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Research Article

# Factors Influencing Mortality of Metastatic Bladder Cancer: A Single-Center Experience

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## Abstract

**Objectives:** Bladder cancer predominantly affects the elderly and exhibits poor survival in the metastatic stage, where the five-year survival rate is approximately 15% with contemporary regimens. Geriatric patients with metastatic bladder cancer generally have low-performance status and multiple comorbid diseases, therefore they often are unable to receive optimal therapy. We aimed to evaluate the rate of metastatic bladder cancer patients receiving systemic treatment, chemotherapy regimens, response to treatments, survival data, and factors influencing mortality.

**Methods:** Patients with metastatic bladder cancer who were treated at our clinic between January 2011 and October 2021 were retrospectively reviewed. Factors affecting survival were evaluated using the long-rank test. Multivariate analysis was performed using cox regression.

**Results:** A total of 121 patients with metastatic disease were included in the study. The median age of the patients was 68 (41-86) years. The median overall survival was 9 months. Overall one-, two- and five-year survival rates were 31%, 17%, and 0.5%, respectively. 52 (43%) of the patients died without receiving any systemic treatment at the metastatic stage. The median overall survival was 3.3 months in patients who received no systemic therapy at the metastatic stage, while it was 11.6 months in patients who received at least one line of therapy (p<0.01). The presence of liver metastasis (HR 1.9; %95 CI 1.17 to 3.09; p<0.01) and the absence of systemic treatment in the metastatic stage (HR 4.26; %95 CI 2.81 to 6.46; p<0.01) were among the independent risk factors for mortality. The rate of patients aged 65 and over was higher in the group not receiving chemotherapy (71.2% vs 47.8%, p=0.01). While 76.9% of the patients who did not receive chemotherapy had recurrent disease, this rate was 49.3% in the group receiving chemotherapy (p<0.01).

**Conclusion:** Nearly half of the patients with metastatic bladder cancer died without any systemic treatment. Independent risk factors associated with mortality included absent treatment and the presence of liver metastasis. Patients who did not receive treatment were older and had higher rates of recurrent metastatic disease.

**Keywords:** Bladder cancer, metastatic, mortality, survival

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Bladder cancer (BC) is the most common malignancy involving the urinary system and the ninth most common malignancy worldwide.[1] Urothelial carcinoma is the predominant histologic type in the United States and Europe, where it accounts for 90% of all bladder cancers. BC predominantly affects men and the elderly, with a median age at diagnosis of 72 years.[2]

Before effective chemotherapy (CT) development, the median survival of advanced BC rarely exceeded 3 to 6 months.[3, 4] Platinum-based combined systemic CT is currently the

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standard first-line treatment for advanced BC. Treatment with these regimens is associated with a median overall survival (mOS) estimate of 9 to 15 months. BC still exhibits poor survival in the metastatic stage, where the five-year survival rate is approximately 15% with contemporary regimens.[4-6] In the past ten years, immuno-oncology (IO) therapies and targeted agents such as fibroblast growth factor receptor inhibitors and antibody-drug conjugates have shown promising results in metastatic BC.[7] However, these agents still do not hold a sufficient place in daily practice as they are expensive, not covered by most health insurance policies, and may be unsuitable for some patients. Cytotoxic agents continue to be the main treatment agent in daily practice in Turkey.

Geriatric patients with metastatic BC generally have low-performance status and multiple comorbid diseases, therefore they often are unable to receive optimal therapy. Participants included in clinical trials are often those with good performance status and normal organ functions, which do not represent the group of patients we treat in real life. Therefore, we believe it will be useful to evaluate real-world data on metastatic bladder cancer.

In this study, we aimed to evaluate the rate of metastatic BC patients receiving systemic treatment, CT regimens, response to treatments, survival data, and factors influencing mortality.

## Methods

Patients with metastatic bladder cancer who were treated at our clinic between January 2011 and October 2021 were retrospectively reviewed. Patient data were obtained from patient files and electronic medical records of the hospital system. Patients older than 18 years of age, with a pathologically confirmed diagnosis of metastatic bladder cancer, were included in the study. Patients with a follow-up period of fewer than 3 months after the diagnosis of metastatic disease and patients with urothelial tumors of the upper urinary tract were excluded from the study.

