



# Clinicopathological Characteristics and Oncological Outcomes of Non-urothelial Bladder Carcinomas: A Multicenter Study

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## Abstract

**Objective:** The incidence of non-urothelial bladder cancers is very low, so our knowledge about their treatment protocols and prognosis is limited. We evaluated the clinicopathological characteristics of 26 patients in three different clinics and aimed to determine the prognostic factors affecting oncological outcomes.

**Materials and Methods:** Between January 2012 and October 2019, we retrospectively analyzed the data of twenty-six patients aged between 44-75 years who were diagnosed and treated due to non-urothelial bladder carcinomas in three clinics.

**Results:** Among twenty-six cases, nineteen (73.1%) were male and seven (26.9%) were female. The mean age at diagnosis was 60.77±8.52. The most common presenting complaint was gross hematuria (84.6%). It was followed by lower urinary tract symptoms (38.4%). Histological types of tumors were squamous cell carcinoma (9 cases, 34.8%), adenocarcinoma (eight cases carrying different histopathologic subtypes: Mucinous, signet ring cell, plasmacytoid/signet ring cell mixed variant and signet ring cell containing osteoclast-like giant cell, 30.8%), small cell carcinoma (3 cases, 11.5%), large cell neuroendocrine carcinoma (2 cases, 7.7%), extra-gastrointestinal stromal tumor (1 case, 3.8%) and malignant undifferentiated mesenchymal tumor (1 case, 3.8%) and leiomyosarcoma (2 cases, 7.6%). At a median follow-up of 13 (2-42) months, the progression-free survival rate was 61.5%, while the overall survival rate was 46.1%. In Kaplan-Meier analysis, the median survival of all cases was found to be 16 (9-33) months. Overall survival times were lower in the presence of advanced (3-4) pathological stages ( $p=0.006$ ) and higher ( $\geq 2$ ) ECOG scores ( $p=0.005$ ).

**Conclusion:** In our cases, we observed that overall survival rates increased in patients undergoing multimodal treatments involving radical cystectomy compared to the bladder-sparing approach. The survival rates were higher in squamous cell carcinomas, while the rate of metastasis was higher in adenocarcinoma and neuroendocrine tumors. Up-staging rates after cystectomy were higher in adenocarcinomas, sarcomas and squamous cell carcinomas.

**Keywords:** Adjuvant chemotherapy, non-urothelial bladder carcinomas, oncological outcomes, radical cystectomy

## Introduction

Bladder cancer constitutes 7% of cancers in men and 3% of cancers in women all over the world. The male/female incidence rate is 3-4/1, and it is generally detected in the fifth-sixth decade (1). Of bladder cancers, 90-95% are urothelial (transitional cell) carcinoma and 5-10% are non-urothelial (epithelial and/or mesenchymal origin) carcinoma (2). Non-urothelial carcinomas have a worse prognosis than urothelial carcinomas, and they are usually diagnosed at an advanced stage. Its diagnosis, staging, and treatment are generally similar to urothelial carcinomas (3). The largest series on non-urothelial carcinomas in the literature was performed by Cohen et al. (4) in 2.201 patients.

Due to the low incidence rates, our knowledge about the treatment protocols and prognosis of non-urothelial bladder carcinomas is based on retrospective case series and very few prospective studies (3,5). The basic treatment approach is adjuvant chemotherapy (CT)/radiotherapy (RT) applied after radical surgical resection, especially in the locally advanced stage. However, due to the scarcity of randomized studies, adjuvant treatment protocols are still not standardized (3). Since our knowledge about non-urothelial carcinoma was limited, in this study, we aimed to evaluate the clinical and pathological characteristics and oncological results of patients diagnosed in three different centers in our country.

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## Materials and Methods

The clinical and pathological data and postoperative follow-up findings of 26 patients aged 44-75 years, who were treated and followed up in three different centers between January 2012 and October 2019, and diagnosed as having non-urothelial carcinoma, were retrospectively analyzed. Demographic data of the patients, complaint at presentation, location of the tumor in the bladder, tumor size, cystoscopy findings, transurethral tumor resection of bladder tumor (TUR-BT) pathology, clinical tumor stage, radical cystectomy status, adjuvant treatments applied during the postoperative follow-up period, postoperative follow-up period, local recurrence, progression and survival conditions were recorded. Eastern Cooperative Oncology Group (ECOG) score and Charlson Comorbidity index, which were used to evaluate the morbidity status of the patients during the preoperative period, were found from the patient data and recorded. Radical cystectomy and bilateral expanded pelvic lymph node dissection (LND) were routinely performed in patients undergoing radical surgery. Colonoscopy was performed in all patients with TUR-BT pathology of adenocarcinoma to investigate the primary focus in the colorectal system. American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system was used for staging of tumors (6). In addition, every increase observed in the pathological staging performed after radical cystectomy compared to the clinical TNM stage after TUR-BT was defined as up-staging.

