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Research Article

CHAARTED and LATITUDE in Predicting Prognosis in Metastatic Hormone-Sensitive Prostate Carcinoma Comparison of Criteria

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Abstract

Objectives: Prostate carcinoma is the most common cancer in men and the second most common cancer causing death in the world. In this study, we will evaluate the CHAARTED and LATİTUDE classifications in predicting the prognosis in patients with mCSPC, investigate which group of patients are more reliable in predicting the prognosis according to these classifications, and examine which criteria show us the prognosis better in conflicting classifications.

Methods: This retrospective, cross-sectional study included 296 patients who were treated for the diagnosis of prostate adenocarcinoma between January 1, 2010, and June 1, 2021. Patients were categorized as having high-volume disease (HVD) and low-volume disease (LVD) according to the definition used in the CHAARTED study, and HRD and low-risk disease (LRD) according to the LATITUDE trial. The patients were classified as low or high volume based on the CHAARTED study criteria and as low or high risk based on the LATITUDE trial criteria.

Results: When two study criteria were matched, 74(%25) patients had cLaL, 46(%15.5) had cHaL, 10(%3.4) had cLaH and 166(%56.1) had cHaH. In addition, two study criteria were concordant %81.1 of patients and discordant %18.9 of patients. Median overall survival (OS) was 58 months (CI%95, 51.26-64.73) in the overall cohort (p<0.001). OS was found significantly lower on patients cHaH group (median: 41.06 months; CI%95, 34.88-47.25) compared to patients on cLaL (median:109.80 months; CI%95, 85.20-115.34)(p<0.001). Moreover, no significant differance was found when cLaH group (median:69 months.56;CI%95,29.02-110.10) compared with cHaL group. same results was found in progression-free survival (PFS) and cancer spesific survival (CSS).

Conclusion: Our study showed a lack of complete concordance between the CHAARTED and LATITUDE classifications. The need for new biomarkers and/or new classification criteria for these two groups still remains.

Keywords: concordance,CHAARTED, LATITUDE, prostate cancer, prognosis

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Prostate carcinoma is the most common cancer in men and the second most common cancer causing death in the world.[1] Metastatic prostate carcinoma accounts for approximately 18% of all prostate carcinomas. As a result of new treatments developed in recent years, survival times have exceeded 5 years. In metastatic castration-sensitive prostate carcinoma (mCSPC), androgen deprivation therapy (ADT) has been the mainstay of treatment since the 1940s.[2] However, with ADT alone, patient survival times varied. Some patients survived less than two years,

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while others lived longer than ten years. 90% of patients responded to treatment, but the majority of patients progressed to the castration-resistant stage. Nevertheless, ADT was seen as the basic standard in mCSPC until the 2010s. However, the use of docetaxel in the CHAARTED, GETUG-AFU15 and STAMPEDE studies, abiraterone in the LATITUDE and STAMPEDE studies, and enzalutamide in the ADT with the addition of enzalutamide in the ENZAMET study in mCSPC prolonged disease-free survival and overall survival.[3, 4] With the effective use of new generation hormonal therapies and chemohormonal therapies, survival times have exceeded five years.

In the CHAARTED study, high-volume and low-volume criteria were determined by the researchers(four or more bone metastases (at least one outside the axial skeleton) and/or visceral organ metastases were associated with high volume).[5] As a result of this study, docetaxel was shown to improve survival in high-volume patients, but not in low-volume patients.[6] In the LATITUDE study, patients were divided into two groups, high risk and low risk. i) those with Gleason 8 and above as a result of prostate biopsy, ii) those with 3 or more bone metastases iii) those with two of the three criteria determined as those with visceral organ metastases were considered high risk. Abiraterone has been shown to prolong survival in high-risk patients.[3] Today, the criteria of this study have become an important criterion in predicting prognosis, choosing treatment and predicting treatment response. However, there are conflicting data regarding which of the two studies' criteria determines the prognosis better.[7]

In this study, we aimed to investigate the effect of CHAARTED and LATITUDE criteria in predicting prognosis in metastatic castration-sensitive prostate carcinoma, which of these criteria predicts a better prognosis, and whether there is a difference in prognosis when the two criteria conflict with each other.

