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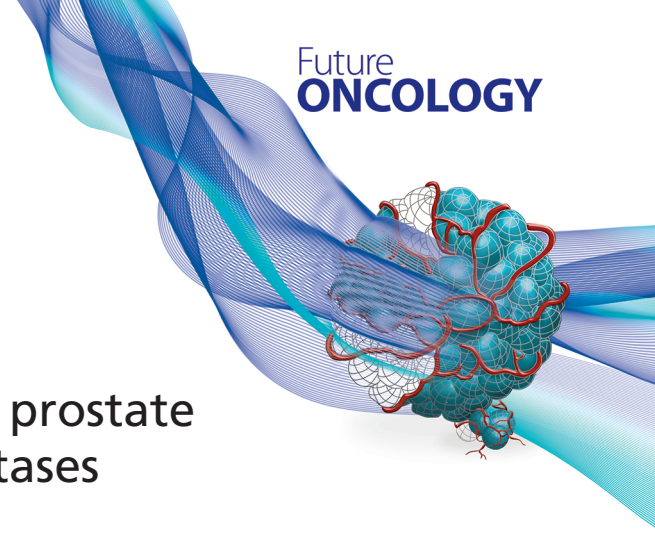

# Efficacy and tolerability of current treatments for hormone-refractory prostate cancer patients with visceral metastases

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**Aim:** To assess the efficacy and tolerability of the first-line treatment options for hormone-refractory prostate cancer patients with visceral metastases. **Materials & methods:** The records of 191 patients diagnosed with hormone-refractory prostate cancer with visceral metastases were analyzed retrospectively. **Results:** Docetaxel was administered to 61.2% (n = 117), abiraterone to 14.2% (n = 27) and enzalutamide to 9.4% (n = 18) as the first-line treatment. The median survival of the patients receiving docetaxel, abiraterone and enzalutamide as the first-line treatment during the hormone-refractory period was 15 (95% CI: 12.9–17) months, 6 (95% CI: 1.8–10.1) months and 11 (95% CI: 0.9–23.1) months (p = 0.038), respectively. **Conclusion:** The present study established a statistically significant difference in favor of docetaxel in terms of overall survival and progression-free survival.

**Lay abstract:** The optimal therapeutic option for castration-resistant prostate cancer (CRPC) patients with visceral metastases is unknown. We assessed the efficacy and tolerability of the first-line treatment options for CRPC patients with visceral metastasis. One hundred ninety-one patients diagnosed with CRPC with visceral metastases were included in the study. The present study established a statistically significant difference in favor of docetaxel in terms of overall survival and progression-free survival between first-line docetaxel, abiraterone and enzalutamide treatments in CRPC patients with visceral metastases. For patients who cannot undergo chemotherapy, enzalutamide, among novel androgen pathway inhibitors, may be the most appropriate option, given its numerical, although statistically insignificant, difference in overall survival and its fewer side effects compared with abiraterone.

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**Keywords:** hormone-refractory disease • prostate cancer • visceral metastasis

Visceral metastatic disease occurs in 16–18% of patients with hormone-refractory prostate cancer and is associated with poor prognosis; its occurrence is more likely with disease progression and in advanced stages [1–3]. Epidemiological studies have identified an increased incidence of visceral disease in prostate cancers in recent years. It is

believed that patient survival has been prolonged by the introduction of new therapeutic options into the treatment algorithm for prostate cancer, resulting in a higher incidence of visceral metastases [4].

Previous studies have identified the metastatic site as a significant predictor of survival in patients with metastatic castration-resistant prostate cancer (mCRPC) [2,3,5]. A meta-analysis by Halabi *et al.* evaluating five Phase III studies reported that the median overall survival (OS) was 20 months in mCRPC patients with only bone metastasis, compared with 17 and 12 months for those with lung and liver metastasis, respectively [2].

Approved options for the first-line treatment of mCRPC patients include docetaxel (a chemotherapeutic antimicrotubule agent) and novel hormone therapy agents (enzalutamide and abiraterone) [6,7], although the optimal therapeutic option for CRPC patients with visceral metastases is still unknown. There is a tendency to administer a more aggressive treatment through chemotherapy to patients with visceral metastases in prostate cancer, as is the case with several other types of cancer [8]. Pezaro *et al.* reported visceral metastases to be associated with poor prognosis but not as a predictor of treatment response [9]. Retrospective analyses of recent Phase III randomized clinical trials have indicated that novel hormone therapies may also be a therapeutic option for patients with visceral metastases [1,10–12].

Abiraterone and enzalutamide both target the androgen receptor signaling pathway [13,14]. Abiraterone is an irreversible inhibitor of CYP17 and has been found to improve overall survival in both pre- and post-docetaxel settings [13,15]. Enzalutamide, on the other hand, is a second-generation androgen receptor antagonist that, like abiraterone, has been approved for use in mCRPC treatment in post- and pre-docetaxel settings based on the results of Affirm and Prevail trials, respectively [16,17].

There have been several studies to date broadly evaluating the prognostic significance of various metastatic sites in mCRPC [2,5,18] but only a limited number of studies focusing on the treatment of visceral metastatic disease, which is a disease group with poor prognosis. Clinical trials have usually assessed the efficacy of therapeutic agents in the visceral disease group through subgroup analysis results, although these studies have included a very low number of patients due to the rare occurrence of visceral disease [3,5,19].

The aim in the present study is to present real-life data on first-line treatments in prostate cancer patients with hormone-refractory visceral metastases.

## Materials & methods

### Study design & inclusion criteria

The records of patients diagnosed with hormone-refractory prostate cancer with visceral metastases, who were under follow-up or treatment at 12 medical oncology centers in Turkey between 2010 and 2020, were analyzed retrospectively. The study sample included 191 patients with a histopathological diagnosis of prostate adenocarcinoma who had visceral metastases when diagnosed with hormone-refractory disease. The study included those who were medically unfit, ineligible for chemotherapy and had rejected chemotherapy. Patients who received docetaxel and abiraterone in the castration-sensitive period were excluded from the study because docetaxel and/or novel antihormone therapy (abiraterone and enzalutamide) during this period may affect the treatment of subsequently developing mCRPC and the associated outcomes. Studies of prostate cancer with visceral metastases usually group lymph node metastases under the category of soft tissue metastases. However, patients with lymph node metastases have much better survival outcomes than those with bone metastases, and so the present study included only patients with solid organ metastases [19,20].

