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# Time to Castration Resistance as a Predictor of Response to Docetaxel in Metastatic Castration Resistance in Prostate Cancer

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## ABSTRACT

**Introduction:** For metastatic prostate cancer (PC), androgen deprivation therapy (ADT) is the primary treatment option. Most patients develop resistance, after an initial response to treatment. This study aimed to evaluate real-life data of first-line docetaxel treatment for metastatic castration-resistant prostate cancer (mCRPC) and analyzed whether the response time to ADT could predict the response to docetaxel treatment.

**Methods:** The study included 111 patients with mCRPC who were treated with docetaxel. Time to castration resistance (TTCR) was defined as the time from initiation to the failure of primary ADT. Patients were divided into two groups based on TTCR. Patients with TTCR ≤12 months were assigned to group 1, while patients with TTCR >12 months were assigned to group 2.

**Results:** The median overall survival (OS) of the patients in group 1 was 16 months, whereas the median OS in group 2 was 38 months. Group 2 had a statistically significantly longer OS than group 1 ($p<0.001$). The median progression-free survival (PFS) of the patients in group 2 was 14 months while the median PFS in group 1 was 7 months. Group 2 had a statistically significantly longer PFS than group 1 ($p<0.001$). TTCR, Gleason score, and liver metastasis parameters were found to be predictive factors for OS.

**Conclusion:** In patients with mCRPC, TTCR was found to be a predictor of OS and PFS who were treated with docetaxel.

**Keywords:** Prostate cancer, androgen deprivation therapy, docetaxel, metastatic castration-resistant prostate cancer

## Introduction

Prostate cancer (PC) is the second most common malignancy in men worldwide (1). The growth and proliferation of tumor cells are androgen-dependent. Therefore, for metastatic PC, androgen deprivation therapy (ADT) is the treatment of choice. Most patients develop resistance, after the initial response to ADT, and are termed castration-resistant prostate cancer (CRPC) at this stage. Previously, docetaxel was the primary treatment option at this stage (2). Recently, there have been many advancements in treatment options, and novel agents (radium-223, sipuleucel-T, abiraterone acetate, and enzalutamide) with various mechanisms of action prolong overall survival (OS) (3-6). Therefore, we should choose between taxane-based chemotherapy and new agents targeting the androgen receptor axis as first-line therapy for patients with metastatic CRPC (mCRPC). Cytotoxic chemotherapy still is central to patients with a visceral metastasis. There is a need for additional predictive markers to distinguish patients who may benefit from docetaxel treatment and to avoid unnecessary adverse effects and costs. Studies have shown that the time to castration resistance (TTCR) may be a predictive factor to use androgen receptor axis targeted agents for treatment choice (7,8). This study purposed to evaluate real-life data of docetaxel treatment and analyze whether TTCR could predict the response to docetaxel treatment in the mCRPC stage.

## Methods

Patients with a diagnosis of mCRPC who were treated with docetaxel between August 2014 and 2021 were retrospectively analyzed. All patients had a pathologically confirmed diagnosis of PC and castrated testosterone level. CRPC was defined as radiological or biochemical progression of castrated testosterone levels with ADT. Biochemical progression was defined as a 50% increase in two of three sequential prostate-specific

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antigen (PSA) measurements obtained at 1-week intervals, provided the PSA value was >2 ng/mL. The files of 126 patients in the mCRPC stage who received first-line docetaxel therapy were analyzed. Six patients were excluded from the study due to the use of abiraterone acetate or enzalutamide during the castration-sensitive period, and nine patients had missing data. One hundred and eleven patients were included in the study. Docetaxel treatment with 5 mg oral prednisolone twice a day was administered 75 mg/m² every 3 weeks for eight cycles in the form of an 1-hour infusion at a standard dose. Biochemical tests were performed and patients with PSA progression were evaluated for radiological response by thorax, abdomen, pelvis-computed tomography and 99mTc-methylenediphosphonate bone scintigraphy or prostate-specific membrane antigen positron emission tomography/computed tomography. Radiologic evaluation was performed after the third course of docetaxel in patients without biochemical progression. Follow-up data, including time to biochemical progression and date of exitus, were available for all patients. TTCR was calculated from the initiation of ADT to the confirmation of CRPC, regardless of the stage. Data of patients were collected by a retrospective review of medical records. Age, stage, Gleason score, previous treatments, metastatic sites, Eastern Cooperative Oncology Group (ECOG), PSA value, and TTCR data were obtained. Patients diagnosed with castration-sensitive metastatic PC, non-metastatic PC and received abiraterone acetate and enzalutamide before docetaxel treatment were excluded from the study.