Age at diagnosis, number of comorbidities, pathological features, Eastern Cooperative Oncology Group (ECOG) performance score (PS), smoking history, primary surgery for bladder cancer, sites of metastasis, number of organ metastases, history of cancer other than BC, CT regimens used in the metastatic setting and treatment responses were recorded and analyzed. Tumor stages were evaluated according to AJCC 8$^{th}$ edition.[8] Treatment responses were evaluated using new response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1).[9] Patients with stage 4 at the time of diagnosis were defined with de novo metastatic disease, and patients exhibiting clinical progression in an early stage were defined with recurrent metastatic disease. Outcomes were classified as patients alive or dead. The follow-up period was defined as the time from metastatic cancer diagnosis to the last visit or death.

Statistical analysis was performed using SPPS V.22. Standard descriptive statistics were used to summarize all variables. The Kolmogorov–Smirnov test was used to analyze the normal distribution of data. The chi-square test was used for categorical variables. Kaplan-Meier plots were used to analyze the survival data. Factors affecting survival were evaluated using the long-rank test. The variables with a univariate $p<0.25$ obtained by the long-rank test were included in the multivariate analysis. Multivariate analysis was performed using cox regression. P values $<0.05$ were accepted as statistically significant.

## Results

We analyzed the data of 176 patients followed up with the diagnosis of bladder cancer between January 2011 and October 2021. A total of 121 patients with metastatic disease were included in the study. The median age of the patients was 68 (41-86) years. The histological type of cancer was urothelial carcinoma in 116 patients (95.9%), squamous cell carcinoma in 2 patients (1.7%), small cell carcinoma in 2 patients (1.7%), and adenocarcinoma in 1 patient (0.8%). Eight patients (6.6%) had malignancies other than bladder cancer. Of these, 2 were lung cancer, 2 were head and neck cancers, and 4 were other malignancies. The demographic and clinical characteristics of the patients are listed in Table 1.

In this study, the median overall survival was 9 months. Overall one-, two- and five-year survival rates were 31%, 17%, and 0.5%, respectively (Fig. 1). The median follow-up time was 17 (0.17-84.6) months. 86% of the patients died by the end of the follow-up period.

52 (43%) of the patients died without receiving any systemic treatment at the metastatic stage. 69 patients (57%) received first-line treatment, 24 patients (19.8%) second-line treatment, and 6 (4.9%) patients 3 or more lines of treatment. CT regimes and treatment responses are shown in Table 2. Of 51 patients who received a combination of gemcitabine plus platinum as first-line treatment, 31 received gemcitabine plus cisplatin, and 20 received carboplatin plus gemcitabine. Median progression-free survival (mPFS) was 5 months and mOS 12 months in patients receiving gemcitabine plus cisplatin. In patients receiving gemcitabine plus carboplatin, mPFS was 5.1 months and mOS was 15.5 months. In patients receiving single-agent gemcitabine, mPFS was 3.2 months and mOS was 8.5 months.

**Table 1.** General characteristics of patients

| Characteristics | n (n=121) | % |
|---|---|---|
| Sex | | |
| Male | 107 | 88.4 |
| Female | 14 | 11.6 |
| Age (years) | | |
| <65 | 51 | 42 |
| ≥ 65 | 70 | 58 |
| Number of comorbidities | | |
| 0 | 47 | 38.8 |
| 1 | 29 | 24 |
| ≥2 | 45 | 37.2 |
| ECOG Performance Status | | |
| 0-1 | 104 | 86 |
| ≥2 | 17 | 14 |
| Smoking history | 110 | 90.9 |
| History of cancer | 8 | 6.6 |
| De novo metastatic disease | 47 | 38.8 |
| Recurrent metastatic disease | 74 | 61.2 |
| Primary tumor surgery (yes) | 56 | 45 |
| Site of metastasis | | |
| Bone | 51 | 43.2 |
| Lung | 35 | 29.7 |
| Liver | 25 | 21.2 |
| Lymph node* | 69 | 58 |
| Brain | 5 | 4.2 |
| Local relapse | 39 | 33.1 |
| Other | 22 | 18.6 |
| Number of metastatic sites | | |
| 1-2 | 83 | 69.2 |
| ≥3 | 37 | 30.8 |

ECOG: Eastern Cooperative Oncology Group; *Mediastinal, abdominal, and recurrent pelvic lymph nodes.