### Statistical Analysis

Kaplan-Meier method was used for survival analysis, while differences between patient groups were evaluated using the log rank test. This study was not suitable for the multivariate model due to its small sample size. Analyses were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. Values of  $p < 0.05$  were considered statistically significant.

## Results

Nineteen (73.1%) of the 26 patients we included in the study were male and 7 (26.9%) were female, and the mean age at diagnosis was  $60.77 \pm 8.52$ . The most common presenting complaint was macroscopic hematuria (22 patients, 84.6%), followed by lower urinary tract complaints (irritative voiding symptoms, difficulty urinating) (10 patients, 38.4%). More rarely, abdominal distension (1 patient, 3.8%), abdominal pain (1 patient, 3.8%) and obstructive uropathy (1 patient, 3.8%) were observed.

Tumor types in histopathological examination were as follows: Squamous cell carcinoma (9 patients, 38.4%), adenocarcinoma (8 patients with different histopathological subtypes, including mucinous, signet ring cell, plasmacytoid/signet ring cell mixed variant, and signet ring cell containing osteoclast-like giant cells, 30.8%), small cell carcinoma (3 patients, 11.5%), large cell neuroendocrine carcinoma (2 patients, 7.7%), extra-gastrointestinal stromal tumor (1 patient, 3.8%) and malignant undifferentiated mesenchymal tumor (1 patient, 3.8%) and leiomyosarcoma (2 patients, 7.6%).

In the median 13-month (2-42) follow-up of the 26 patients included in our study, the progression-free survival rate was 61.5%, and the overall survival rate was 46.1%. While radical cystectomy was applied to 14 of 18 patients, whose clinical stage was determined as T2-T4a N0M0, 9 of them underwent adjuvant CT, 1 of them adjuvant RT, 1 of them neoadjuvant CT, and 1 of them adjuvant CT + RT. Of these 18 patients, adjuvant CT was applied following complete TUR-BT in 3 patients who did not want radical surgery, while partial cystectomy was performed in the patient with extra-gastrointestinal stromal tumor pathology because the tumor was limited to the bladder dome. In the patient with signet ring cell adenocarcinoma with osteoclast-like giant cells without muscle invasion, only complete TUR-BT was performed surgically. These last 2 patients, who did not have a clear treatment scheme, were followed up without adjuvant treatment because the tumor characteristic was not aggressive. Seven patients who were in the metastatic stage at the time of diagnosis were included in the CT program, while palliative RT was applied in 4 patients who developed pain due to bone metastasis during follow-up.

Fourteen patients who underwent radical cystectomy + bilateral expanded pelvic LND and/or neoadjuvant/adjuvant therapy had a median follow-up of 13 (2-42) months, while progression was observed in 4 (28.5%) cancer-related death was observed in 6 (42.8%). In the median 15-month (10-17) follow-up of 3 patients who underwent adjuvant CT and complete TUR-BT, progression and cancer-related death were observed in 2 (66.6%) of them. While no recurrence or progression was observed in the 22-month follow-up of a single patient who underwent partial cystectomy, despite the CT program of 7 patients who were metastatic at the time of diagnosis, 4 (57.1%) had progression and 6 (85.7%) died at a median 9-month (7-22) follow-up. According to the cystectomy pathologies, 9 (60%) of 15 patients had up-staging, while the patient with small cell carcinoma who underwent radical cystectomy after neoadjuvant CT had down-staging.

When we divided the patients into four classes according to histopathological subtype as squamous cell carcinoma, adenocarcinoma, neuroendocrine tumors and sarcomas, the overall survival rates after multimodal treatments were 77.8%, 25%, 20% and 50%, respectively. Metastasis was seen only in patients with adenocarcinoma (62.5%) or neuroendocrine tumors (40%) at the time of diagnosis. Up-staging after cystectomy was observed in 37.5% of patients with squamous cell carcinomas and in all patients with adenocarcinomas or sarcomas. The characteristics of the patients are shown in Table 1. Demographic and clinical characteristics of patients with and without mortality are shown in Table 2.