The study was approved by the Institutional Ethical Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2021-17-15, date: 06.09.2021).

### Statistical Analysis

Progression-free survival (PFS) was defined as the length of time from initiating treatment with docetaxel in a castration-resistant setting to the date of disease progression or death. OS was defined as the length of time from the first diagnosis of mCRPC to the date of death. Exitus from PC and disease progression are acceptable events. Continuous variables were expressed as median and range (interquartile range: Quartile 1-Quartile 3). OS and PFS were calculated using the Kaplan-Meier method. To assess the difference in survival functions among subgroups, the two-sided log-rank test was used. When performing a multivariable analysis (Backward stepwise LR method), the Cox proportional hazards regression model was used, which only included factors that showed statistical significance in the univariable analysis. After calculating a variance inflation factor <5 for factors included in the multivariable analysis, the multicollinearity was also evaluated. PFS and OS were presented as median values with a 95% confidence interval (CI). The level of statistical significance was set at p=0.05. Clinical data were analyzed using IBM SPSS version 23.0 (SPSS Inc, Chicago, IL, USA).

## Results

### Patient Characteristics

The files of 111 patients who received docetaxel treatment for the diagnosis of mCRPC were analyzed. The median patient age was 60.7 (range: 40-88). Sixty-five (59%) patients had an ECOG performance score of 0 and forty-six (41%) patients had an ECOG score of 1-2. Forty-seven (42.3%) patients had a Gleason score of 6 or lower, twenty-two (19.8%) patients had a Gleason score of 7, forty-two (37.8%) patients had a Gleason score of 8 or higher. Fifty-two (47%) patients were admitted for locally advanced disease, while fifty-nine (53%) patients were admitted for metastatic disease. The median PSA at diagnosis and before docetaxel treatment were 16.5 ng/dL, 72.2 ng/dL, respectively. The clinicopathological and demographic characteristics of the patients are presented in Table 1.

### Survival Analysis

The median OS and PFS of the patients included in the study were 26.5 months [(95% CI; 19.6-33.4 months) and 11.5 months (95% CI, 9.5-13.5 months)], respectively. Patients treated with docetaxel were assigned to two groups based on TTCR. Patients with TTCR ≤12 months were assigned to group 1, while patients with TTCR >12 months were assigned to group 2.

In group 1, the median OS of the patients was 38 months, while in group 2 was 16 months, with a statistically significant difference (p<0.001). TTCR less than 12 months was found to be a predictive factor for a short survival time. The OS Kaplan-Meier plot for TTCR status is presented in Figure 1a. In group 2, the median PFS of the patients was 14 months (range, 11.1-16.9), while in group 1 was 7 months (range: 6.2-7.8). Group 2 had a statistically significantly longer PFS than group 1 (p<0.001). The PFS Kaplan-Meier plot for TTCR status is presented in Figure 1b. A TTCR value of less than 12 months was found to be a risk factor for short PFS in patients with mCRPC.

Clinical parameters considered having an effect on OS were analyzed using univariate Cox regression and the results of multivariate Cox regression analysis for the statistically significant variables are shown in Table 2.

TTCR, Gleason score, liver metastasis and high-volume parameters were found to have statistically significant effects (predictor of survival) on survival (p<0.05 in univariate analysis) (Figure 2a, b).

The results of the multivariate Cox regression analysis showed that TTCR, Gleason score and liver metastasis variables had a statistically significant effect on OS (p<0.05) (Table 2).

Clinical parameters considered having an effect on PFS were analyzed and the results of multivariate Cox regression analysis for the statistically significant variables are shown in Table 3. TTCR, visceral metastasis, and high volume were found to be significant predictors of survival independently of PFS (p<0.05 in univariate analysis). The results of the multivariate Cox regression analysis showed that visceral metastasis, TTCR and high-volume variables had statistically significant effects on PFS (p<0.05) (Table 3).