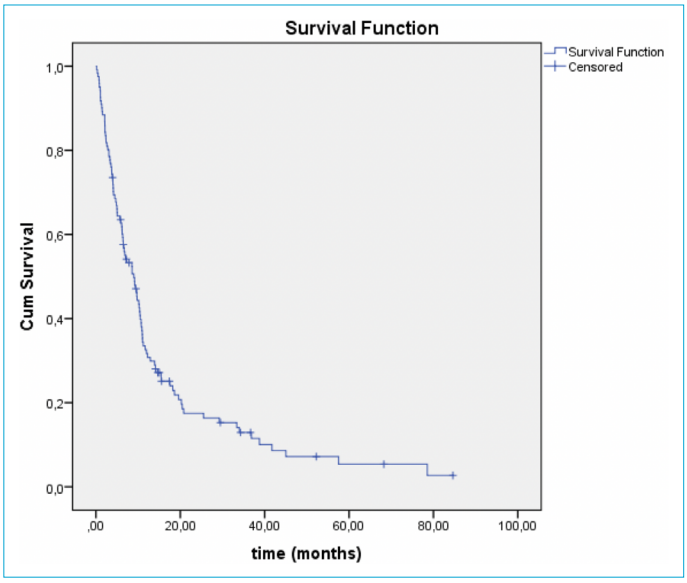


**Figure 1.** Overall survival of patients with metastatic bladder cancer.

As shown by the model created with the factors with p<0.25 in the multivariate analysis, in which each factor that may affect mortality was separately evaluated with the univariate analysis, the presence of liver metastasis (HR 1.9; 95% Confidence Interval [CI] 1.17 to 3.09; p<0.01) and the absence of systemic treatment in the metastatic stage (HR, 4.26; 95% CI 2.81 to 6.46 p<0.01) were among the independent risk factors for mortality. Results of the univariate and multivariate analyses of the parameters are summarized in Table 3.

The mOS was 3.3 months in patients who received no systemic therapy at the metastatic stage, while it was 11.6 months in patients who received at least one line of therapy (p<0.01) (Fig. 2). Median OS was 18.2 months in patients who received at least 2 lines of treatment, and 20.2 months in patients who received at least 3 lines of treatment. The mOS was 9.1 months in patients with ECOG performance scores of 0 and 1, and 7.2 months in patients with an ECOG performance score of 2 or more (p=0.02).

When the patients who received and did not receive CT were compared, the rate of patients aged 65 and over was higher in the group not receiving CT (71.2% vs 47.8%, p=0.01). The rate of two or more comorbidities was similar between the groups (38.5% vs 36.2%, p=0.40). Although the rate of ECOG PS ≥2 patients was higher in the group not receiving CT, it was not statistically significant (17.3% vs 11.6%, p=0.37). Although the rate of patients with three or more metastatic sites was higher in the CT group, it was not statistically significant (35% vs 25% p=0.22). While 76.9% of the patients who did not receive CT had recurrent disease, this rate was 49.3% in the group receiving CT (p<0.01).

