DOI: 10.14744/ejmi.2021.66973
EJMI 2021;5(2):251–255

Research Article

Evaluation of Castration-Resistant Elderly Patients

Serkan Yıldırım,[1] Atike Pınar Erdoğan,[2] Ahmet Özveren,[3] Ferhat Ekinci,[2] Gülcan Bulut[4]

[1]Department of Medical Oncology, Bitlis Tatvan Public Hospital, Bitlis, Turkey
[2]Department of Medical Oncology, Celal Bayar University Faculty of Medicine, Manisa, Turkey
[3]Department of Medical Oncology, İzmir Kent Hospital, Izmir, Turkey
[4]Department of Medical Oncology, Hatay Defne Hospital, Hatay, Turkey

Abstract

Objectives: In the present time suggesting an extended human lifespan and expectancy, elderly patients receive a significant portion of daily healthcare practice whereas they have not been sufficiently addressed in the extensive and comprehensive clinical studies. We have desgined our study to evaluate the treatment options in this metastatic castration-resistant prostate cancer patients older than 70 years.

Methods: Our study is retrospective. The data of the patients from 5 centers of Turkey were obtained. The patients aged 70 years and over were assigned to a group (geriatric group) while the rest of the patients were evaluated in another group (normal group). The primary endpoint of the study was determined as overall survival time.

Results: Totally 113 patients were included in our study. The geriatric and normal groups included 58 and 55 patients, respectively. Overall survival as the primary endpoint of our study demonstrated no statistically significant difference between survival of the patients aged over 70 years and other patients (geriatric group versus normal group, respectively 18.86 versus 23.93 months, respectively, p=0,542). Progresion-free survival as the secondary endpoint; no statistically significant difference was detected between two groups (geriatric group vs normal group, median 7.83 vs 8.5 months, respectively, p=0.73).

Conclusion: It was detected that the age variable has a negative impact on overall survival of prostate cancer cases. The overall survival was found numerically shorter in the patients aged 70 years and over set as age limit, however, this difference was not found statistically significant.

Keywords: Castration resistant, gleason score, geriatric, prostate cancer

Cite This Article: *Yıldırım S, Erdoğan AP, Özveren A, Ekinci F, Bulut G. Evaluation of Castration-Resistant Elderly Patients. EJMI 2021;5(2):251–255.*

Prostate cancer is a disease with an incidence increasing directly proportional with age and frequently seen after 70 years of age. The estimated number of the prostate cancer patients older than 75 years of age is over 1 million people worldwide.[1] Approximately 58% of the patients diagnosed with prostate cancer were 65 years of age in 2018 in USA.[2] In the present time suggesting an extended human lifespan and expectancy, elderly patients receive a significant portion of daily healthcare practice whereas they have not been sufficiently addressed in the extensive and comprehensive clinical studies.[3,4]

Most of the elderly patients are detected in the localized disease period thanks to widespread use of particularly prostate specific antigen (PSA) test. However, the number of the patients diagnosed to have metastatic disease is also high. The palliative treatment has a great importance for the patients with metastatic disease.[5,6] These patients can

Address for correspondence: Serkan Yıldırım, MD. Bitlis Tatvan Devlet Hastanesi, Bitlis, Turkey
Phone: +90 505 542 38 89 **E-mail:** serkan9128@yahoo.com
Submitted Date: March 10, 2021 **Accepted Date:** June 03, 2021 **Available Online Date:** July 12, 2021

receive androgen deprivation therapy (ADT), chemotherapy and hormonal therapy as well as palliative therapy. ADT is the selected treatment particularly for the patients in the castration-sensitive period. The intermittent administration of ADT has been evaluated taking into consideration many side effects of this therapy, however, it is not recommended as a routine treatment option except these clinical trials.[7,8]