Castration-resistant disease in prostate cancer was defined as the occurrence of progression, despite castrate testosterone levels (<50 ng/dl).

Patient data for age, performance status, comorbidities, histopathological characteristics (Gleason score), basal prostate-specific antigen (PSA) values, visceral metastases sites, time of visceral metastases, treatment details and toxicities were collected from medical records. Metastatic disease was determined from radiological findings. Imaging was performed using bone scintigraphy, computed tomography (CT) and magnetic resonance imaging or PSMA/PET (Gallium prostate-specific membrane antigen positron emission tomography). A radiological assessment of treatment responses was made in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), and were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Side effects were assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), 4th edition. Patient performance was determined based on the Eastern Cooperative Oncology Group (ECOG) performance status (PS) criteria.

### Treatments

The study included 191 patients with visceral metastases in the hormone-refractory period, and the efficacy and tolerability of their first-line treatment options (docetaxel, abiraterone and enzalutamide) were assessed. Treatment regimens were abiraterone 1000 mg/day and prednisone 5 mg 2 × 1/day (for cycles of 28 days), enzalutamide 160 mg/day (for cycles of 28 days) and docetaxel 75 mg/m$^2$/day (once every 21 days) or 35 mg/m$^2$/day (once every week) and 5 mg prednisone 2 × 1/day. All treatments were continued until any sign of progressive disease, severe toxicity or death. Treatment response was defined based on clinical, biochemical and radiological progressive disease once in every three cycles according to the Prostate Cancer Clinical Trials Working Group criteria [20].

### Definitions

Progression-free survival (PFS) was defined as the period from the beginning of treatment until documented progression or death. OS was defined as the period from the first day of treatment until the date of last follow-up or death. Objective response rate (ORR) was defined as the sum of PR and complete response (CR). Clinical benefit rate (CBR) was defined as the sum of PR, CR, SD maintained for at least 3 months.

### Statistical analysis

The SPSS 18.0 software package was used for the statistical analysis. The baseline characteristics of the patient subgroups were compared, and the differences between the subgroups were assessed with a log-rank test. The Kaplan–Meier method was used for survival analysis. A univariate analysis with independent variables was carried out, employing a *t*-test, chi-square test and Fisher's exact test. A total of nine clinical variables were identified based on previous clinical trials, and included primary treatment option (docetaxel/AA/enzalutamide), age (<75, ≥75), Gleason score (<8, ≥8), duration of ADT (androgen deprivation therapy) (<10 months, ≥10 months), ECOG PS (0–1, ≥2), baseline PSA (prostate-specific antigen) (<200, ≥200), localization of visceral metastases (liver and nonliver), presence of comorbidities and the status of second-line treatment (yes/no). A multivariate analysis was carried out using the Cox model. The parameters that were identified as prognostic factors for mCRPC with visceral metastasis in the univariate analysis were included in the Cox model. A p-value $< 0.05$ was considered significant.

## Results

Involved in the study were 191 patients identified with visceral metastases when diagnosed with hormone-refractory disease. The basal characteristics of the patients are presented in Table 1. Patients had a median follow-up of 11.3 (1–56) months and a median age of 71 (44–90) years. Among the patients, 47.6% (n = 91) had comorbidities. The Gleason score was <8 in 23.5% (n = 45) and ≥8 in 76.5% (n = 146) of the patients, and the performance status was ≥2 in 33% (n = 63) of the patients.

At the time of diagnosis of prostate cancer, 58.6% (n = 112) had metastatic disease, while 19.4% (n = 37) had visceral metastatic disease. The median interval between diagnosis and the occurrence of hormone-refractory disease was 16 (2–147) months, with a mean interval of 28.4 (2–147) months. The median interval between the diagnosis of cancer and the occurrence of visceral metastasis was 13 (0–147) months. The mean duration of androgen deprivation therapy until the occurrence of hormone-refractory disease was 23.8 (2–107) months. The median PSA was 100 ug/dl (0.80–4695).

A classification of the patients with liver metastases and those with nonliver visceral organ metastases revealed 44% (n = 84) of the patients to have liver metastases. Among those with nonliver metastases, 38.8% (n = 74) had lung metastasis, 5.8% (n = 11) had bone metastasis, 4.7% (n = 9) had brain metastasis, 3.6% (n = 7) had adrenal metastasis and 3.1% (n = 6) had metastases to other organs.

Among the mCRPC patients with visceral metastases, docetaxel was administered to 61.2% (n = 117), abiraterone to 14.2% (n = 27) and enzalutamide to 9.4% (n = 18) as the first-line treatment. Due to treatment rejection, performance decrease and comorbidities, 15.2% (n = 29) of the patients were followed-up with only hormone therapy and supportive care. The docetaxel patients underwent a mean 7 (1–24) treatment cycles. The mean duration of treatment was 5.5 (1–33) months for abiraterone and 6.5 (1–20) months for enzalutamide.

Differences were noted in the age, comorbidities and performance status of the treatment groups. When the patient groups receiving docetaxel and novel androgen pathway inhibitors (enzalutamide and abiraterone) were compared, the docetaxel patients were found to be younger and recorded better performances ($p < 0.05$). When the enzalutamide and abiraterone groups were compared, there was no statistically significant difference in age or performance status ($p > 0.05$). The mean age was 67 (44–80) years in the docetaxel group, 77 (61–87) years in