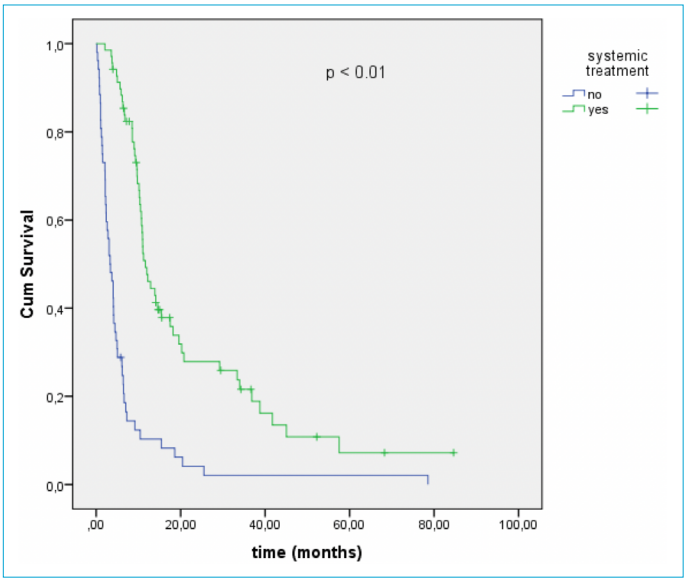


**Figure 2.** Survival of patients who received and did not receive systemic treatment.

**Table 2.** Treatment regimens and responses

| Characteristics | First-line CT n=69 | Second-line CT n=24 | Third-line CT and above n=6 |
|---|---|---|---|
| CT regimen, (%) | | | |
| Gemcitabine/platinum | 51 (73.9) | 6 (25) | 2 (33.3) |
| Gemcitabine | 10 (14.4) | - | 1 (16.6) |
| Paclitaxel | 6 (8.6) | 14 (58.3) | 3 (50) |
| Carboplatin/etoposide | 1 (1.4) | - | - |
| Immunotherapy | 1 (1.4) | 3 (12.5) | - |
| Vinflunine | - | 1 (2.4) | |
| Number of the cycle (median, range) | 4 (1-8) | 4 (1-15) | 2.5 (1-4) |
| Response to treatment, (%) | | | |
| Complete response | 10 (14.5) | 1 (4.1) | 0 |
| Partial response | 27 (39.1) | 6 (25) | 1 (16.6) |
| Stable disease | 3 (4.3) | 1 (4.1) | - |
| Progressive disease | 23 (33.3) | 10 (41.6) | 4 (66.6) |
| Unknown | 6 (8.7) | 6 (25) | 1 (16.6) |

CT: Chemotherapy.

## Discussion

It is known that bladder cancer is mainly a disease of the geriatric population where patients are highly fragile accompanied by a high rate of comorbidities. In our study, the median age was 68 years, which was consistent with the literature, and more than 60% of the patients had at least one comorbid disease.[2,11,12] In our study, 43% of the patients had never received CT at the metastatic stage. We found that the absence of treatment increased mortality by over 4 times compared to receiving at least one line of treatment. Another independent risk factor for mortality was the presence of liver metastasis. Patients who did not receive treatment were older and had higher rates of recurrent metastatic disease than those who did.

In the present study, one of the remarkable results was that 43% of the patients died without receiving any systemic treatment at the metastatic stage. We did not evaluate the reasons for the absence of treatment separately in the study. Some of these patients may have refused the recommended treatment. They may have been unable to receive treatment due to medical conditions such as poor performance or organ failure. In addition, these patients may have died due to reasons such as infection, kidney failure, and cancer-related embolism before the initiation of planned treatment. In our study, the absence of systemic treatment was the most important risk factor for mortality (HR 4.2, p <0.01). For this reason, we compared the characteristics of the groups that received and did not receive treatment. Patients who did not receive CT were observed to be older (The rate of patients aged 65 years and older was 71.2% vs 47.8%, p=0.01). We thought that the tendency to refuse treatment may be higher due to the reduced life expectancy of elderly patients and their relatives. Therefore, geriatric assessment gains importance in the treatment planning of geriatric oncology patients. Although comprehensive geriatric assessment (CGA) is the gold standard in the evaluation of elderly cancer patients, it is difficult to apply to every patient due to the time-consuming (approximately 45 minutes) and trained personnel required. Geriatric screening tools such as G8 and VES-13 can be used to detect fragile patients who will need CGA evaluation. International Society of Geriatric Oncology recommends performing the G8 test and mini COG test in bladder cancer patients.[13] Cases with abnormal results in these tests should be evaluated with CGA.

In addition, patients who did not receive treatment had a higher rate of recurrent metastatic disease. In other words, they consisted of patients who had previously undergone surgery, CT, and radiotherapy in the muscle-invasive stage. The rate of de novo disease was higher in the CT group. We thought that patients who had previously received oncological treatment may have avoided treatment in the metastatic stage because of their negative past experiences.

Limited data were found regarding the rate of receiving treatment in patients with metastatic bladder cancer. In a large population-based study, only 46.3% of the metastatic bladder cancer patients followed up between 1988 and 2014 were able to receive CT, in which low socioeconomic status, and being single were the social factors associated with not receiving CT. However, the study report-