Docetaxel and abiraterone are also used together with ADT in the castration-sensitive period. CHAARTED study involving the addition of docetaxel to ADT revealed the positive impact of combination treatment also in the patients aged over 70 years old as well as general population.[9] The rate of the patients over 75 years of age was approximately 20% in the LATITUDE study carried out using abiraterone. The combination of ADT and abiraterone achieved statistically significantly prolonged progression-free survival in this population, even though no statistically significant improvement could be obtained in the overall survival.[10] The progression-free survival significantly prolonged in favor of combinations for both abiraterone and docetaxel in the meta-analysis that has evaluated over 70-year-old patients regarding castration-sensitive metastatic prostate cancer. However, this extension was not reflected in overall survival.[11]

Some studies have been conducted with apalutamide,[12] enzalutamide[13] and darolutamide[14] in the non-metastatic patients in the castration-resistant period. An improvement has been achieved by administration of these agents. However, there is no large number of studies carried out with metastatic castration-resistant patients. Therefore, we have desgined our study to evaluate the treatment options in this patient group.

Methods

Our study is retrospective. The data of the patients from 5 centers of Turkey were obtained. The files of the patients were examined and included in the study. The inclusion criteria of our study were being diagnosed with metastatic prostate cancer, having no history of surgical or radiotherapy treatment for pancreatic cancer and being progressed under treatment of ADT alone or combined with docetaxel. The patients meeting inclusion criteria were analyzed in by dividing into two groups based on 70 years of age. The patients aged 70 years and over were assigned to a group (geriatric group) while the rest of the patients were evaluated in another group (normal group).

The primary endpoint of the study was determined as overall survival time. Overall survival was calculated as the interval elapsed from the date of progression after treatment of ADT alone or combined with docetaxel to the date of death or last examination. The secondary endpoint was defined as the progression-free survival. The progression-free survival was calculated as the time from the date of progression after the treatment of ADT alone or combined with docetaxel to the date of next progression or death.

Gleason score which has a significant impact on prognosis was assessed similarly with overall survival and progression-free survival. The patients were divided into two groups based on Gleason score (The patients with Gleason score 9-10 and those with Gleason Score≤8). The impact of Gleason score on all the patients and groups was evaluated. Our study was conducted as per the Declaration of Helsinki and performed with the approval of the Local Ethics Committee.

All analyses were performed using the SPSS statistical software program package (SPSS version 20.0 for windows). The chi-square test analyzed the differences in the clinical characteristics between the two groups. OS was calculated with the log-rank test. The Kaplan–Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to determine statistically significant variables related to OS. Differences were assumed to be significant when the p-value of less than 0.05.

Results

Totally 113 patients were included in our study. The geriatric and normal groups included 58 and 55 patients, respectively. The impact of Gleason score on prognosis and its distribution in the groups were evaluated. Gleason score was found to statistically significantly influence the overall survival in whole population (Gleason score 9-10 versus ≤8 with respectively median of 16.06 versus 23.8 months, p=0.029) (Fig. 1). The distribution evaluation of the patients

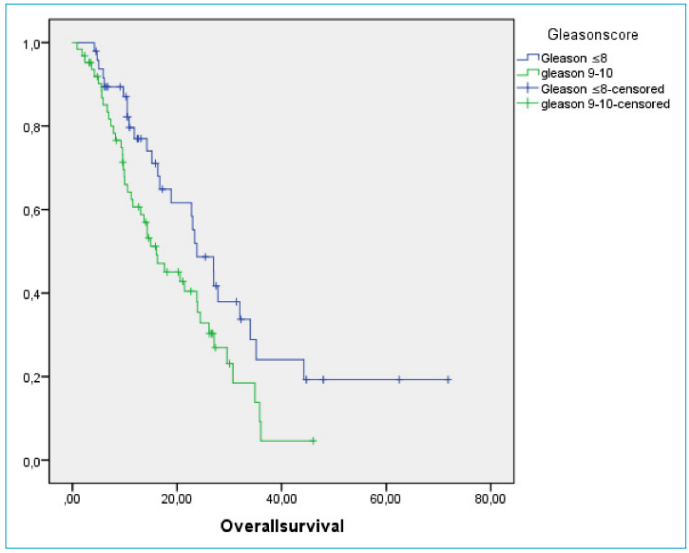

Figure 1. Overall Survival of Patient with Gleason Score 9-10 versus Gleason Score ≤8.

with higher Gleason score and thus lower survival in two groups revealed that the number of the patients with a Gleason score of 9-10 was statistically higher in the normal group (geriatric and normal group, 23 and 40 patients, respectively, p=0.006) (Table 1).