**Table 1. Baseline Characteristics of Patients.**

| Characteristic | Patients, n (%), (n = 191) | Docetaxel, n (%), (n = 117) | Abiraterone, n (%), (n = 27) | Enzalutamide, n (%), (n = 18) | p-value |
|---|---|---|---|---|---|
| **Age, (years)** | | | | | |
| – Median (range) | 71 (44–90) | 67 (44–80) | 77 (61–87) | 75 (53–90) | <0.05 |
| – ≥75 (%) | 27.7 (53) | 18 (21) | 74 (20) | 66.6 (12) | |
| **ECOG PS** | | | | | |
| – 0–1 | 67 (128) | | | | <0.05 |
| – ≥2 | 33 (63) | 17.9 (21) | 59.3 (16) | 55.5 (10) | |
| **Gleason score at initial diagnosis** | | | | | |
| – <8 | 23.5 (45) | 27.3 (32) | 14.8 (4) | 22.2 (4) | 0.78 |
| – ≥8 | 76.5 (146) | 72.7 (85) | 85.2 (23) | 77.8 (14) | |
| Metastatic disease rate at initial diagnosis | 58.6 (112) | | | | |
| Visceral disease rate at initial diagnosis | 19.4 (37) | | | | |
| **Metastasis localization** | | | | | |
| – Liver | 44 (84) | 41.9 (49) | 48.1 (13) | 50 (9) | 0.71 |
| – The other sites | 56 (107) | 58.1 (68) | 51.9 (14) | 50 (9) | |
| – Lung | 38.8 (74) | | | | |
| – Brain | 4.7 (9) | | | | |
| – Adrenal | 3.6 (7) | | | | |
| – Bone marrow | 5.8 (11) | | | | |
| – The others | 3.1 (6) | | | | |
| Mean ADT time (range, months) | 23.8 (2–107) | 22.6 (2–107) | 27.9 (4–88) | 24.9 (3–100) | 0.2 |
| Median PSA (range, ug/l) | 100 (0.8–4694) | | | | |
| **Comorbidities** | | | | | |
| – Yes | 47.6 (91) | 42.7 (50) | 59.3 (16) | 66.7 (12) | 0.075 |
| – No | 52.4 (100) | | | | |
| **First treatment options** | | | | | |
| – Abiraterone | 14.2 (27) | | | | |
| – Enzalutamide | 9.4 (18) | | | | |
| – Docetaxel | 61.2 (117) | | | | |
| – Best supportive care | 15.2 (29) | | | | |
| **Subsequent therapies** | | | | | |
| – Second line | 75.6 (74/162) | | | | |
| – Third line | 12.9 (21/162) | | | | |

ADT: Androgen deprivation therapy, ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: Prostate-specific antigen.

the abiraterone group and 75 (53–90) years in the enzalutamide group ($p < 0.05$). Among the patients receiving enzalutamide and abiraterone as a first-line treatment, the majority had low performance status and comorbidities. There was a history of comorbidities in 42.7% (n = 50), 59.3% (n = 16) and 66.7% (n = 12) of the patients in the docetaxel, abiraterone and enzalutamide treatment groups, respectively ($p = 0.075$). ECOG PS was ≥2 in 17.9% (n = 21) of the patients in the docetaxel group, 59.3% (n = 16) in the abiraterone group and 55.5% (n = 10) in the enzalutamide group (p: < 0.05).

The Gleason score was ≥8 in 72.7% (n = 85) of the patients in the docetaxel group, 85.2% (n = 23) in the abiraterone group and 77.8% (n = 14) in the enzalutamide group ($p = 0.78$).

There was liver metastasis in 41.9% (n = 49) and nonliver metastasis in 58.1% (n = 68) of the patients in the docetaxel group; liver metastasis in 48.1% (n = 13) and nonliver metastasis in 51.9% (n = 14) in the abiraterone group; and 50% (n = 9) had liver metastasis and 50% (n = 9) had nonliver metastasis in the enzalutamide group ($p = 0.71$). There was no statistically significant difference in the localization of the metastases of the different treatment groups.

The mean age was 22.6 (2–107) years in the docetaxel group, 27.9 (4–88) years in the abiraterone group and 24.9 (3–100) years in the enzalutamide group. No significant difference was found in the duration of ADT between the

Table 2. Outcomes in patients with visceral metastasis and by site.

| Outcomes (months) | Docetaxel | Abiraterone | Enzalutamide | p-value |
|---|---|---|---|---|
| All patients | | | | |
| – Median OS | 15 | 6 | 11 | 0.038 |
| – Median PFS | 8 | 4 | 3 | 0.001 |
| Liver metastases | | | | |
| – Median OS | 10 | 4 | NYR | 0.001 |
| Noniver metastases | | | | |
| – Median OS | 23 | 7 | 11 | 0.001 |

NYR: Not yet reached; OS: Overall survival; PFS: Progression-free survival.

groups (p = 0.22). Among the 162 treated patients, 75.6% (n = 74) received second-line treatment, whereas only 12.9% (n = 21) could receive third-line treatment.

In the entire patient sample, the median OS was 13 (95% Cl: 9.8–16.1) months and the median PFS was 6 (95% Cl: 4.5–7.4) months. In the patients who received first-line treatment with docetaxel, abiraterone and enzalutamide in the hormone-refractory period, the mean OS was 15 (95% CI: 12.9–17) months, 6 (95% Cl: 1.8–10.1) months and 11 (95% Cl: 0.9–23.1) months, respectively (p = 0.038). When all three treatment groups were compared, the median PFS with docetaxel, abiraterone and enzalutamide was 8 (95% CI: 5.8–10.1) months, 4 (95% Cl: 2.7–5.2) months and 3 (95% Cl: 0.5–5.5) months, respectively (p < 0.001). When compared with both abiraterone (hazard ratio [HR]: 0.41; 95% Cl: 0.24–0.69; p = 0.001) and enzalutamide (HR: 0.43; 95% Cl: 0.23–0.81; p = 0.009), docetaxel performed better in terms of progression-free survival. When enzalutamide and abiraterone were compared, there was no statistically significant difference in the risk of progression between the two groups (HR: 0.94; 95% Cl: 0.45–1.96; p = 0.86). When docetaxel and abiraterone were compared for OS, a survival advantage was noted in favor of docetaxel (HR: 0.52; 95% Cl: 0.30–0.89; p = 0.018). When docetaxel and enzalutamide were compared, there was no statistically significant difference in OS between the two groups (HR: 0.67; 95% Cl: 0.30–1.47; p = 0.32). A comparison of the novel agents enzalutamide and abiraterone revealed a numerical difference in OS in favor of enzalutamide, although the difference was not statistically significant (HR: 0.77; 95% Cl: 0.32–1.88; p = 0.58) (Figure 1).

Regarding the localization of metastases, the median OS for patients with liver metastases was 7 (95% CI: 5.1–8.8) months, compared with 15 (95% CI: 13.1–16.8) months (p = 0.001) for those with nonliver metastases (Figure 2). A survival analysis of the site of visceral metastases revealed the median OS to be 10 months (95% CI: 7.3–12.6) in patients with liver metastases compared with 23 months (95% CI: 13.9–32.0) in patients with nonliver metastases in the docetaxel group and 4 months (95% CI: 0.1–9.5) in patients with liver metastases compared with 7 months (95% CI: 0.1–19.3) in patients with nonliver metastases in the abiraterone group. The median OS could not be ascertained in patients with liver metastases in the enzalutamide group, whereas it was 11 months (95% CI: 0.26–21.7) in the patients with nonliver metastases (Figure 2). The median OS was shorter in patients with liver metastases than in those with nonliver metastases to a statistically significant degree (p = 0.001) (Table 2).