Methods

Patients and Trial Design

This retrospective, cross-sectional study included 296 patients who were treated for the diagnosis of prostate adenocarcinoma at the Health Sciences University (SBU) Tepecik Training and Research Hospital and Dokuz Eylul University between January 1, 2010, and June 1, 2021. Inclusion criteria for the study were as follows: (i) the patient was diagnosed with stage 4 CSPC, (ii) the patient was monitored in the clinic for at least three months, (iii) the patient had no therapy for mCSPC (ADT, docetaxel, or any new generation hormonal agents). Patients with missing data in the hospital database were excluded from the study. The study protocol was approved by the decision of Dokuz Eylul University Ethics Committee dated 13/04/2022 and numbered 2022/14-12. The Declaration of Helsinki was closely followed from the beginning to the end of the study.

Patients were categorized as having high-volume disease (HVD) and low-volume disease (LVD) according to the definition used in the CHAARTED study, and HRD and low-risk disease (LRD) according to the LATITUDE trial. HVD was defined as presence of visceral metastasis or ≥4 bone metastases with ≥1 beyond the vertebral bodies and pelvis.[5] HRD was defined as at least 2 of the following criteria: Gleason score ≥8 (grade group ≥4), visceral metastasis or≥3 bone metastases.[3]

Definitions

The patients were classified as low or high volume based on the CHAARTED study criteria and as low or high risk based on the LATITUDE trial criteria. Subsequently, patients were reclassified according to risk and volume levels in the LATITUDE and CHAARTED studies criteria. This classification was grouped as follows: i) cHaH: CHAARTED high volume-LATITUDE high risk; ii) cLaL: CHAARTED low volume-LATITUDE low risk; iii) cHaL: CHAARTED high volume-LATITUDE low risk; and iv) cLaH: CHAARTED low volume-LATITUDE high risk. CSS data were collected by calculating the time between the date of metastatic cancer diagnosis and the patient death or last visit. The time from the first diagnosis to death or the final follow-up visit was used to calculate the OS data. The period passed from the start of treatment for CSPC and the first PSA increase or radiographic progression (whichever occurred first) was regarded as the time elapsed until the onset of castration resistance. This period was also associated with PFS.

Statistical Analysis

In the data analysis, in addition to descriptive statistics (mean, standard deviation, median values, and interquartile range), chi-square and Fisher's exact tests were performed to evaluate the data for categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used as appropriate to determine whether continuous variables were compatible with a normal distribution. ANOVA, Student's t-test, Mann-Whitney u test, and Kruskal-Wallis tests were used in the analysis of the variables indicated by the measurements, according to their convenience. The Kaplan-Meier method was used for OS, CSS, and PFS estimations. A log- rank test was performed to investigate the difference in survival. The study's median follow-up time was computed using reverse Kaplan-Meier. All data was analyzed using the SPSS (version 24.0) package program. A two-sided $p<0.05$ was used to quantify statistical significance.

Results

The median age of the 296 patients who included this study, was 68.77(62.93-74.95) years and median PSA at the time of diagnosis was 100 (29.92-216.37) µg/L. The total number of de novo metastatic patients was 238 (80.4%). The proportion of those who received chemohormonal therapy in the castration- sensitive stage was %38.9 (n=115). Other descriptive and clinicopathological features of the patients are examined and presented in Table 1.

Based on CHAARTED study criteria, 84 patients (%28.4) were classified low volume (cL) disaese and 212 (%71.6) as high volume (cH) of disaese. According to LATITUDE criteria, 120 patients (%40.5) were classified low risk (aL), 176 (%59.5) as high risk (aH)of disaese. When two study criteria were matched, 74 (%25) patients had cLaL, 46 (%15.5) had cHaL, 10 (%3.4) had cLaH and 166 (%56.1) had cHaH. In addition, two study criteria were concordant %81.1 of patients and discordant %18.9 of remaining. Table 2 summarizes the number of patients and the treatments received according to the criteria of both studies.