According to the evaluation of metastasis site; the number of the patients with only bone metastasis was 39 in the geriatric group whereas that number was 20 in the normal group. The number of the patients with only bone metastasis was statistically significantly higher in the geriatric group (p<0.001). The number of the patients with visceral metastasis was 3 in the geriatric whereas 11 patients had visceral metastasis in the normal group. The number of the patients with visceral metastasis was statistically significantly higher in the normal group (p=0.027) (Table 1).

The evaluation based on overall survival as the primary endpoint of our study demonstrated no statistically significant difference between survival of the patients aged over 70 years and other patients (geriatric group versus normal group, respectively 18.86 versus 23.93 months, respectively, p=0.542) (Fig. 2). With respect to progresion-free survival as the secondary endpoint; no statistically significant difference was detected between two groups (geriatric group vs normal group, median 7.83 vs 8.5 months, respectively, p=0.73) (Fig. 3).

The analysis of the treatments received in the castration-resistant period indicated that 22 of the 55 patients received treatment of docetaxel in the geriatric group whereas remaining 33 patients were administered hormonal therapy (abiraterone or enzalutamide). On the other side, 31 of 58 patients received hormonal therapy (abiraterone or enzalutamide) whereas docetaxel was administered in 27 patients. No statistically significant difference was determined between the groups regarding the administration rates of hormonal or docetaxel therapy (p=0.304) (Table 1).

Table 1. Patient Characteristics

	≥70 age group (Geriatric Group) (n=58)	<70 age group (Normal Group) (n=55)	Overall (n=113)
Gleason score			
9-10	23	40	63
≤8	35	15	50
p=0.029			
Only bone metastasis			
p<0.001	39	20	59
Visseral metastasis			
p=0.027	3	11	14
Therapy			
Hormonal therapy	33	31 64	
Chemotherapy	22	27	59
p=0.304			

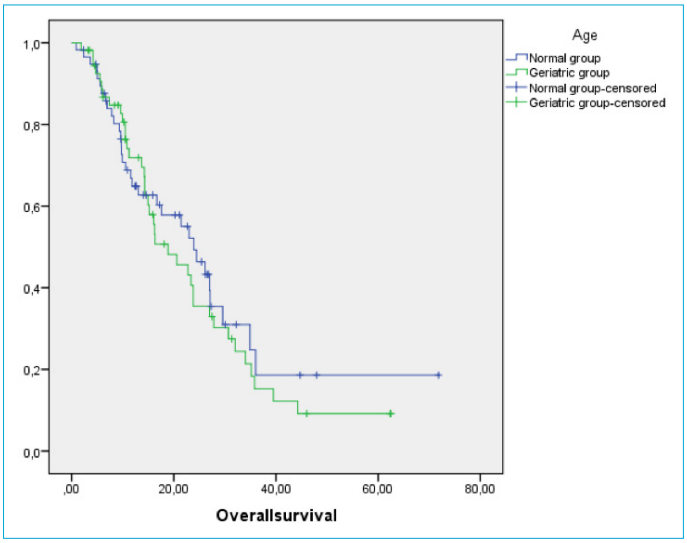

Figure 2. Overall Survival of Patients.