Twenty-three of the patients who progressed after docetaxel treatment were unable to continue treatment because of poor performance status or death. Fifty patients received abiraterone acetate, 29 patients received enzalutamide and 9 patients received cabazitaxel; in the second-line

**Table 1. Clinical and pathological characteristics of patients with duration castration resistance**

| | TTCR <12 months | | TTCR >12 months | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Age median** | 66 | - | 66.5 | - | - |
| <65 | 19 | 44.2 | 25 | 36.8 | 0.436 |
| >65 | 24 | 55.8 | 43 | 63.2 | - |
| **Gleason score** | | | | | |
| <6 | 16 | 37.2 | 31 | 45.6 | **0.046** |
| 7 | 5 | 11.6 | 17 | 25 | - |
| >8 | 22 | 51.2 | 20 | 29.4 | - |
| **PSA on diagnosis** | | | | | |
| Below the median PSA | 24 | 55.8 | 32 | 47.1 | 0.369 |
| Above the median PSA | 19 | 44.2 | 36 | 52.9 | - |
| **PSA before docetaxel treatment** | | | | | |
| Below the median PSA | 13 | 30.2 | 42 | 61.8 | **<0.001** |
| Above the median PSA | 30 | 69.8 | 26 | 38.2 | - |
| **Metastasis at initial diagnosis** | | | | | |
| No | 18 | 41.9 | 34 | 50 | 0.402 |
| Yes | 25 | 58.1 | 34 | 50 | - |
| **Local treatment** | | | | | |
| No treatment | 23 | 53.5 | 29 | 42.6 | 0.329 |
| Radiotherapy | 11 | 25.6 | 16 | 23.5 | - |
| Surgery | 9 | 20.9 | 23 | 33.8 | - |
| **ECOG** | | | | | |
| 0 | 23 | 53.5 | 42 | 61.8 | 0.389 |
| 1-2 | 20 | 46.5 | 26 | 38.2 | - |
| Visceral metastasis | 28 | 65.1 | 15 | 22.1 | **<0.001** |
| Liver metastasis | 15 | 34.9 | 4 | 5.9 | **<0.001** |
| High volume | 36 | 83.7 | 21 | 30.9 | **<0.001** |
| Lung metastasis | 5 | 11.6 | 7 | 10.3 | 0.826 |
| Bone metastasis | 41 | 95.3 | 66 | 97.1 | 0.638 |

P-value was obtained from Exact or Pearson chi-square test. TTCR: Time to castration resistance, PSA: Prostate-specific antigen, ECOG: Eastern Cooperative Oncology Group

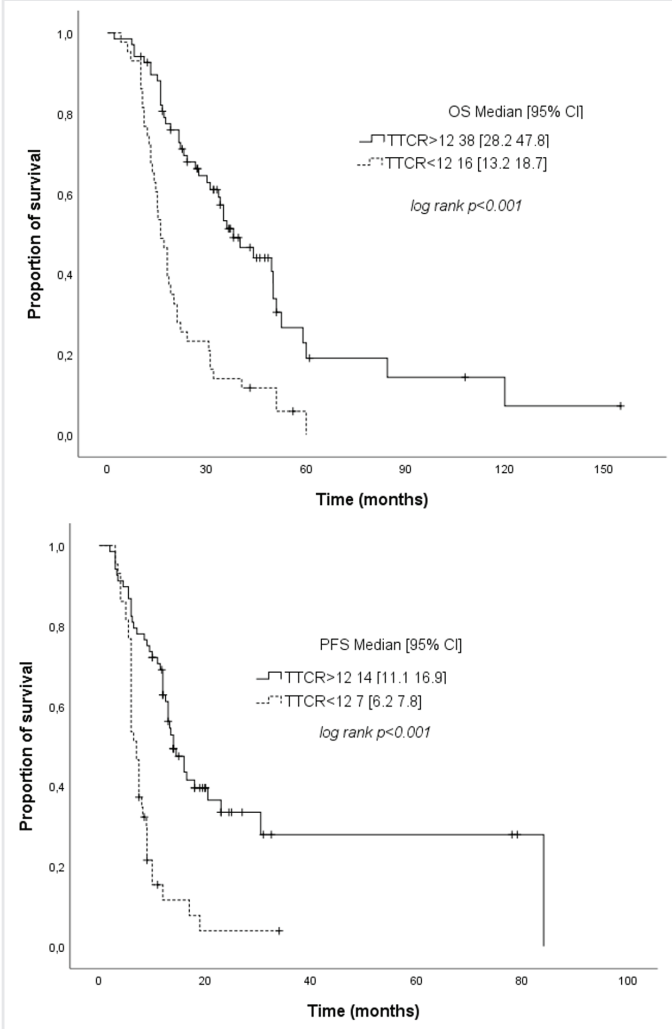


**Figure 1.** (**a**) Overall survival according to the time to castration resistance duration (over or under 12 months) (hazard ratio: 0.35). (**b**) Progression-free survival to the time to castration resistance duration (over or under 12 months) (hazard ratio: 0.30)
TTCR: Time to castration resistance, CI: Confidence interval, OS: Overall survival, PFS: Progression-free survival

treatment after docetaxel. The most common side effects related to docetaxel treatment; fatigue (n=24), diarrhea (n=13) and stomatitis (n=11) were observed. The incidence of grade 3 and 4 neutropenia was relatively low (n=8), and febrile neutropenia was rare (n=1). Side effects were managed with dose modification and no patients discontinued treatment.