The nine clinical variables that were identified from previous clinical trials [primary treatment option (docetaxel/AA/Enza), age (<75, ≥75), Gleason score (<8, ≥8), duration of ADT (<10 months, ≥10 months), ECOG PS (0–1, ≥2), baseline PSA (<200, ≥200), localization of visceral metastasis (liver and non-liver), presence of comorbidities and the status of second-line treatment (yes/no) were examined with univariate and multivariate analyses. The results of the analyses are presented in Table 3 and 4.

The multivariate analysis identified the primary treatment option, Gleason score and performance status as independent prognostic factors for PFS. The most significant prognostic factors for OS, in turn, included the primary treatment option, Gleason score, performance status, visceral metastases localization and receipt of second-line treatment.

Grade 3–4 side effects that required dose reductions and/or chemotherapy delays were observed only in the docetaxel group of patients and were reported to be hematological toxicities, fatigue and neuropathy. Fatigue was the most commonly reported side effect for both AA and enzalutamide. The side effects specific to the androgen blockade inhibitors (mineralocorticoid-related side effects [hypertension, peripheral edema, electrolyte imbalance],

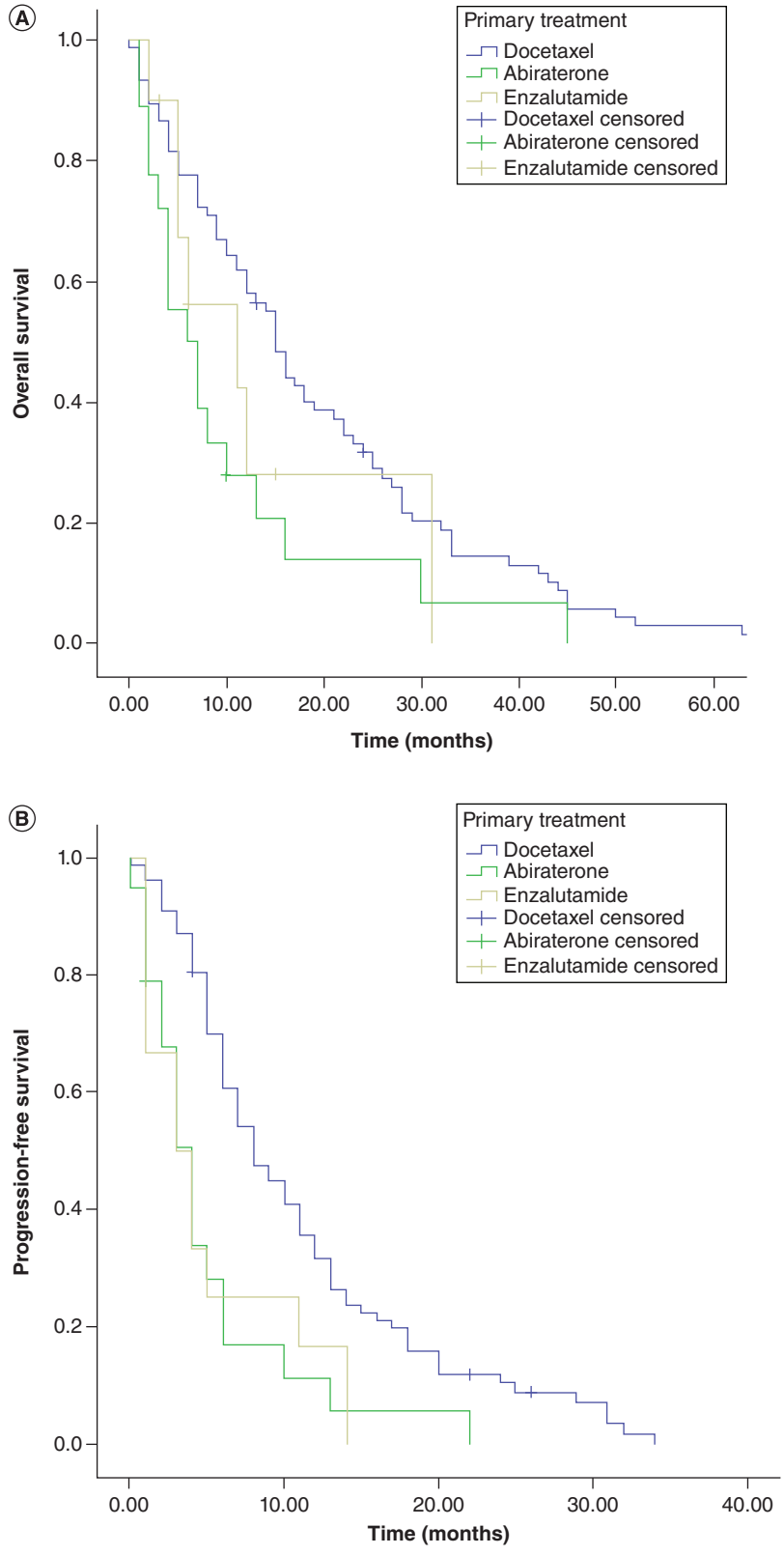


**Figure 1. Kaplan–Meier curves. (A)** Overall and **(B)** progression-free survival of three treatment groups.

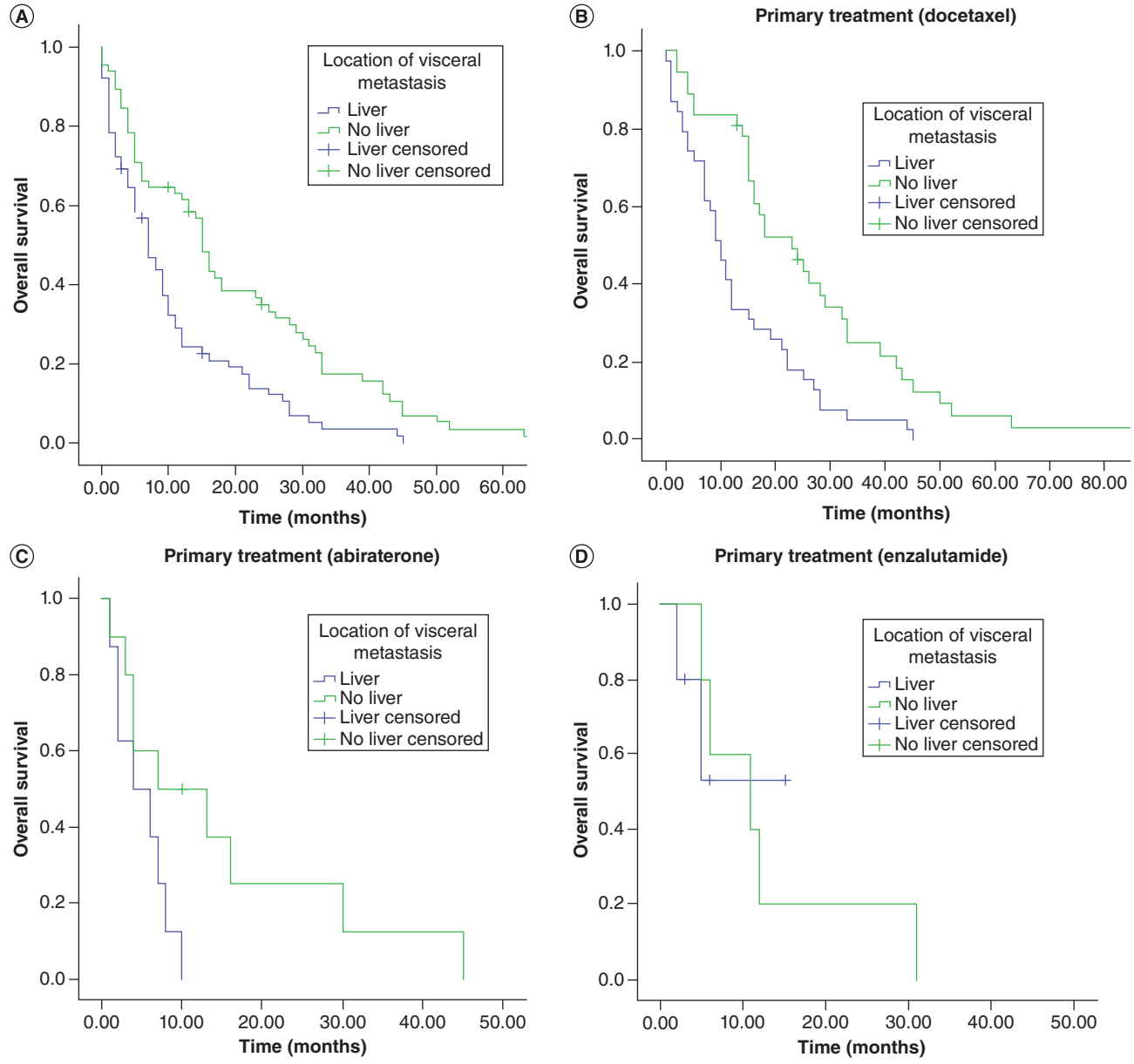


**Figure 2. Kaplan–Meier curves. (A)** overall survival according to different site-specific visceral metastases ($p < 0.001$) and overall survival according to different site-specific visceral metastases in the patients treated with **(B)** docetaxel, **(C)** abiraterone, and **(D)** enzalutamide.

abnormal liver function tests, seizure, etc.) were more common in the abiraterone group. The side effects with all three agents are presented in Table 5.

