volume	59 (29,2%)	46,80	35,81-57,78	**P=0,001**
High Volume	141 (69,8%)	29,03	34,27-33,79	

was seen that orchiectomy was performed in 5.4% of the patients (12), and this rate was higher with 17.8% in our study. The low socioeconomic status of cancer patients living in the region where our oncology clinic is may have caused this. Because it is known that as the socioeconomic level decreases, the preference for orchiectomy as a castration method increases (13). Zoledronic acid treatment is not recommended in CSPC with bone metastases after the CALGB 202 trial in 2014 (14), which showed that the use of zoledronic acid therapy in patients with bone metastases in the castration-sensitive stage did not reduce SRE. In our study, the use of zoledronic acid in the CSPC stage was 53%, and the rate of bone-preserving treatment in the CRPC stage was 62.6%. Since this rate was high in the castration-sensitive

stage, it was thought that 75 patients in our patient group were diagnosed before 2014. At the CSPC stage, 31.5% of our patients received chemotherapy. In our study, we did not see a significant effect of systemic chemotherapy on survival at the CSPC stage. In the GETUG-AFU 15 study conducted by Gravis G et al. in 2013, it was shown that adding docetaxel to ADT at the CSPC stage had no survival benefit (15). However, contrary results were obtained later in the STAMPEDE arm C and the CHAARTED trial (16). In the CHAARTED trial published in 2015, it was shown that chemotherapy contributes to survival in CSPC (17). In the light of these data, chemotherapy has become the primary reason for preference for patients diagnosed after 2015, which is necessary. 14.5% of patients received

Table 4. Effect of Chemotherapy on Survival by Volume and Risk Status

Characteristics	% (n)	Median (mo)	% 95 CI	P Value
CSPC LATITUDE Rısk				
Low Risk				
Not Received Chemotherapy	28 (29,1%)	37,03 mo	13,18-60,87	
Received Chemotherapy	68 (70,8%)	46,23 mo	34,87-57,59	
High Risk				P= 0,636
Not Received Chemotherapy	34 (34,3%)	35,70 mo	20,48-50,92	
Received Chemotherapy	65 (65,6%)	26,56 mo	22,52-30,60	
CSPC CHAARTED Volume				
Low Volume				
Not Received Chemotherapy	14 (24,1%)	Not reached		
Received Chemotherapy	44 (75,9%)	46,23	42,20-50,26	
High Volume				
Not Received Chemotherapy	48 (35%)	29,13	21,57-36,48	P=0,511
Received Chemotherapy	89 (65%)	29,03	22,60-35,66	

Table 5. Disease Status Concordance According to CHAARTED and LATITUDE

			Risk according to LATITUDE		P Value
			Low Risk	High Risk	
Volume according to CHAARTED	Low Volume	n	58	1	
		%	98,3	1,7	**P= <0,001**
	High Volume	n	39	102	
		%	27,7	72,3	

chemotherapy before 2015 for CSPC. Administration of chemotherapy for CSPC in patients diagnosed after 2015 has been increased with the CHAARTED (44.9 % of patients). In whole study population, the rate of chemotherapy in low-volume CSPC was 24.1%, while in high-volume disease was 35%.

Considering the factors that have an effect on survival in our study, it was seen that advanced age, low BMI, high volume and high risk disease had a statistically significant poor prognostic effect on survival. When we look at the literature, contrary to the result of our study, there are studies showing that prostate cancer recurrence and mortality increase as the degree of obesity increases (18). While there is a study showing that patients diagnosed with prostate cancer under the age of 40 have a lower survival rate and the tumor is more aggressive than the elderly group (19), there is also a study showing that those aged 49 and younger have a 10-year survival rate higher than those aged 80 and over (20). Both high-risk patients in the LATITUDE trial (21) and patients with high-volume disease in the CHAARTED trial (17) had a shorter survival time, and the data in our study were