## Discussion

This study aimed to evaluate the relationship between survival and TTCR in patients who developed castration following ADT and were treated with first-line docetaxel in the mCRPC stage. The study results showed that patients with a response time shorter than 12 months to ADT before docetaxel had a poor response to chemotherapy. Moreover, this patient group had shorter OS and PFS compared to the other patient group. Furthermore, the multivariate analyses showed that it was a significant predictive factor of both OS and PFS. Prolonged TTCR can be considered a predictive factor to identify patients who may benefit from docetaxel in the castration resistance stage. A shorter TTCR is associated with shorter doubling time, a poor prognostic parameter, and a faster cell cycle. The cell cycle is fundamentally important in cancer treatment since many chemotherapy drugs only act on actively proliferating cells. Docetaxel stabilizes microtubules and prevents their depolymerization. This mechanism of action, is considered more effective in malignancies with a rapid cell cycle. There are a few studies in the literature evaluating the relationship between TTCR and the response to docetaxel treatment in PC. In this regard, the study of Bournakis et al. (7) including docetaxel and non-docetaxel regimens showed that TTCR <2 years for PFS and OS was an independent prognostic factor. Similar to that study, this study showed that shorter TTCR was linked with shorter OS and PFS. Especially, patients with TTCR <12 months showed a poorer prognosis in our study.

Docetaxel has been included for treating CRPC based on the results of two large, randomized studies (2,9). These studies showed that

**Table 2. Prognostic factors for overall survival**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| **Variables** | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** |
| **Age** | | | | |
| <65 years old | 1 | 0.089 | - | - |
| ≥65 years old | 1.48 (0.94-2.33) | | | |
| **TTCR** | | | | |
| <12 months | 1 | **<0.001** | 1 | **0.003** |
| >12 months | 0.35 (0.22-0.55) | | 0.42 (0.24-0.73) | |
| **Gleason score** | | | | |
| ≤6 | 1 | **0.023** | 1 | - |
| 7 | 1.06 (1.00-1.93) | **0.014** **0.048** | 1.59 (1.01-3.02) | - |
| ≥8 | 1.91 (1.17-3.11) | **0.048** **0.009** **0.004** | 2.13 (1.28-3.54) | - |
| **PSA (diagnosis)** | | | | |
| PSA < median | 1 | 0.360 | - | - |
| PSA > median | 0.81 (0.53-1.26) | | | |
| **PSA (before docetaxel treat)** | | | | |
| PSA < median | 1 | 0.277 | - | - |
| PSA > median | 1.27 (0.82-1.97) | | | |
| **Metastatic on initial diagnosis** | | | | |
| Non-metastatic | 1 | 0.479 | - | - |
| Metastatic | 0.86 (0.56-1.32) | | | |
| **Local treatment** | | | | |
| (Ref: No treatment) | 1 | 0.369 | - | - |
| Radiotherapy | 1.02 (0.60-1.74) | | | |
| Surgery | 0.184 (0.85-2.37) | | | |
| **ECOG** | | | | |
| (ref: 0) | 1 | 0.647 | - | - |
| 1-2 | 1.11 (0.71-1.72) | | | |
| **Visceral metastasis** | | | | |
| No | 1 | 0.195 | - | - |
| Yes | 1.33 (0.86-2.06) | | | |
| **Liver metastasis** | | | | |
| No | 1 | **0.004** | 1 | - |
| Yes | 2.19 (1.29-3.72) | **0.037** | 1.85 (1.04-3.31) | |
| **High volume** | | | | |
| No | 1 | **0.002** | - | - |
| Yes | 2.01 (1.29-3.14) | | | |
| **Lung metastasis** | | | | |
| No | 1 | 0.265 | - | - |
| Yes | 0.66 (0.32-1.37) | | | |
| **Bone metastasis** | | | | |
| No | 1 | 0.761 | - | - |
| Yes | 1.20 (0.38-3.81) | | | |