## Discussion

This multicenter retrospective study reflects our clinical experience of the first-line treatments of CRPC patients with visceral metastases who were treated and followed up in Turkey. We established that docetaxel used as the first-line treatment in CRPC patients with visceral metastases was superior to abiraterone (HR: 0.52; 95% Cl: 0.30–0.89; p = 0.018) on OS, and superior to both abiraterone (HR: 0.41; 95% Cl: 0.24–0.69; p = 0.001) and enzalutamide (HR: 0.43; 95% Cl: 0.23–0.81; p = 0.009) on PFS. No statistically significant difference in OS (p = 0.58) and PFS (p = 0.86) was identified in a comparison of the abiraterone and enzalutamide groups, although

**Table 3. Univariate and multivariate analysis of progression-free survival of patients.**

| Variables | Univariate, OR | Analysis | | Multivariate, OR | Analysis | |
|---|---|---|---|---|---|---|
| | | 95% CI | p-value | | 95% CI | p-value |
| Primary treatment option (Doc/AA/Enza) | 0.87 | 0.66–1.3 | 0.35 | 0.45 | 0.2–0.95 | 0.04† |
| Age, years (<75, ≥75) | 1.1 | 0.68–1.5 | 0.86 | | | |
| Gleason score (<8, ≥8) | 1.2 | 0.99–1.4 | 0.05 | 1.2 | 01.01.2005 | 0.049† |
| Performance status (0–1, ≥2) | 1.3 | 0.88–2.1 | 0.16 | 2.2 | 1.6–3.8 | 0.004† |
| Comorbidity | 1 | 0.73–1.5 | 0.68 | | | |
| Location of visceral metastasis (liver/no liver) | 1 | 0.69–1.4 | 0.93 | | | |
| Baseline PSA level (<200, ≥200) | 1.2 | 0.81–2 | 0.27 | | | |
| ADT time (<10 ay, ≥10 ay) | 0.9 | 0.6–1.4 | 0.73 | | | |
| Second-line treatment (±) | 1.3 | 0.9–2 | 0.14 | | | |

†p-value is considered significantly considered.
AA: Abiraterone; ADT: Androgen deprivation therapy; Doc: Docetaxel; Enza: Enzalutamide, PSA: Prostate-specific antigen.