In the Kaplan-Meier analysis; while the median survival time of all patients was found to be 16 (9-33) months (Figure 1), in the presence of advanced pathological stage (3-4,  $p=0.006$ ) and higher ECOG score ( $\geq 2$ ,  $p=0.005$ ), it was observed that overall survival times were shorter (Figure 2,3).

## Discussion

Non-urothelial bladder carcinomas constitute approximately 5-10% of all bladder carcinomas. The most common

Table 1. Demographic, clinical, pathological data and oncological results of the patients									
Patient no	Age	Gender	Complaint at admission	Risk factor and comorbidity status	Localization of the tumor in the bladder	Pathological diagnosis	Treatment	Postoperative follow up period	Recurrence/ progression status
1	54	Male	Painless, clotted hematuria	Paraplegic patient due to a traffic accident, Applying CIC ECOG score: 2 Charlson comorbidity index: 3	Widespread, multiple solid-based masses in the anterior bladder wall	TUR-BT: Squamous cell carcinoma, There was muscle invasion Clinical stage 2  Radical cystoprostatectomy: Squamous cell carcinoma, pT4aN2M0	Radical cystoprostatectomy bilateral pelvic LND + ileal conduit  Adjuvant 3 cures of cisplatin + gemcitabine	9 months	Liver and bone metastasis in the 4 <sup>th</sup> month  Palliative RT for bone metastasis was given. Ex in the 9 <sup>th</sup> month
2	47	Male	Clotted hematuria, irritative voiding symptoms	Smoking history ECOG score: 3 Charlson comorbidity index: 5	Papillary-looking mass with a diameter of 5 cm in the posterior wall of the bladder	TUR-BT: Mucinous adenocarcinoma, muscle invasion was present Clinical stage 2  Radical cystoprostatectomy: Mucinous adenocarcinoma, pT4bN1M0	Radical cystoprostatectomy bilateral pelvic LND + ileal conduit  Adjuvant 4 cures of 5-Fluorouracil + Doxorubicin + Cisplatin	16 months	Lung metastasis in the 8 <sup>th</sup> month Ex in the 16 <sup>th</sup> month
3	48	Male	Non-clotted hematuria Increase in KFT, Bilateral grade 3 hydronephrosis	Smoking history ECOG score: 3 Charlson comorbidity index: 5	7.5 cm diameter solid-based mass at the bladder floor	TUR-BT: Signet ring cell adenocarcinoma, muscle invasion was present Clinical stage 2  Radical cystoprostatectomy: Signet ring cell adenocarcinoma, pT3bN1M0	Radical cystoprostatectomy + bilateral pelvic LND + ureterocutaneostomy  Adjuvant 4 cures of 5-Fluorouracil + Doxorubicin + Cisplatin	4 months	Postoperative impairment of general condition, bilateral deep vein thrombosis, acute renal failure, Respiratory Failure  Ex in the 4 <sup>th</sup> month
4	53	Female	Non-clotted hematuria, irritative voiding symptoms	Applying CIC due to neurogenic bladder, ECOG score: 1 Charlson comorbidity index: 2	3 cm diameter solid-based mass at the bladder floor	TUR-BT: Squamous cell carcinoma, There was muscle invasion Clinical stage 2  Radical cystectomy: Squamous cell carcinoma, pT2N0M0	Radical cystectomy + urethrectomy + bilateral pelvic LND + ileal conduit +  Adjuvant 4 cures of MVAC	42 months	No recurrence,  Alive
5	74	Male	Difficulty urinating	Smoking history ECOG score: 3 Charlson comorbidity index: 3	On the bladder floor and right sidewall, multiple, solid mass with 9 cm diameter, invading the prostate	TUR-BT: Small cell carcinoma There was muscle invasion  CT: clinical stage T4N2M1 (prostate invasion, bone metastasis, bilateral Grade 2 hydronephrosis)	The patient did not want radical surgical treatment,  Adjuvant 6 cures of carboplatin + etoposide + RT (because of pain due to bone metastasis)	9 months	Progression of bone metastases in the 6 <sup>th</sup> month  Ex in the 9 <sup>th</sup> month