**Table 3.** Univariate and multivariate analyses for mortality in metastatic bladder cancer patients

| Characteristics | Univariate analysis OS, m (95% CI) | p | Multivariate analysis Adjusted HR (95% CI) | p |
|---|---|---|---|---|
| Age (year) | | | | |
| <65 | 9.1 (4.8-13.3) | 0.79 | | |
| ≥65 | 8.5 5.3-11.8) | | | |
| Number of comorbidities | | | | |
| 0 | 9.7 (7.7-11.6) | | | |
| 1 | 6.6. (3.8-9.4) | | | |
| ≥2 | 9.1 (5.9-12.3) | 0.85 | | |
| ECOG Performance Status | | | | |
| 0-1 | 9.1 (6.1-12.0) | 0.02 | | 0.22 |
| ≥2 | 7.2 (4.1-10.4) | | 1.45 (0.79-2.63) | |
| Smoking | | | | |
| No | 4.0 (2.3-5.6) | 0.14 | 1 | |
| <20 pack /year | 9.1 (6.6-11.7) | | 0.71 (0.35-1.44) | 0.35 |
| ≥20 pack /year | 9.0 (4.3-13.6) | | 1.03 (0.50-2.12) | 0.92 |
| Cancer history | | | | |
| No | 9.1 (6.1-12.0) | 0.22 | 1.39 (0.65-2.95) | 0.38 |
| Yes | 4.9 (0-13.2) | | | |
| Primary tumor surgery | | | | |
| Yes | 10.2 (8.3-12) | | | |
| No | 7.2 (4.8-9.6) | 0.24 | 1.11 (0.70-1.75) | 0.64 |
| De novo metastatic disease | 9.6 (8.1-11.1) | | | |
| Recurrent metastatic disease | 6.8 (3.1-10.4) | 0.95 | | |
| Bone metastasis | | | | |
| Yes | 9.0 (5.7-12.2) | 0. | 1.35 (0.90-2.02) | 0.14 |
| No | 9.1 (5.8-12.4) | | | |
| Lung metastasis | | | | |
| Yes | 6.6 (0.7-12.6) | 0.78 | | |
| No | 9.1 (6.6-11.6) | | | |
| Liver metastasis | | | | |
| Yes | 6.3 (0.2-12.4) | 0.14 | 1.9 (1.17-3.09) | <0.01 |
| No | 9.1 (6.3-12.0) | | | |
| Lymph node metastasis | | | | |
| Yes | 9.0 (6.1-11.8) | 0.55 | | |
| No | 7.2 (3.0-11.4) | | | |
| Brain metastasis | | | | |
| Yes | 10.7 (0-25.1) | 0.80 | | |
| No | 9.0 (6.5-11.4) | | | |
| Local relapse | | | | |
| Yes | 6.6 (1.3-11.86) | 0.94 | | |
| No | 9.3 (7.4-11.1) | | | |
| Other metastasis | | | | |
| Yes | 10.9 (4.2-17.5) | 0.93 | | |
| No | 8.5 (5.9-11.1) | | | |
| Number of metastatic sites | | | | |
| 1-2 | 9.1 (6.6-11.5) | 0.37 | | |
| ≥3 | 6.6 (2.2-11.1) | | | |
| First-line treatment | | | | |
| Yes (at least 1 line) | 11.6 (9.5-13.7) | <0.01 | | |
| No | 3.3 (1.8-4.7) | | 4.26 (2.81-6.46) | <0.01 |
| Second-line treatment | | | | |
| Yes (at least 2 lines) | 18.2 (11-25.1) | | | |
| No (0 or 1 line) | 6.4 (4.5-8.2) | <0.01 | 1.58 (0.88-2.83) | 0.12 |
| Third-line treatment | | | | |
| Yes (at least 3 lines) | 20.2 (8.2-32.2) | | | |
| No (0 or ≤2) | 8.5 (6.1-10.9) | 0.05 | 1.03 (0.32-3.24) | 0.95 |

ed that the rates of not receiving CT decreased over time.[14] Our data was more recent and came only from patients referred to medical oncology. We estimate the actual rate to be even higher considering the patients who did not apply to medical oncology or died without being able to. More extensive studies are needed to evaluate the rates and reasons for not receiving CT in patients with metastatic bladder cancer.

In our study, patients who did not receive CT had an mOS of 3.3 months while patients who received at least one line of treatment had an mOS of 11.6 months (Fig. 2). This result strikingly demonstrates the importance of providing patients with at least one line of treatment. The mOS was 18.2 months in patients who received at least 2 lines of treatment, and 20.2 months in patients who received at least 3 lines of treatment despite a drastic decrease in the ratio of patients receiving treatment in each line (Table 2). Of course, we cannot say that the only reason for the increased survival is receiving multiple lines of CT. Patients who have a good PS and respond well to treatments probably have received more lines of treatment. In the light of these data, we would like to emphasize the importance of systemic oncological treatment accompanied with the best supportive care, while managing comorbidities, before the performance status deteriorates in patients following the diagnosis of metastatic disease.