**Table 4. Univariate and multivariate analysis of overall survival of patients.**

| Variables | Univariate | Analysis | | Multivariate | Analysis | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Primary treatment option (Doc/AA/Enza) | 1.2 | 0.6–2.4 | 0.005 | 0.83 | 0.4–1.7 | 0.036† |
| Age, years (<75, ≥75) | 1.3 | 0.88–2 | 0.16 | | | |
| Gleason score (<8, ≥8), | 1.1 | 0.96–1.4 | 0.11 | 1.2 | 0.9–1.2 | 0.05† |
| Performance status (0–1, ≥2), | 1.5 | 0.9–2.3 | 0.056 | 2.2 | 1.6–3.9 | 0.04† |
| Comorbidity | 1 | 0.5–1.6 | 0.8 | | | |
| Location of visceral metastasis (liver/no liver) | 0.5 | 0.37–0.8 | 0.003 | 0.6 | 0.3–0.9 | 0.02† |
| Baseline PSA level (<200, ≥200) | 1.0 | 0.69–1.2 | 0.7 | | | |
| ADT time (<10 ay, ≥10 ay) | 0.65 | 0.43–1 | 0.06 | | | |
| Second-line treatment (±) | 0.38 | 0.25–0.57 | 0.001 | 0.4 | 0.25–0.64 | 0.001† |

†p-value is considered istatistically significant.
AA: Abiraterone; ADT: Androgen deprivation therapy; Doc: Docetaxel; Enza: Enzalutamide, PSA: Prostate-specific antigen.

there were statistically significant differences in the patient characteristics of the treatment groups. Compared with the docetaxel group, the patients in the abiraterone and enzalutamide groups were older, had comorbidities and poorer performance, and this difference is likely to have an impact on the results. Because prostate cancer is an advanced-age disease, some patients may not have the chance to receive effective treatment due to both their age and comorbidities [21,22]. Advanced age (>75) is also a risk factor for poor survival in prostate cancer patients, and previous studies have reported higher Gleason scores and a more aggressive tumor histology in older patients than in younger patients [23,24]. In the present study, patients treated with enzalutamide and abiraterone also had a much more aggressive tumor histology than those receiving chemotherapy, although the difference was not statistically significant (Table 1). Novel antiandrogen agents (abiraterone and enzalutamide) were shown to have a good tolerability and to improve survival in older patients and in those with comorbidities [21,22], and so can be considered a good therapeutic option for patients who cannot tolerate chemotherapy.

There are no predictive markers for treatment choice in metastatic CRPC, and therefore patient-specific (PS, age, comorbidity) and disease-specific (extent of involvement, metastatic sites) factors that impact prognosis are important [6,7]. A study by Cu *et al.* evaluated all survival-related prognostic factors in 1358 prostate cancer patients diagnosed with visceral metastases at the initial diagnosis. Significant prognostic factors predicting OS were identified as age (>70), T stage (T3/T4 disease), high Gleason score (>8) and the number and localization of visceral metastases for patients with visceral metastases [18]. Furthermore, a previous study established that the response to ADT, as an indicator of sensitivity to the new-generation androgen receptor axis-targeted agents, was associated with poor survival outcomes in chemo-naive patients with mCRPC when the response time to ADT is

Table 5. Most common adverse events occurring during the therapies.

| Adverse events, % (n) | Docetaxel (n = 117) | | Abiraterone (n = 27) | | Enzalutamide (n = 18) | |
|---|---|---|---|---|---|---|
| | Grade 1/2 | Grade 3/4 | Grade 1/2 | Grade 3/4 | Grade 1/2 | Grade 3/4 |
| Neutropenia | 25.5 (30) | 8.5 (10) | 0 | 0 | 0 | 0 |
| Thrombocytopenia | 1.7 (2) | 0.85 (1) | 0 | 0 | 0 | 0 |
| Anemia | 15.2 (18) | 1.7 (2) | 3.7 (1) | 0 | 5.5 (1) | 0 |
| Febrile neutropenia | 7.6 (9) | 6 (7) | 0 | 0 | 0 | 0 |
| Fatigue | 76.9 (90) | 12 (14) | 40.7 (11) | 0 | 33.3 (6) | 0 |
| Appetite loss | 68.3 (80) | 0 | 2 | 0 | 11 (2) | 0 |
| Nausea | 6.1 (75) | 0 | 3.7 (1) | 0 | 5.5 (1) | 0 |
| Alopecia | 68.3 (80) | 0 | 0 | 0 | 0 | 0 |
| Stomatitis | 8.5 (10) | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 17.9 (21) | 0 | 0 | 0 | 0 | 0 |
| Constipation | 13.6 (16) | 0 | 3.7 (1) | 0 | 5.5 (1) | 0 |
| Diarrhea | 5 (6) | 0 | 3.7 (1) | 0 | 0 | 0 |
| Renal toxicity | 0 | 0 | 0 | 0 | 0 | 0 |
| Neuropathy | 49.5 (58) | 6.8 (8) | 0 | 0 | 0 | 0 |
| Allergic reaction | 3.4 (4) | 0 | 0 | 0 | 0 | 0 |
| Arthralgias | 2.5 (3) | 0 | 0 | 0 | 0 | 0 |
| **Specific adverse events of ABI** | | | | | | |
| Hypertension | 0.85 (1) | 0 | 14.8 (4) | 0 | 0 | 0 |
| Peripheral edema | 3.4 (4) | 0 | 11.1 (3) | 0 | 0 | 0 |
| Electrolyte imbalance | 0 | 0 | 11.1 (3) | 0 | 0 | 0 |
| Elevated ALT | 0 | 0 | 7.4 (2) | 0 | 0 | 0 |
| Seizure | 0 | 0 | 0 | 0 | 0 | 0 |

ABI: Androgen blockade inhibitors.

<10 months [22,25]. In the present study, the multivariate analysis revealed the primary treatment option to be an independent prognostic factor for both PFS and OS in patients with visceral metastases. The present study further confirmed that the Gleason score, performance status, localization of visceral metastases and receipt of second-line treatment were all factors with an impact on prognosis [11,18]. On the other hand, baseline PSA, duration of ADT, age and comorbidities were not found to be statistically significant prognostic factors. The insignificance of well-established variables such as age and comorbidities may be due to the low number of patients.

Visceral metastases typically occur in the liver (20%) and lungs (13%) [9,26]. The prognostic significance of different visceral organ involvement varies between patients groups with visceral metastases. Liver metastasis in particular is associated with poor survival outcomes [3,18]. In the present study, the median OS of patients with liver metastases was 7 (95% CI: 5.1–8.8) months, compared with 15 (95% CI: 13.1–16.8) months in those with nonliver metastases (p = 0.001). The present study also found liver metastases to have a greater negative prognostic effect than other visceral metastatic sites. Patients with liver metastases in all three treatment groups (docetaxel, abiraterone and enzalutamide) had poorer survival outcomes than those with nonliver metastases (Table 2).