6	57	Male	Painless, clotted hematuria	Smoking history ECOG score: 3 Charlson comorbidity index: 4	4 cm diameter solid-based mass in the right lateral wall of the bladder	TUR-BT: Large cell neuroendocrine carcinoma There was muscle invasion  CT: Clinical stage T3bN0M0 (invasion in perivesical adipose tissue)	The patient did not want radical surgical treatment,  Adjuvant 6 cures of cisplatin + etoposide	15 months	Involvement of right internal iliac lymph nodes in the 8 <sup>th</sup> month  Ex in the 15 <sup>th</sup> month
7	49	Male	Abdominal pain, bloating, weakness, hematuria	Smoking history ECOG score: 3 Charlson comorbidity index: 4	Widespread, multiple, polypoid lesions on the left lateral wall of the bladder	TUR-BT: adenocarcinoma with high grade plasmacytoid / signet ring cell mixed variant There was muscle invasion  CT: Left pleural effusion, bilateral iliac, pararectal, and widespread LN with a large diameter of 2 cm in the right parailiac area. LN biopsy result for adenocarcinoma metastasis Clinical stage: T3bN2M0	The patient's general condition was not appropriate for radical surgery,  Adjuvant 5 cures of gemcitabine + carboplatin	7 months	The patient whose general condition deteriorated further in the 7 <sup>th</sup> month
8	66	Male	Painless, clotted hematuria, difficulty urinating	None ECOG score: 1 Charlson comorbidity index: 1	Two solid-based masses on the right lateral wall of the bladder with a diameter of 2 cm.	TUR-BT: Signet ring cell adenocarcinoma with osteoclast-like giant cells Lamina propria invasion was present  Clinical stage: T1N0M0	In this subtype, which did not have a clear treatment scheme, the patient did not want additional treatment after complete TUR-BT, and was followed up.	14 months	No recurrence,  Alive
9	67	Male	Painless, clotted hematuria	Paraplastic patient due to CVA, Applying CIC ECOG score: 2 Charlson comorbidity index: 2	Widespread solid-based mass at the bladder floor, 2 bladder stones with a diameter of 2 cm.	TUR-BT: Squamous cell carcinoma, There was muscle invasion  Clinical stage: T2N0M0	The patient did not want radical surgical treatment,  Following complete TUR-BT + endoscopic cystolithotripsy,  Adjuvant 4 cures of Cisplatin + gemcitabine were administered.	17 months	No recurrence in 17 months of follow-up,  After that, the patient was out of follow-up.
10	61	Female	Non-clotted hematuria, abdominal distension	None ECOG score: 1 Charlson comorbidity index: 2	A solid mass with a diameter of 8 cm and a necrotic appearance originating from the bladder dome	TUR-BT: Extra-gastrointestinal stromal tumor, There was muscle invasion  CT: A solid mass of 20 cm in diameter in the right adnexal area pushing the intestinal segments, invading the ileum, and suppressing the vena cava.  Partial cystectomy: pT4N0M0	Partial cystectomy + ileal resection + partial omentectomy  In this subtype, which did not have a clear treatment scheme, the patient was followed up.	22 months	No recurrence,  Alive