The median follow-up time of the patients in the study was 70 months (CI%95, 54.08-85.71). At the date of analysis, 165 (%55.7) patients were dead and median OS was 58 months (CI%95, 51.26-64.73) in the overall cohort (p<0.001). OS was found significantly lower on patients cHaH group (median: 41.06 months; CI%95, 34.88-47.25) compared to patients on cLaL (median:109.80 months;CI%95, 85.20-115.34) (p<0.001). Moreover, no significant difference was found when cLaH group(median:69 months; CI%95, 29.02-110.10) compared with cHaL group (median: 62.43 months; CI%95, 58.13-66.73) (p=0.650) (Fig. 1).

According to analysis, median CSS was found 43.97 months (CI%95, 37.31-50.62) overall. CSS was found significantly lower on patients cHaH group (median:34.7 months; CI%95,26.12-43.28) than patients on cLaL (median: 66.93 months; CI%95, 41.45-92.41) (p<0.001). CSS was not found significant stastistically differance between cLaH group (median:68.83 months; CI%95, 0.42-137.23) and cHaL group (median:58.03 months; CI%95, 30.63-85.43) (Fig. 2).

Median PFS was found 31.83 months (CI%95, 24.85-38.81) overall. When we analysed in subgroups CHAARTED and LATITUDE criteria, PFS was found signifacntly lower on cHaH group (median:24 months; CI%95, 19.80-28.19) then cLaL group (median: 41.06 months; CI%95, 23.91-58.21) (p<0.001). Unlike OS and CSS, PFS was found longer in cHaL group (median:45.73 months; CI%95, 25.62-65.84) than cLaH group (median:19.33 months; CI%95, 5.21-34.65), but not statistically significant (p=0.06) (Fig. 3).

Table 1. Demografic and clinicopathological features of the study group

Variables	Total (n=296)
PSA at diagnosis (median, interquartile range), µg/L	100 (29.92-216.37)
Age groups, n (%)	
<70	166 (56.1%)
≥70	133 (43.9%)
The final status, n (%)	
Alive	131 (44.3%)
Dead	165 (55.7%)
Treatment in the castration-sensitive stage, n (%)	
ADT	181 (61.1%)
Docetaxel	105 (35.5%)
Abirateron acetate	7 (2.4%)
Enzalutamide	3(1%)
ISUP Grade group, n (%)	
1	1 (0.3%)
2	12 (4%)
3	56 (18.9%)
4	90 (30.4%)
5	133 (44.9%)
History of primary surgery, n (%)	
None	258 (87.2%)
Radical	38 (12.8%)
Radiotherapy, n (%)	
No	145 (49%)
Adjuvant	6 (2%)
Definitive	39 (13.2%)
Palliative	104 (35.1%)
Salvage	2 (0.7%)
Metastasis at the diagnosis, n (%)	
M1a	27 (9.1%)
M1b	202 (68.2%)
M1c	67 (22.6%)
CHAARTED volume, n (%)	
Low Volume	84 (28.4%)
High Volume	212 (71.6%)
LATITUDE risk, n (%)	
Low Risk	120 (40.5%)
High Risk	176 (59.5%)
Metastasis status	
De novo	238 (80.4%)
Recurrent	58 (19.6%)

CSPC: Castration-sensitive prostate carcinoma; ISUP: The International Society of Urological Pathology.