There are no biomarker that can help in making the optimal choice between docetaxel and new hormone therapies as a first-line treatment for mCRPC, and there is still a lack of consensus on the optimal treatment algorithm [27]. It is particularly challenging to decide on which agent to use as the first-line treatment of mCRPC with visceral metastases, which is a poor prognostic group. The overall approach is chemotherapy in patients with symptomatic bone disease or visceral metastases [6,8,27], although previous studies have reported on the benefit of both docetaxel chemotherapy and second-generation antiandrogens in visceral metastatic disease [1]. Although there are only limited data from clinical trials on visceral disease in prostate cancer due to the low number of patients, subgroup analyses of such trials have clarified the effect of visceral metastases on clinical outcomes in mCRPC patients.

The retrospective subgroup analysis in the TAX-327 study confirmed the efficacy of docetaxel in patients with visceral metastases [28]. In the study, 23% of the patients had visceral disease, and a survival data analysis recorded a median survival of 18.3 months in patients with bone and/or lymph node involvement compared with 13.1 months

in those with visceral metastases. Despite the shorter median OS in patients with visceral metastases than in those without visceral metastases, the OS benefit was maintained in the group treated with docetaxel when compared with the control group [19,28]. A meta-analysis by Halabi *et al.* evaluated docetaxel trials and reported visceral metastases in 20.8% of 8820 patients. Among those with visceral metastases, 41.4% had liver metastases and 43.5% had lung metastases; patients with both lung and liver metastases were counted under the liver group. The median OS was 16.3 (95% CI: 15.6–17.3) months in the patients with any visceral metastasis, 13.5 (95% CI: 12.7–14.4) months in those with liver metastases and 19.4 (95% CI: 17.8–20.7) months in those with lung metastases ($p < 0.05$) [3]. In the present study, the OS outcomes of the docetaxel group were similar to those reported in earlier studies. The median OS was 15 months (95% CI: 12.9–17) in the overall group, 10 months (95% CI: 7.3–12.6) in patients with liver metastases and 23 months (95% CI: 13.9–32.0) in patients with nonliver metastases.

It may be difficult to administer chemotherapy regimens to patients with visceral metastases due to advanced age, comorbidities and the side effect profile of chemotherapy. In such cases, it is a reasonable approach to evaluate new therapeutic options with less toxicity and with proven efficacy in such patients [25,29]. Abiraterone and enzalutamide have been shown to improve survival in mCRPC in both pre-docetaxel and post-docetaxel settings. A subgroup analyses of the COU-301 study for abiraterone (HR: 0.79 [0.60–1.05]) and an AFFIRM trial for enzalutamide (HR: 0.78 [0.56–1.09]) showed that patients with visceral diseases may benefit from the inhibition of AR [16,25,29–31].

The PREVAIL study identified enzalutamide as effective in the visceral disease group in a pre-docetaxel setting, whereas the COU-AA-302 trial for abiraterone in a pre-docetaxel setting contained no patients with visceral metastases. Both the COU-AA-302 [13] and PREVAIL studies were limited to docetaxel-naive asymptomatic and minimally symptomatic patients [10]. Evans *et al.* made a prospective evaluation of the visceral and nonvisceral groups included in the PREVAIL study and found that 204 (12%) of the 1717 patients had visceral metastases. Enzalutamide, compared with placebo, resulted in an apparent improvement in radiological PFS in visceral disease (HR: 0.28; 95% Cl: 0.16–0.49), and it also showed a tendency to increase in median OS (HR: 0.82; 95% Cl: 0.55–1.23) [10]. In the PREVAIL study, the median OS could not be ascertained in the nonvisceral group, whereas it was 27.8 (20.9–not yet reached) months in the visceral group. On the basis of the results of this study, enzalutamide is recommended for use in CRPC patients with visceral metastases [10,27]. In the present study, enzalutamide resulted in numerically poorer survival outcomes than docetaxel but performed better than abiraterone (11 months (95% Cl: 0.9–23.1). The survival outcomes in our study were less than half those recorded in the PREVAIL study, although it should be kept in mind that the visceral group in the PREVAIL study included both asymptomatic and minimally symptomatic patients, in contrast to the group in our study. When the patients in the PREVAIL study were evaluated based on the site of visceral disease, enzalutamide was found to improve rPFS in those with liver metastases (HR: 0.44; 95% Cl: 0.22–0.90), whereas there was no improvement in OS (HR: 1.04; 95% Cl: 0.57–1.87), unlike other metastatic sites [12]. The authors of the study concluded that enzalutamide did not result in any difference in patients with liver metastases due to the low number of patients. In the present study, the median OS could not be ascertained in the patients with liver metastases in the enzalutamide group, whereas it was 11 months (95% CI: 0.26–21.7) in patients with nonliver metastases ($p < 0.001$). Because our study included patient groups with a poor prognostic, the survival outcomes were much poorer than those of the clinical trials. Clinical trials involve selected patient groups and so may not reflect real life, although the results drawn from real-life data make more valuable contributions to literature.

The COU-AA-301 study demonstrated the efficacy of abiraterone in patients with visceral metastases in the post-docetaxel period [32], although it is not clear whether abiraterone is effective in chemo-naive mCRPC patients with visceral metastases, symptomatic disease and poor performance status because this patient group was excluded from the COU-AA-301 study. In a study reporting on real-life data on abiraterone in the post-docetaxel and pre-docetaxel periods, 6.9% of 58 chemo-naive patients and 15.4% (n = 52) of post-docetaxel patients were identified with visceral metastases. Among the chemo-naive patients, those with visceral metastases had shorter OS and PFS than those without visceral metastases (median OS: 2.8 vs. 18.0 months, $p = 0.0007$; median PFS: 2.8 vs. 6.8 months, $p = 0.0088$) [33]. Likewise, patients in the present study recorded inferior outcomes with AA in the chemo-naive period compared with the other two therapeutic agents (median OS: 6 months, 95% Cl: 1.8–10.1; median PFS: 4 months, 95% Cl: 2.7–5.2). The results may suggest that the treatment efficacy of abiraterone differs in chemo-naive and post-chemotherapy patients. Furthermore, the findings of the present study may support the treatment algorithm toward AA in mCRPC patients with a relatively low tumor burden, and chemotherapy in patients with a high tumor burden and visceral metastases.

There have been several clinical trials to date examining the first-line treatment of mCRPC, but no large Phase III study evaluating any of the first-line treatments (docetaxel, abiraterone and enzalutamide) with superiority over the others with respect to efficacy in both non-visceral and visceral disease groups. Zheng *et al.* made an indirect comparison (docetaxel, AA, enzalutamide and cabazitaxel) of the results of 23 studies, and could establish no statistically significant difference, but recommended the use of docetaxel as the primary agent in mCRPC, being associated with the longest OS (HR: 0.74; 95% CI: 0.64–0.85) and PFS (HR: 0.50; 95% CI: 0.32–0.79). Enzalutamide, in turn, had the best secondary outcomes (PFS, PSA response, quality of life and side effect profile), and it was thus recommended as a non-chemotherapeutic agent [34]. This meta-analysis, however, did not include an analysis of the survival outcomes associated with different metastatic sites.