11	63	Male	Non-clotted hematuria	Smoking history ECOG score: 3 Charlson comorbidity index: 4	Multiple solid masses on the bladder floor, right sidewall and dome	TUR-BT: Large cell neuroendocrine carcinoma There was muscle invasion  PSA: 33, TRUS-biopsy: prostate adenocarcinoma Gleason 5 + 5 Clinical stage of the mass in the bladder: T2N2M0	The patient did not want radical surgical treatment,  For bladder carcinoma 6 cures of cisplatin + etoposide following complete TUR-BT  RT + HT for prostate adenocarcinoma	10 months	Liver metastasis in the 6 <sup>th</sup> month  Ex in the 10 <sup>th</sup> month
12	55	Male	Painless, clotted hematuria	None ECOG score: 3 Charlson comorbidity index: 5	Multiple solid masses on the bladder floor, both sidewalls and domes	TUR-BT: Malignant undifferentiated mesenchymal tumor There was muscle invasion Clinical stage 2  Radical cystoprostatectomy: malignant undifferentiated mesenchymal tumor, pT3bN0M0	Radical cystoprostatectomy + bilateral pelvic LND + ileal conduit  Adjuvant 3 cures of doxorubicin, cyclophosphamide, cisplatin	8 months	Lung metastasis in the 3 <sup>rd</sup> month  Ex in the 8 <sup>th</sup> month
13	74	Female	Painless, clotted hematuria	Performing CIC ECOG score: 2 Charlson comorbidity index: 5	Multiple solid masses 3x2 cm in size in the bladder dome	TUR-BT: Squamous cell carcinoma, There was muscle invasion Clinical stage: T2N0M0 Radical cystectomy: Squamous cell carcinoma, T3aN0M0	Radical cystectomy bilateral pelvic LND + ileal conduit Adjuvant RT	18 months	No recurrence, Alive
14	44	Female	Non-clotted hematuria	None ECOG score: 0 Charlson comorbidity index: 2	Multiple solid masses on the bladder floor, both sidewalls and domes	TUR-BT: small cell carcinoma showing neuroendocrine differentiation There was muscle invasion Clinical stage: T2N0M0 Radical cystectomy: No residual tumor was observed TON0M0	Neo-adjuvant 3 cycles of cisplatin + etoposide Radical cystectomy bilateral pelvic LND + ileal conduit	6 months	No recurrence, Alive
15	61	Female	Painless, clotted hematuria	None ECOG score: 0 Charlson comorbidity index: 4	Multiple solid masses 3x3 cm in size on the right side wall of the bladder	TUR-BT: Squamous cell carcinoma,  There was muscle invasion Clinical stage: T2N0M0 Radical cystectomy: Squamous cell carcinoma, T2N0M0	Radical cystectomy bilateral pelvic LND + ileal conduit	26 months	No recurrence, Alive
16	67	Male	Lower urinary tract complaint	Smoking history ECOG score: 1 Charlson comorbidity index: 9	Multiple solid-based mass of 7x7 cm in the right lateral wall of the bladder	TUR-BT: Leiomyosarcoma High grade  Clinical stage: T2N0M0 Radical cystectomy: Leiomyosarcoma with a component of small cell neuroendocrine carcinoma. T3bN1M0	Radical cystoprostatectomy bilateral pelvic LND + ileal conduit	2 months	General condition disorder in the postoperative period, Ex in the 2 <sup>nd</sup> month

17	59	Female	Painless, clotted hematuria	Smoking history ECOG score: 0 Charlson comorbidity index: 3	Multiple solid-based mass of 6x5 cm in the left lateral wall of the bladder	TUR-BT: Leiomyosarcoma High grade Clinical stage: T2N0M0 Radical cystectomy: Leiomyosarcoma T3bN1M0	Radical cystectomy bilateral pelvic LND + ileal conduit Adjuvant RT + 3 cures of ifosfamide/ mesna and doxorubicin	13 months	No recurrence, Alive
18	72	Male	Painless, clotted hematuria, lower urinary tract symptoms	Smoking history ECOG score: 1 Charlson comorbidity index: 3	Multiple solid-based mass 7x5 cm in size at the bladder floor	TUR-BT: Signet ring cell adenocarcinoma There was muscle invasion Clinical stage: T2N1M1	Since there was bone metastasis at the time of diagnosis 3 cures of gemcitabine monotherapy were performed	8 months	No recurrence or metastasis was observed. Ex in the 8 <sup>th</sup> month due to poor general condition
19	60	Male	Non-clotted hematuria	Smoking history ECOG score: 2 Charlson comorbidity index: 5	Multiple solid-based masses of 5x4 cm in size in the bladder dome and base	TUR-BT: Mucinous adenocarcinoma, Muscle invasion was present Clinical stage: T2N0M1	Since there was liver metastasis at the time of diagnosis 6 cures of gemcitabine + carboplatin were performed	7 months	No recurrence or metastasis was observed. Ex in the 7 <sup>th</sup> month due to poor general condition
20	75	Male	Non-clotted hematuria	Smoking history ECOG score: 2 Charlson comorbidity index: 5	Multiple solid-based masses, 3x3 cm in size, on the left sidewall and base of the bladder	TUR-BT: Signet ring cell There was muscle invasion Clinical stage: T2N2M1	Since there was lung metastasis at the time of diagnosis 6 cures of gemcitabine + cisplatin were performed.	16 months	Atezolizumab was added due to the progression in the 5 <sup>th</sup> month. Ex in the 16 <sup>th</sup> month
21	58	Male	Non-clotted hematuria	Smoking history ECOG score: 1 Charlson comorbidity index: 4	Multiple solid-based masses of 4x4 cm in size at the bladder floor	TUR-BT: Mucinous adenocarcinoma, muscle invasion was present Clinical stage: T2N1M1	Since there was liver metastasis at the time of diagnosis 6 cures of gemcitabine + cisplatin were performed	22 months	6 cycles of atezolizumab were added due to the progression in the 9 <sup>th</sup> month. Stable illness in the 22 <sup>nd</sup> month, alive
22	62	Male	Non-clotted hematuria	Paraplegic patient due to a traffic accident, Applying CIC ECOG score: 1 Charlson comorbidity index: 4	Widespread, multiple solid-based mass in the bladder floor	TUR-BT: Squamous cell carcinoma, There was muscle invasion Clinical stage 2 Radical cystoprostatectomy: Squamous cell carcinoma, pT3aN1M0	Radical cystoprostatectomy bilateral pelvic LND + ileal conduit Adjuvant 3 cures of cisplatin + gemcitabine	11 months	Bone metastasis in the 6 <sup>th</sup> month Palliative RT for bone metastasis Ex in the 11 <sup>th</sup> month
23	61	Female	Irritative voiding symptoms	Applying CIC due to neurogenic bladder, ECOG score: 0 Charlson comorbidity index: 5	Solid-based multiple masses with a diameter of 3x3 cm on the bladder floor and left sidewall	TUR-BT: Squamous cell carcinoma, There was muscle invasion Clinical stage 2 Radical cystectomy: Squamous cell carcinoma, pT2N0M0	Radical cystectomy + urethrectomy + bilateral pelvic LND + ileal conduit + Adjuvant 4 cures of MVAC	17 months	No recurrence, Alive