In univariate analyses, higher volume according to CHAARTED and higher risk according to LATITUDE were associated with worse OS (p=0.021, p<0.001, p<.0.001, respectively)

Table 2. Treatments received by patients according to CHAARTED and LATITUDE criteria

Parameters	Treatment options *number of participants (percent)*					
	Only ADT *	**Definitive radiotherapy**	**Docetaxel**	**Abiraterone**	**Enzalutamide**	**Total**
cLaL	28 (37.9%)	29 (39.1 %)	16 (21.6%)	1 (1.4%)	-	74 (100 %)
cLaH	9 (90%)	-	-	1(10%)	-	10 (100%)
cHaL	18(39.1%)	10 (21.8%)	18 (39.1%)	-	-	46 (100 %)
cHaH	87 (52.4%)	-	71 (42.8 %)	5 (3%)	3 (1.8%)	166 (100%)

ADT: Androjen deprivation therapy, cHaH: CHAARTED high volume-LATITUDE high risk; cLaL: CHAARTED low volume-LATITUDE low risk; cHaL: CHAARTED high volume-LATITUDE low risk; cLaH: CHAARTED low volume-LATITUDE high risk. * adjuvant or short-term use is not included.

and worse CSS (p=0.003, p<0.001, p<0.001, respectively) (Table 3). ISUP grade group 4-5, on the other hand, was associated with worse prognosis only for OS (p=0.006). Age was determined to be an independent prognostic factor for CSS only (HR: 1.038, 95% CI: 1.001-1.076) (p=0.042) (Table 4).

Discussion

In the last ten years, management paradigms for mCSPC have been developing. chemohormonal therapy or ADT with enzalutamide or abirateron represent possible therapeutic options for some mHSPC patients, challenging the approach to mCSPC. the CHAARTED trial demonstrated

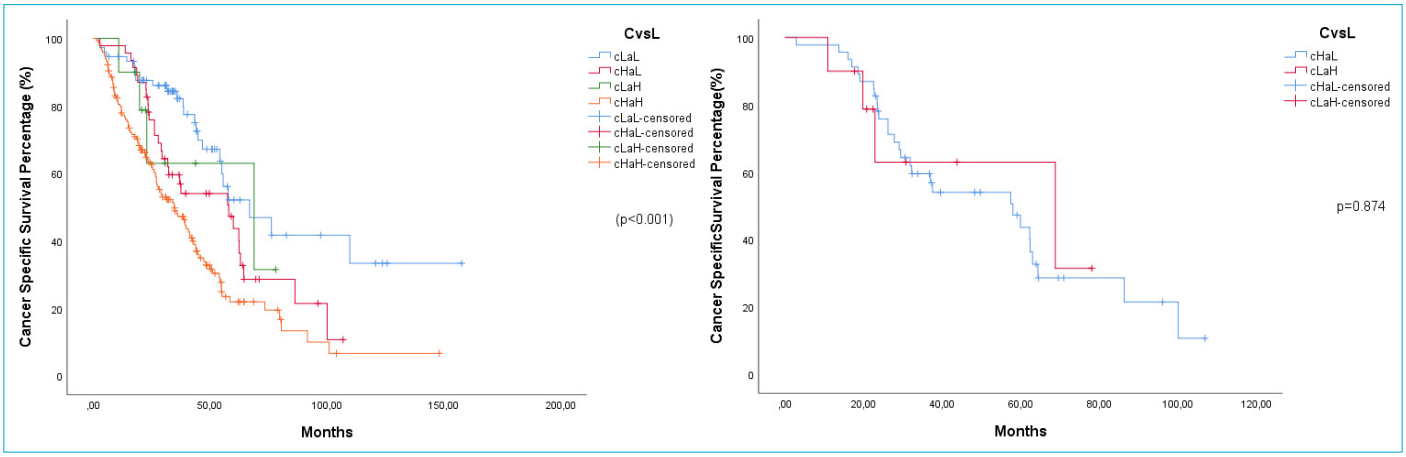

Figure 1. (a) Cancer specific survival (CSS) in all metastatic castration sensitive prostate cancer (mCSPC). **(b)** Comprasion CSS in cHaL and cLaH groups.