consistent with the results of these two study. The CHAARTED and LATITUDE trials demonstrated a prolonged OS for metastatic hormone-naïve prostate cancer (mCSPC) patients who receive up-front docetaxel or abiraterone acetate. These studies used their own risk criteria: CHAARTED trial defined high- and low-volume diseases and LATITUDE trial targeting a high-risk disease. In a study of the Japanese population, both the high-volume patient ratio according to CHAARTED and high-risk patients rate according to LATITUDE 57.7%, high volume according to CHAARTED low-risk patients rate according to LATITUDE 8.8%, high-risk patients rate according to LATITUDE low volume patients according to CHAARTED as 12.8% was found (22). In another study, the rate of patients with high volume/high risk according to both studies were 44.8%, the rate of patients with high risk compared to CHAARTED but low risk compared to LATITUDE was 10%, and the rate of patients with high risk compared to LATITUDE and CHAARTED was 10%. The rate of low-volume patients was 7.7% (23). In our study, the rate of patients with high volume according to
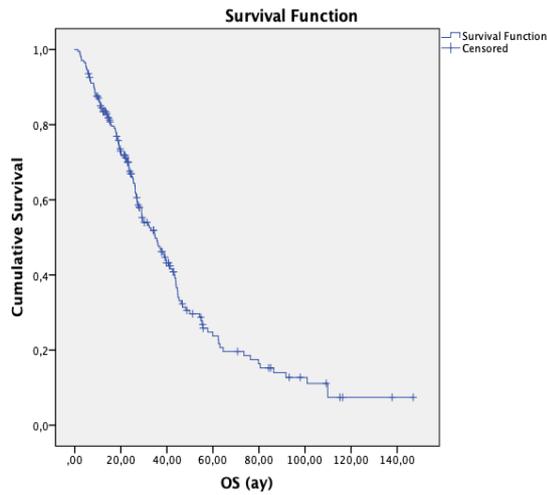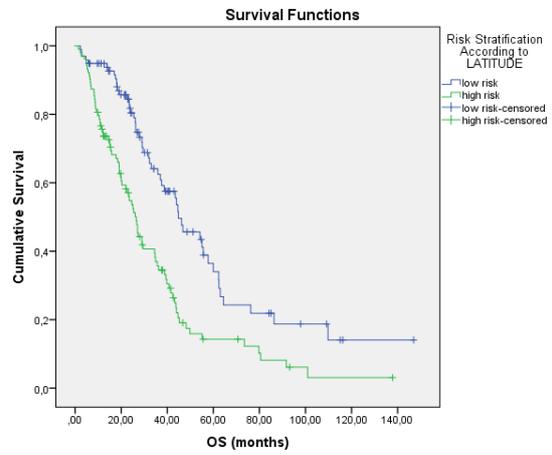
Figure 1. Median Overall Survival
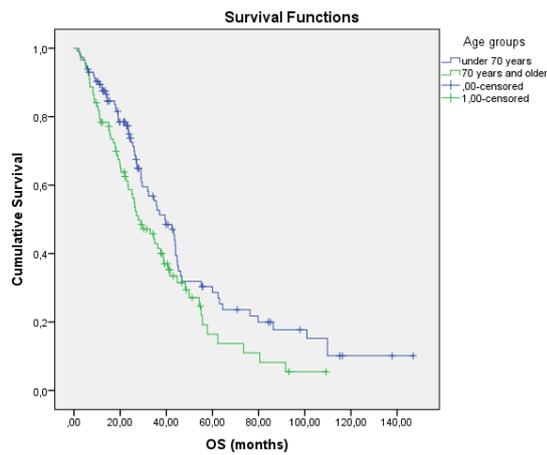

Figure 2. Overall Survival According to Age

Figure 3. Overall Survival According to BMI
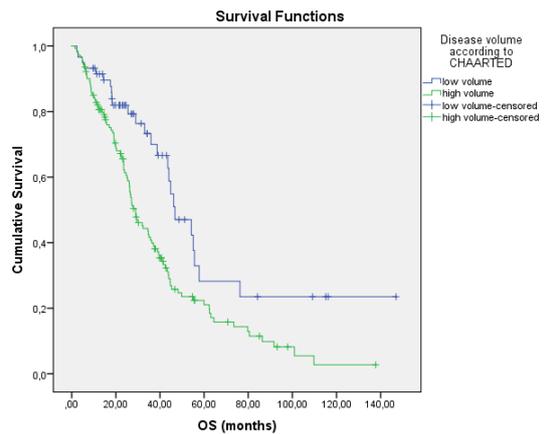

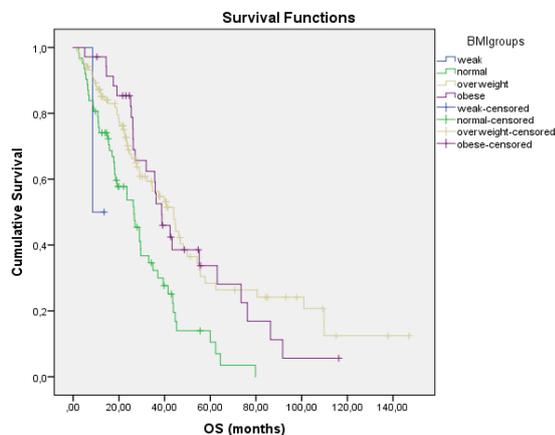**Figure 4.** Overall Survival According to LATITUDE

Figure 5. Overall Survival According to CHAARTED

CHAARTED and high risk according to LATITUDE is 72.3%, the rate of patients with low risk according to high volume LATITUDE according to CHAARTED is 27.7%, which is higher than the literature was found. The rate of high-risk patients according to LATITUDE with low volume compared to CHAARTED was 1.7%, which was found to be low compared to the literature. As it can be understood from here, it is seen that the discordance between LATITUDE and CHAARTED varies according to studies. As a result, in this study in which data from a single center were shared, some of our results were compatible with the literature, but some of our results had contradictory results with the literature. It is thought that this discrepancy may be due to the smaller number of patients and information obtained from a single center compared to the

literature, and that recent studies that lead to changes in treatment may explain these differences.

CONCLUSION

With the development of new treatment modalities, survival has reached a very good level compared to previous years, but metastatic prostate carcinoma still remains a deadly disease. Many randomized phase 3 studies have demonstrated the survival benefit of adding systemic therapies (docetaxel, abiraterone, enzalutamide) to ADT during the CSPC phase. However, patients with a diagnosis of mCSPC that we encounter in clinical practice may have worse prognostic features, a much higher number of comorbidities, and a shorter life expectancy than patients entering these clinical trials. However, it is an undeniable fact that all mCSPC patients with appropriate performance status should be given systemic treatment together with ADT.

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