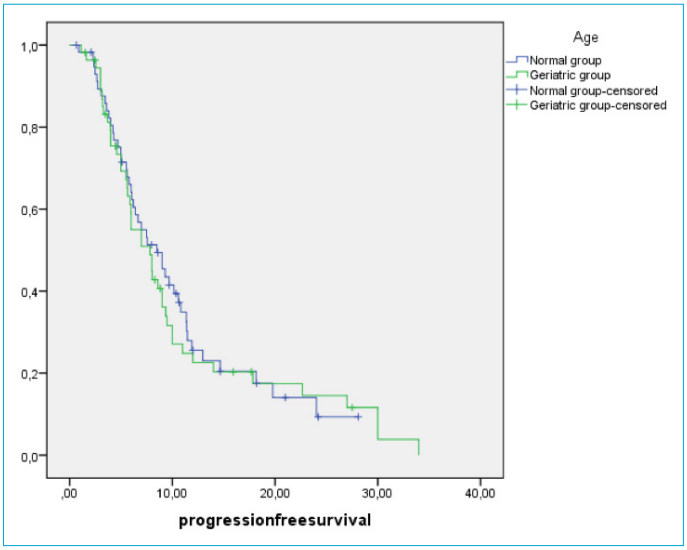

Figure 3. Progression Free Survival of Patients.

Discussion

The expected lifespan is shorter after development of castration resistance in metastatic prostate cancer. Even though many treatment methods are administered, the most commonly used treatments are chemotherapy (docetaxel or cabazitaxel) and drugs acting through androgen pathway (abiraterone and enzalutamide). The impacts of these agents on survival in the castration-resistant patients have been investigated since a long time. Docetaxel is the first used chemotherapy and was compared with mitoxantrone in castration-resistant disease in its first study. Docetaxel has provided a statistically significant advantage for survival and median survival was found 19.2 months.

[15] Cabazitaxel was compared with docetaxel in castration-resistant disease and no statistically significant difference was detected between these two agents regarding survival.[16] Abiraterone provided a significant difference in survival compared with placebo in the castration-resistant metastatic cancer patients who had previously received docetaxel treatment and median overall survival was found 15.8 months.[17] Likewise, abiraterone achieved a significant difference in survival compared with placebo in the castration-resistant patients who had previously received no chemotherapy and median survival was detected to be 34.7 months.[18] Similarly with abiraterone, enzalutamide was evaluated in two separate studies on the patients who had previously received docetaxel and those who had previously received no chemotherapy and showed statistical superiority to placebo in both studies.[19,20] Median survivals were determined to be 18.4 and 35.3 months, respectively.

The evaluation of the impact of age on survival which is the essential cutoff point of our study indicated that the impact of age on survival has not been investigated since the studies on chemotherapeutic agents have been carried out in the younger patient populations. Age limits were set as 65 and 75 years in the study of abiraterone on the patients who had previously received chemotherapy and the impact of these ages on survival was analyzed. A difference was achieved in survival also in the patients aged over 65 and 75 years as found in the other age groups. Furthermore, the best hazard ratio was detected in the patients over 75 years of age (hazard ratio 0.52 vs 0.66, respectively).[17] Likewise, age limits were set as 65 and 75 years in the study of abiraterone carried out on the castration-resistant prostate cancer patients who had previously received no chemotherapy. All the age groups presented a similar contribution to overall survival.[18] No age limit was set for enzalutamide in the mentioned studies.

In our study, median overall survival was 18.86 months in the patients over 70 years of age whereas that value was median 23.93 months in the patients below 70 years of age. This numerical difference was not statistically significant. That may be resulting from the heterogeneity between the patient groups. Because, high Gleason score which is the indicator of poor prognosis and the presence of visceral metastasis were significantly opposed to the patient group below 70 years of age. In addition, the number of the patients who had only bone metastasis and relatively better prognosis was statistically higher in the group including over 70-year-old patients. The difference might have not reached statistically significant level due to these disadvantages in patient selection.

The overall survival values of our study were found numerically close to the Phase 3 Study that compared docetaxel and cabazitaxel. Mean survival rates were detected to be approximately 24 months in that study. However, these survival rates reached 34 months in the studies of enzalutamide and abiraterone in the patients who had previously received no chemotherapy. The survival rates of our study were determined to be lower compared with these studies. The reason of this difference is the patient selection in the same way. This difference might have been obtained since more fit patients without symptoms were included in the studies of enzalutamide and abiraterone.