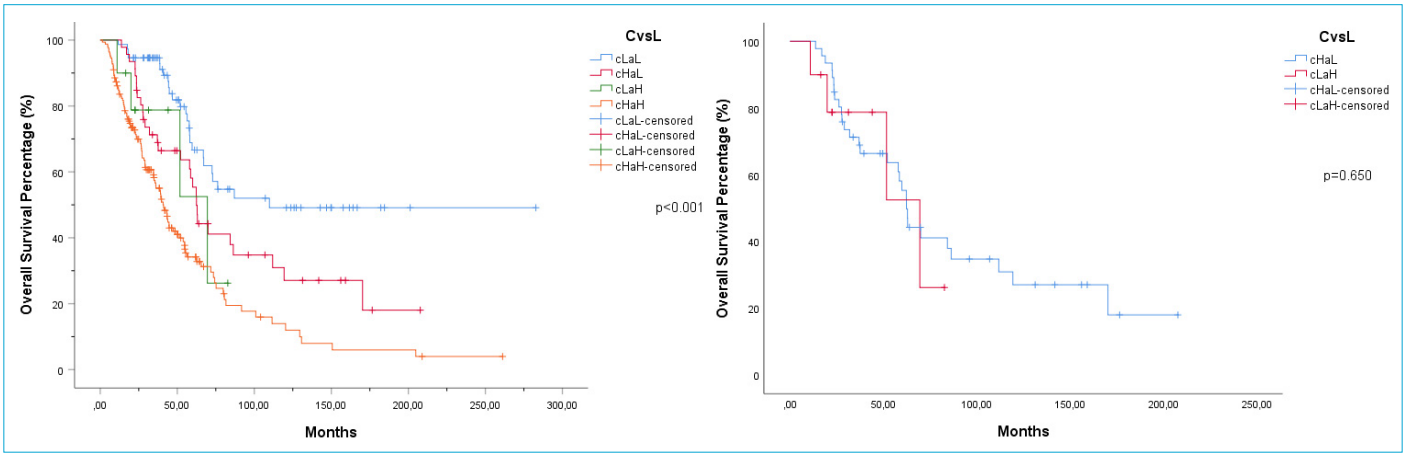

Figure 2. (a) Overallsurvival (OS) in all mCSPC. **(b)** Conprasion OS in cHal and cLaH groups.