Evaluation of the treatment regimens received by the patients showed that 73.9% received gemcitabine plus platinum-based regimens as first-line treatment. Regimens with a cisplatin-based combination are considered the standard first-line treatment in the metastatic stage.[4,5] Carboplatin/gemcitabine may be a good alternative for patients who are not eligible for cisplatin.[6] A standard first-line combination of MVAC (methotrexate, vincristine, adriamycin, cisplatin) was not given to any patient in our study. The reason for not using the MVAC regimen was attributed to its higher toxicity profile and similar survival and response rates with cisplatin plus gemcitabine. In our study, 14.4% of the patients received only gemcitabine in the first line. The probable reason for this was some patients had a significantly poor performance where they were unable to tolerate combined CT. In daily practice, single-agent gemcitabine is not a recommended first-line regimen for cisplatin-ineligible patients with poor performance; IO is recommended for this group of patients. However, single-agent gemcitabine was administered to the patients as IO was not yet an option at the time of the study and there was no access to the drug. Only 1 patient was able to receive immunotherapy in the first line. Phase-2 studies showed that single-agent gemcitabine exhibits significant activity in metastatic urothelial carcinoma with a safe toxicity profile.[10] Six patients were given a taxane-based regimen in the first line as they had received a platinum-based regimen in the adjuvant or neoadjuvant setting within the last 1 year.

Evaluation of the data of 24 patients who could receive a second-line therapy shows that paclitaxel was the most frequently used agent, followed by repeated gemcitabine/platinum regimen, and then IO. Currently, IO is the standard second-line therapy in advanced BC. However, our patients received either a taxane-based regimen, which was the standard at the time, or, if it was longer than a year since the first-line treatment, another gemcitabine plus platinum regimen since IO was not an option.

In our study, patients receiving cisplatin plus gemcitabine had a mPFS of 5 months and a mOS of 12 months, which was close to the reference study (mPFS 7.7 months, mOS 14 months).[5] Shorter survival may be related to the smaller number of patients, as well as the use of real-world data representing more fragile patients. In the first line, patients receiving gemcitabine plus carboplatin had a mOS of 15.5 months, which was significantly longer than the reference study (mOS of 9.3 months).[6] This might be associated with the low number of our sample. Nevertheless, we believe that these data bear significant importance due to real-world data showing that carboplatin plus gemcitabine can be a good alternative in cisplatin-ineligible patients.

Clinical studies establish poor performance scores, and liver and bone metastases as clinical prognostic factors associated with mortality in metastatic bladder cancer patients.[4,5,12,15] In our study, liver metastasis was an independent risk factor for mortality, which was consistent with the literature. Univariate analysis revealed shorter survival (7.2 vs 9.1 months p=0.02) in patients with poor PS. However, these findings were not reflected in the multivariate analysis. Available literature data only include prognostic factors reported by studies with patients receiving first-line or second-line systemic therapy. In our study, all patients who received and did not receive therapy were included in the analysis as we aimed to investigate the factors affecting mortality from the diagnosis of advanced BC. We think that poor PS and bone metastases may not have been reflected in the multivariate analysis due to this difference.

One of the limitations of our study was the absence of a separate evaluation of reasons for not receiving treatment. Another limitation was the small size of our sample. On the other hand, our study is one of the few studies reflecting the rates of absent treatment in metastatic bladder cancer patients with real-world data, which was one of our strengths.

## Conclusion

Metastatic bladder cancer remains to be associated with poor survival despite advances in oncology. Our results are compatible with the literature. Nearly half of the patients died without any systemic treatment, which is a significant proportion. Independent risk factors associated with mortality included absent treatment and the presence of liver metastasis. Patients who did not receive treatment were older and had higher rates of recurrent metastatic disease. The integration of IO and targeted therapies into routine clinical practice remains to be insufficient. We think that the most important steps to increase survival in metastatic disease include providing systemic treatment accompanied by the most suitable supportive care for patients with metastatic BC before their performance status deteriorates, and making current treatments such as IO accessible.

### Disclosures

**Ethics Committee Approval:** The ethical approval for the study was obtained from Haydarpasa Numune Training and Research Hospital Institutional Review Board. No: 2022-33.

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

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – E.A., M.S.; Design –E.A., M.S., E.T.S.; Supervision – M.S., E.T.S., M.I.O.; Materials – E.A, E.C., G.G.; Data collection &/or processing – E.A., E.C, R.T., G.G.; Analysis and/or interpretation – E.A., M.S., E.T.S.; Literature search – E.A.; Writing – E.A.; Critical review – E.T.S., R.T., M.I.O.

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