In a retrospective study that included 115 chemo-naive patients, the survival data for AA and docetaxel was analyzed in mCRPC patients with and without poor prognostic characteristics (visceral metastases, symptomatic disease and/or poor performance status $\geq$2), and AA and docetaxel were found to have similar survival outcomes, independent of poor prognostic factors. The group with poor prognostic characteristics had a median OS of 7.8 months with abiraterone and 15.7 months with docetaxel ($p = 0.16$), whereas the median OS was 20.5 and 18.2 months with abiraterone and docetaxel, respectively ($p = 0.78$), in the good prognostic characteristics group [11]. No survival superiority associated with docetaxel and AA could be established in either the good or poor prognostic characteristics groups, although the study had a low number of patients, and numerically poorer survival outcomes with AA. Statistically significant differences may be observed if the number of patients can be increased. It should be further noted that docetaxel dose intensity was much lower than recommended in 25% of the patients in the study.

There has as yet been no head-to-head study evaluating abiraterone and enzalutamide. A meta-analysis making an indirect comparison of AA and enzalutamide in mCRPC identified no statistically significant difference in OS between the two agents in both pre-docetaxel and post-docetaxel settings (pre HR: 0.90, 95% CI: 0.73–11.1) [35]. All secondary endpoints (PSA progression, radiological PFS, PSA response and impaired quality of life), however, were found to favor enzalutamide. The subgroup analysis in this meta-analysis revealed the efficacy of enzalutamide to be relatively better than AA in the nonvisceral group (HR: 0.81; 95% CI: 0.62–1.06) and almost equal in the visceral disease group (HR: 0.99; 95% CI: 0.64–1.53). The present study established no statistical difference in OS and PFS between enzalutamide and abiraterone, despite the numerical difference in OS in favor of enzalutamide. Both treatment groups included low numbers of patients, and the numerical difference may reach statistical significance if the number of patients is increased. Current treatments (such as AA and enza) are generally more effective in patients without poor risk factors in the mCRPC patient group. However, although limited, efficacy of these agents in the poor-risk group can be seen in the results of trials.

Treatment decisions for mCRPC patients with visceral metastases should be made taking into account treatment-related toxicities and quality of life. In randomized clinical trials, the first-line treatments (AA, docetaxel and enzalutamide) showed no apparent increase in treatment-related side effects in patients with visceral metastases compared with the nonvisceral cohort [10,28,32,35]. In the present study, the safety and tolerability of the first-line treatments among visceral mCRPC patients were consistent with those previously reported for mCRPC [18,28,32,35]. As expected, chemotherapies are associated with much greater toxic side effects than novel antihormone therapies (Table 5). A comparison of androgen pathway inhibitors revealed greater side effects with abiraterone than with enzalutamide, which is believed to be attributable to the use of steroids along with abiraterone. Mostly grade 1–2 side effects were recorded in the present study, with grade 3–4 toxicity, which requires dose reductions and/or chemotherapy delays, being observed only in the docetaxel group of patients. The reported grade 3–4 side effects included hematological toxicities, fatigue and neuropathy. Side effects specific to the androgen blockade inhibitors (mineralocorticoid-related side effects [hypertension, peripheral edema, electrolyte imbalance], abnormal liver function tests, seizure, etc.) were more common with abiraterone than with enzalutamide (Table 5). On the other hand, fatigue was the most commonly reported side effect for both AA and enzalutamide.

There are certain limitations to the present study, the main limitations being its retrospective design, the limited number of patients and the heterogeneous patient group due to the inclusion of patients from multiple cancer centers. The heterogeneous baseline disease and patient characteristics of the patient groups complicated the interpretation of the results. Because it was a multicenter study, the tests used to confirm the diagnosis of visceral metastases were also heterogeneous. Furthermore, patients treated with AA and enzalutamide were considerably fewer in number than those treated with docetaxel, which may affect the comparison of the differences between treatment groups. The greater number of chemotherapies may be due to the tendency to administer chemotherapy

in visceral disease, as well as to the requirement of approval for the off-label use of AA and enzalutamide in first-line treatments in Turkey. Gaining approval for off-label use requires patients to wait some time for treatment approval. Because an immediate initiation of treatment is preferred in poor prognostic patient groups, such as those with visceral diseases, a more accessible treatment option may have been selected. The deficiencies in data collection associated with the multicenter nature of the study (changes in PSA levels, such as PSA doubling time and PSA response; number of bone and visceral metastases; missing side effects) led to difficulties in accessing certain details. Despite the lack of a control group and the limited number of patients, the present study has provided significant information.

## Conclusion

In conclusion, this study recommends docetaxel treatment as the primary choice for patients with tolerability as the first-line treatment of CRPC with visceral organ metastases, despite its disadvantages related to quality of life and toxicities. For visceral disease patients who cannot undergo chemotherapy, enzalutamide, among the novel androgen pathway inhibitors, may be the most appropriate option, given its numeric difference, although statistically insignificant, in OS and its fewer side effects compared with abiraterone. Although this study has provided important information on all three options, the results should be confirmed by prospective, randomized clinical trials involving larger samples.

### Summary points

- Visceral metastatic disease occurs in 16–18% of patients with hormone-refractory prostate cancer and is associated with poor prognosis.
- There is a limited number of studies focusing on the treatment of visceral metastatic disease.
- This study recommends docetaxel treatment as the primary choice for patients with tolerability as the first-line treatment of CRPC with visceral organ metastases.
- For visceral disease patients who cannot undergo chemotherapy, enzalutamide, among the novel androgen pathway inhibitors, may be the most appropriate option.

### Author contributions

Z Oruç and MA Kaplan: conception and design of study and writing of the article. M Karaağaç, N Özyurt and A Isikdogan: data analysis and interpretation. AM Tatlı, AO Kaya, S Menekşe, E Kut, S Koca, ÖN Sever, İ Yasin, S Ebinç, E Zeynelgi, A Sakin and NS Turhal: acquisition of clinical data.

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### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations (permit no:10/2019).

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