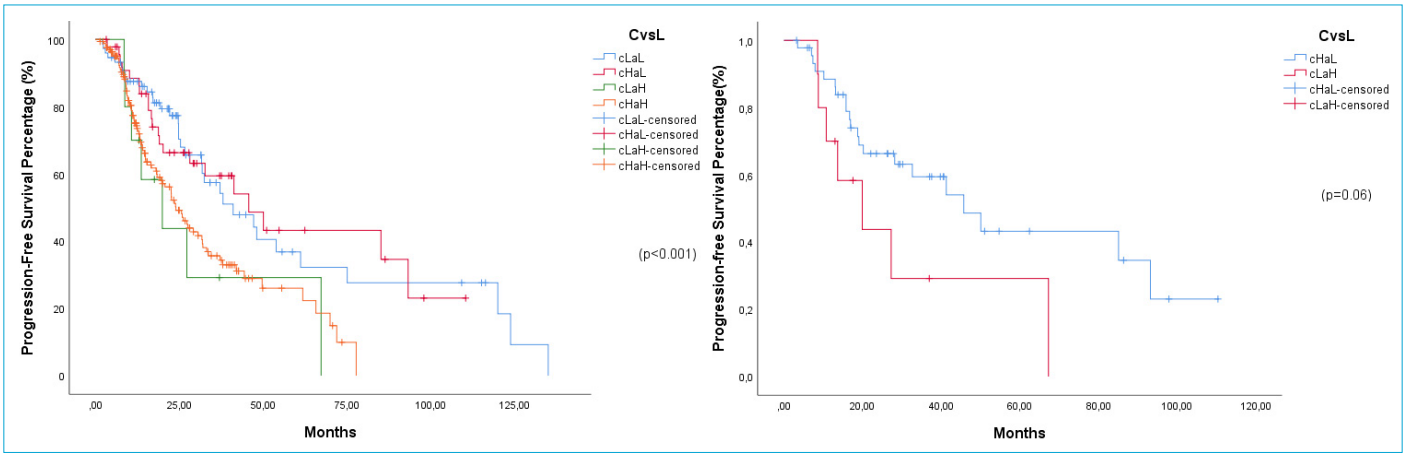

Figure 3. (a) Progression free survival (PFS) in all mCSPC. **(b)** Comprasion PFS in cLaH and cHaL gropus.

Table 3. Univariate analyzes of various clinical parameters in prostate cancer patients

Parameter	Overall Survival		Survival after metastasis	
	HR (%95 CI)	p	HR (%95 CI)	p
Age (years)	1.020 (0.988-1.053	.223	1.019 (0.988-1.050)	.226
PSA (µg/L)	1.000 (1.000-1.001)	.555	1.001 (1.00-1.001)	0.847
PNI				
<48.9	1	.021	1	.003
>48.9	0.546 (0.327-0.911)		0.451 (0.269-0.757)	
ISUP grade group				
1-3	1	.006	1	.102
4-5	2.467 (1.304-4.668)		1.648 (0.906-2.998)	
CHAARTED				
Low Volume	1	<.001	1	<.001
High Volume	4.249 (2.013-8.965)		0.251 (0.119-0.529)	
LATITUDE				
Low risk	1	<.001	1	<.001
High risk	3.322 (1.926-5.731)		0.251 (0.119-0.529)	

Table 4. Multivariate analyzes of various clinical parameters in prostate cancer patients

Parameter	Overall Survival		Survival after metastasis	
	HR (%95 CI)	p	HR (%95 CI)	p
Age (years)	1.036 (0.998-1.075	.066	1.038 (1.001-1.076)	.042
PSA (µg/L)	1.000 (1.000-1.001)	.853	1.001 (1.00-1.001)	0.856
PNI				
<48.9	1	.004	1	.001
>48.9	0.435 (0.248-0.765)		0.388 (0.220-0.683)	
ISUP grade group				
1-3	1	.001	1	.034
4-5	3.164 (1.598-6.265)		1.933 (1.051-3.553)	

the greatest benefit with concurrent ADT plus docetaxel in the subgroup of men with high-volume disease showing a 17-month OS improvement (49.2 versus 32.2 months; HR 0.60, p=0.0006).[5] The LATITUDE study showed a 38% reduction in the risk of death in hormone-naïve high-risk metastatic PC, defined ifat least two of the following fac-

tors were met: Gleason score ≥8, presence of ≥3 bone lesions or visceral metastasis.[3] However, a direct comparison between these two strategies is still lacking. Moreover, a validated prognostic score that helps clinicians with an adequate treatment selection for denovo mHSPC has to be identified. The CHAARTED and LATITUDE trials used two different prognostic classifications, based on the presence of phenotypic features retrospectively associated with worse cancer-specific survival.[8, 9] Both classifications identify the presence of visceral disease as a predictor of poor prognosis. Conversely, the CHAARTED trial acknowledged sites and number of bone metastases, whereas the LATITUDE classification stratified patients based on the number of skeletal metastases and Gleason score. When we analyzed, the CHAARTED and LATITUDE risk classifications maintained their prognostic value in our study, with a statistically significant difference in OS between cLaL group and cHaH group (109.8 months v 41.06 months, p<0.001).