This discrimination was not defined based on age in the progression-free survival data in the studies mentioned above. On the other side, we have detected in our study that age had no impact on progression-free survival. The progression-free survival of the patients aged over 70 years was found statistically similar compared with the other patients.

As a consequence, age influences survival negatively in the castration-resistant period particularly in a disease seen in the elderly population such as prostate cancer. In our study, survival of the elderly population was found numerically lower, however, that difference was not statistically significant. That was concluded to be resulting from the heterogeneity in the patient selection such as lower Gleason scores in the patients over 70 years of age and larger number of the patients with visceral metastasis. On the other hand, no impact of age on progression-free survival was determined. Besides, treatments received by the patients (hormonal therapy or chemotherapy) were analyzed and no difference was found between the groups. It was concluded that age has a negative impact on survival, however, it has no importance to be considered regarding treatment selection since there was no difference in progression-free survival.

Conclusion

It was detected that the age variable has a negative impact on overall survival of prostate cancer cases. The overall survival was found numerically shorter in the patients aged 70 years and over set as age limit, however, this difference was not found statistically significant. That may be resulting from the heterogeneity in patient selection depending on retrospective design of the study. The age variable was not evaluated to be effective in progression-free survival. Larger-size randomized studies are needed to clarify the subject.

Disclosures

Ethics Committee Approval: Manisa Celal Bayar University Faculty of Medicine Ethics Committee (No: 20.478.486, Date: 23/12/2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.Y.; Design – A.P.E.; Supervision – A.Ö.; Funding – None; Materials – F.E.; Data collection and/or processing – G.B.; Data analysis and/or interpretation – S.Y.; Literature search – S.Y.; Writing – S.Y.; Critical review – S.Y.

References

1. SEER Cancer Statistics Review, 1975-2006, Horner MJ, Ries LAG, Krapcho M, et al, editors. National Cancer Institute, Bethesda. Based on November 2008 SEER data submission, posted t o the SEER web site 2009. Avaialable at: https://seer.cancer.gov/csr/1975_2006/ (Accessed on July 26, 2019).
2. National Cancer Institute. SEER Cancer Stat Facts: Prostate cancer. Available at: https://seer.cancer.gov/statfacts/html/prost.html (Accessed on July 24, 2019)
3. Droz JP, Albrand G, Gillessen S, Hughes S, Mottet N, Oudard S, et al. Management of prostate cancer in elderly patients: recommendations of a task force of the international society of geriatric oncology. Eur Urol 2017;72:521-31.
4. Grummet JP, Plass K, N'Dow J. Prostate cancer management in an ageing Population. Eur Urol 2017;72:532–33.
5. Boyle HJ, Alibhai S, Decoster L, Efstathiou E, Fizazi K, Mottet N, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. Eur J Cancer 2019;116:116-36.
6. Ferrell BR, Temel JS, Temin S, Smith TJ. Integration of palliative care into standard oncology care: ASCO clinical practice guideline update summary. J Oncol Pract 2017;13:119–21.
7. Loblaw DA, Virgo KS, Nam R, Somerfield MR, Ben-Josef E, Mendelson DS, et al; American Society of Clinical Oncology. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007;25:1596–605.
8. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314–25.
9. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080–7.
10. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al; LATITUDE Investigators. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017;377:352–60.
11. Landre T, Guetz GD, Chouahnia K, Fossey-Diaz V, Taleb C, Culine S. Is there a benefit of addition docetaxel, abiraterone, celecoxib, or zoledronic acid in initial treatments for patients older than 70 years with hormone-sensitive advanced prostate cancer? A meta-analysis. Clin Genitourin Cancer 2019;17:e806–13.
12. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408–18.
13. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465–74.
14. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al; ARAMIS Investigators. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med 2019;380:1235–46.
15. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–5.
16. Oudard S, Fizazi K, Sengeløv L, Daugaard G, Saad F, Hansen S, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III Trial-FIRSTANA. J Clin Oncol 2017;35:3189–97.
17. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al; COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.
18. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152–60.
19. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
20. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.