HR: Hazard ratio, CI: Confidence interval, TTCR: Time to castration resistance, PSA: Prostate-specific antigen, ECOG: Eastern Cooperative Oncology Group

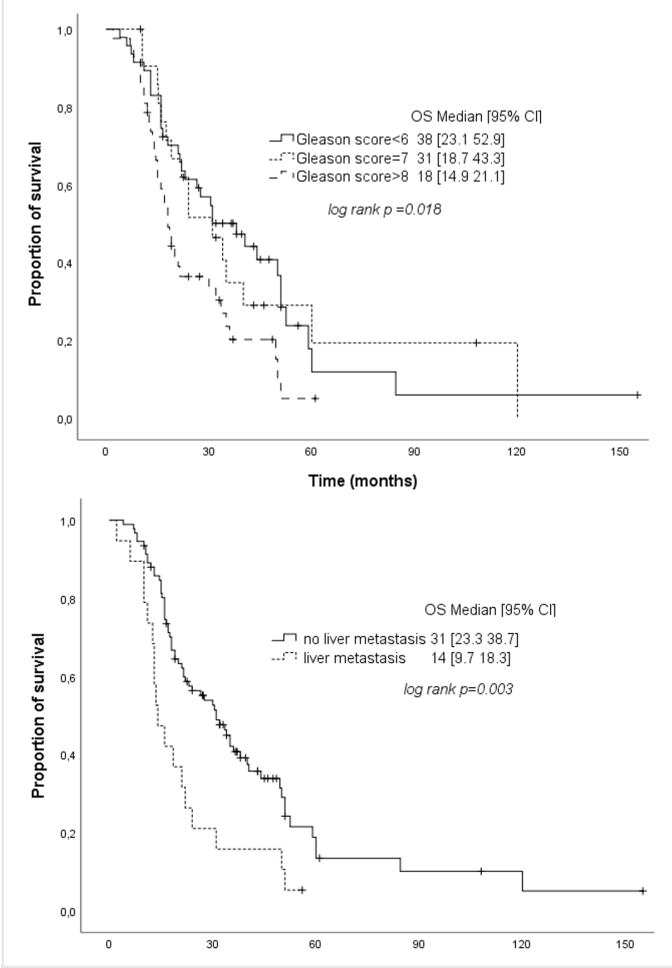


**Figure 2.** (**a**) Overall survival according to the Gleason score (hazard ratio: 1.59-2.13), (**b**) overall survival according to the liver metastasis (hazard ratio: 1.85)
CI: Confidence interval, OS: Overall survival, PFS: Progression-free survival

docetaxel treatment improved the quality of life of the patients as well as prolonged the OS time. It is important to initiate the right patient on the treatment at the right time since PC is seen in a relatively older population compared to other types of cancer and chemotherapy-related side effects cause more morbidity and mortality. To simplify these clinical decisions, a nomogram was created using independent prognostic factors in the TAX 327 studies. These prognostic factors include the Karnofsky performance status, pre-treatment PSA doubling time, baseline alkaline phosphatase, presence of liver metastases, number of metastatic sites, tumor grade baseline PSA, clinically significant pain, and baseline hemoglobin level (10). Additionally, the secondary analysis study of TAX 327 defined four independent risk factors to predict PSA decline and OS in patients with mCRPC and developed risk groups. These independent risk factors were defined as pain, visceral metastases, anemia, and progression of bone lesions (11). This study found that patients with liver metastases and patients with high-volume tumor burden had a faster disease progression and shorter OS. It was also observed that liver metastasis and high-volume tumor burden were significantly higher in the group with shorter TTCR (less than 12 months) compared to the group with longer TTCR.