Moreover, despite the different parameters used, it is of considerable importance to understand if the two prognostic systems overlap, for example if de novo mHSPC patients with high-risk (or low-risk) disease according to the LATITUDE trial can also be considered as high-volume (or low-volume) based-on the CHAARTED study, and vice versa. In our study, we found no complete concordance and approximately %20 patients have discordance. Comprasion the other studies in CHAARTED and LATITUDE classification, they determined discordance between %13 and %20.[10, 11] Approxiamately %20 lack of the concordance between the two risk scores is of utmost importance for its consequences in clinical practice. In particular, discordance in two subgroup maybe miss patients who are need more aggresive treatment. Where a concordance between the CHAARTED and LATITUDE systems was observed (in about %80 of cases), two opposite clinical disease patterns can be depicted: Low-volume/low risk disaese have better median OS then high volüme/high risk disease (109.8 months v 41.06 months, p<0.001). Similar OSs were obtained in a study of mCSPC patients between cLaL group and cHaH group (72.6 months v 26.3 months).[10]

Discordance between two subgrops according to CHAARTED and LATITUDE studies is very important because potential risk is indeed to exclude patients who are considered unsuitable for docetaxel from being treated with abiraterone, or vice versa. This subgroups represents a greyer area as some of these patients may profit from the addition of docetaxel/abiraterone acetate to hormone therapy, which highlights the need of accurate biomarkers for identification, whereas other subjects would probably benefit more from a different treatment.[12] A critical analysis of mCSPC patients, by matching the CHAARTED and LATITUDE prognostic classifications,can help determine which patients are more likely to benefit from ADT alone or combined with early docetaxel or abiraterone. However, it is known that there may be significant discordance between the criteria and which better prognostic significance is unknown.We think that metastatic patients with low Gleason scores, patients with multiple metastases but no metastases outside the vertebral and pelvic regions are the possible reasons for this situation. Therefore, we think that these criteria alone are not sufficient to influence the treatment decision.Indeed, given the absence of a direct comparison between these treatment options, and lacking biomarkers with predictive value, to date the disease characteristic (albeit still incompletely defined) are the only factors to take into account for treatment selection.

In two retrospective studies, no significant survival difference was observed in patients whose CHAARTED and LATITUDE criteria did not match.[10,13] In our study, median OS, PFS and CSS did not statistically differ between this two subgroups, but PFS was differance numerically (45.73 months in cHaL and 19.3 months in cLaH). This differance may be due to the small number of patients (10 patients) in the cHaL group.

Our study confirms patient age as a negative prognostic factor in mCSPC.[14] The age and ISUP grade group 4-5 could be added to the CHAARTED and LATITUDE classifications as independent prognostic factors to better predict patients prognosis.

Our study has several limitations. Given the retrospective design, all analyses are subject to selection biases and imbalances in variables not quantifiable. Moreover, the small sample size,especially in one group, the single center cohort with confounders and no consistent follow-up period might limit the reproducibility of our results.

Before the era chemohormonal therapy, standart therapy was ADT and in our study,186 patients had treated only ADT. Chemohormonal therapy and the new generation hormonal therapies in mCSPC have changed in our perspective on treatment mCSPC. Therefore,studies done in this new therapies will give more accurate results.

Conclusion

The CHAARTED high-volume and LATITUDE high-risk group showed a shorter survival and a poorer OS than the CHAARTED low-volume group and the LATITUDE low-risk group among metastatic castration-sensitive metastatic prostate cancer patients. No significant survival difference was found when the patients with conflicting criteria were compared. The need for new biomarkers and/or new classification criteria for these two groups still remains.

Disclosures

Ethics Committee Approval: This study was approved by the Dokuz Eyül University Medicine Faculty Ethics Committee with decision dated 13/04/2022 and numbered 2022/14-12.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.I.E., H.S.S.; Design – H.S.S., M.U., H.I.E.; Supervision – M.K., O.U.U.; Materials – M.U., H.I.E.; Data collection &/or processing – H.I.E., M.U.; Analysis and/or interpretation – H.I.E., M.K., H.S.S.; Literature search – H.S.S., H.I.E., M.U.; Writing – H.I.E., M.U.; Critical review – H.S.S., M.K., O.U.U.

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