**Table 3. Prognostic factors for PFS**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| **Variables** | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** |
| **Age** | | | | |
| <65 years old | 1 | 0.413 | - | - |
| ≥65 years old | 1.21 (0.77-1.92) | | | |
| **TTCR** | | | | |
| <12 months | 1 | **<0.001** | 1 | **0.007** |
| >12 months | 0.30 (0.19-0.48) | | 0.44 (0.24-0.80) | |
| **Gleason score** | | | | |
| ≤6 | 1 | 0.062 | - | - |
| 7 | 0.78 (0.41-1.48) | | | |
| ≥8 | 1.55 (0.95-2.52) | | | |
| **PSA (diagnosis)** | | | | |
| <Median | 1 | 0.504 | - | - |
| >Median | 0.86 (0.55-1.34) | | | |
| **PSA (before docetaxel treatment)** | | | | |
| <Median | 1 | 0.356 | - | - |
| >Median | 1.23 (0.78-1.92) | | | |
| **Metastatic on initial diagnosis** | | | | |
| Non-metastatic | 1 | 0.531 | - | - |
| Metastatic | 1.15 (0.74-1.80) | | | |
| **Local treatment** | | | | |
| No treatment | 1 | 0.680 | - | - |
| Radiotherapy | 0.79 (0.45-1.40) | | | |
| Surgery | 1.02 (0.61-1.71) | | | |
| **ECOG** | | | | |
| 0 | 1 | 0.217 | - | - |
| 1-2 | 1.33 (0.85-2.08) | | | |
| **Visceral metastasis** | | | | |
| No | 1 | **0.044** | 1 | **0.003** |
| Yes | 1.58 (1.01-2.47) | | 2.71 (1.39 5.29) | |
| **Liver metastasis** | | | | |
| No | 1 | 0.061 | - | - |
| Yes | 1.73 (0.99-3.01) | | | |
| **High volume** | | | | |
| No | 1 | **<0.001** | 1 | **0.001** |
| Yes | 2.59 (1.64-4.11) | | 3.98 (1.77 8.95) | |
| **Lung metastasis** | | | | |
| No | 1 | 0.404 | - | - |
| Yes | 0.73 (0.35-1.53) | | | |
| **Bone metastasis** | | | | |
| No | 1 | 0.597 | - | - |
| Yes | 0.76 (0.28-2.09) | | | |

PFS: Progression-free survival, CI: Confidence interval, TTCR: Time to castration resistance, PSA: Prostate-specific antigen, ECOG: Eastern Cooperative Oncology Group,

A retrospective study including 437 metastatic PC patients showed a relationship between the Gleason score and TTCR and OS (12). Our study also showed an inverse relationship between the Gleason score and TTCR and OS. It was found that patients' life expectancy and TTCR were shorter as their Gleason score increased. This result caused a statistically significant difference in patients who were assigned to two groups based on TTCR.

The approval of abiraterone and enzalutamide has increased the need to determine patients who may benefit more from chemotherapy for treating PC. The parameters that could predict the response to docetaxel treatment, which were analyzed in this study, were also investigated in some secondary hormone therapy studies. It has been shown that; short response time to previous ADT (<16 months) and patients with a high Gleason score at diagnosis, do not respond well to abiraterone and enzalutamide treatment (13,14). The study of Loriot et al. (14) evaluated the median response time to ADT in patients treated with ARATA. This study showed that patients with a longer initial ADT response responded better to secondary hormone therapies, and the ADT cut-off time was deemed 12 months (14). Bellmunt et al. (15) analyzed patients included in the COU-AA-301 and COU-AA-302 studies and demonstrated the positive effects of longer exposure to ADT on survival.

PC is more common in the geriatric population, which may have additional comorbidities. It is important to determine the appropriate treatment option to avoid undesired adverse effects in this patient group. For this reason, this study showed that TTCR could predict the response of mCRPC to docetaxel treatment.

### Study Limitations

The limitations of this study are the small sample size, its retrospective design and the absence of patients receiving abiraterone, enzalutamide, and docetaxel treatments in the castration-sensitive stage.

## Conclusion

This study demonstrated that TTCR could be a prognostic and predictive factor for the survival time of patients with mCRPC who were candidates for docetaxel therapy. For patients who show early progression in TTCR <12 months, close follow-up is needed. There is a need for prospective, randomized studies with longer follow-up periods and more patients to more effectively demonstrate the effect of TTCR on the survival of patients with mCRPC.

**Ethics Committee Approval:** The study was approved by the Institutional Ethical Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2021-17-15, date: 06.09.2021).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Srugical and Medical Practices: İ.G., G.Ş.E., M.Y., S.Y.T., A.Ö., D.T.; Concept: İ.G., M.Y., D.T.; Design: İ.G., M.Y., A.Ö., D.T.; Data Collection or Processing: İ.G., G.Ş.E., G.B.S., S.Y.T., D.T.Ö., Ö.D., İ.Ç.; Analysis or Interpretation: İ.G., M.Y., D.T.; Literature Search: İ.G., S.Y.T., A.Ö.; Writing: İ.G., G.B.S.

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