24	59	Male	Painless, clotted hematuria, lower urinary tract symptoms	Paraplastic patient due to a traffic accident, Applying CIC ECOG score: 1 Charlson comorbidity index: 4	Diffuse solid-based multiple masses with a diameter of 5x5 cm on the bladder floor	TUR-BT: Squamous cell carcinoma, There was muscle invasion  Clinical stage 2  Radical cystectomy: Squamous cell carcinoma, pT2N0M0	Radical cystoprostatectomy bilateral pelvic LND + ileal conduit  Adjuvant 4 cures of MVAC	13 months	No recurrence, Alive
25	69	Male	Non-clotted hematuria lower urinary tract symptoms	Smoking history ECOG score: 2 Charlson comorbidity index: 7	Widespread solid-based multiple masses in all bladder walls	TUR-BT: Small cell carcinoma There was muscle invasion  CT: Clinical stage T2N2M1	Since there was bone metastasis at the time of diagnosis Adjuvant 6 cures of carboplatin + etoposide + palliative RT were applied due to pain due to bone metastasis.	11 months	Progression of bone metastases in the 7 <sup>th</sup> month Ex in the 11 <sup>th</sup> month
26	65	Male	Lower urinary tract symptoms	Paraplastic patient, Applying CIC ECOG score: 1 Charlson comorbidity index: 3	Solid-based multiple masses with a diameter of 3x3 cm on the bladder floor	TUR-BT: Squamous cell carcinoma, There was muscle invasion  Clinical stage 2  Radical cystectomy: Squamous cell carcinoma, pT2N0M0	Radical cystoprostatectomy bilateral pelvic LND + ileal conduit  Adjuvant 4 cures of cisplatin + gemcitabine	14 months	No recurrence, Alive

CIC: Clean intermittent catheterization, ECOG: Eastern cooperative oncology group, LND: Lymph node dissection, TUR-BT: Transurethral tumor resection, KFT: Kidney function test, MVAC: Methotrexate, Vinblastine, Adriamycin, Cisplatin, CT: Computed tomography, LN: Lymph node, CVA: Cerebrovascular accident, PSA: Prostate specific antigen

histopathological type in Western population is squamous cell carcinoma (3-5%), followed by adenocarcinoma (0.5-2%), and small cell carcinoma (0.35-0.70%). Other histological types such as neuroendocrine carcinoma, sarcomas, and carcinosarcoma are less common and the incidence has been reported as 0.1-0.5% (7). In our study consisting of 26 patients, the most common type was squamous cell carcinoma, in accordance with the literature.

In all types of non-urothelial bladder carcinomas, the most common risk factor observed was smoking (63%) and the most common complaint at presentation was reported as macroscopic hematuria (64%) (8,9). In these tumors with a male/female incidence rate of 3-4.8/1, the presence of muscle invasion at the time of diagnosis is between 72.2-100% in different series (5,10). In our patient group, male/female ratio was 2.71 and macroscopic hematuria and lower urinary tract symptoms, which were the most common complaints at presentation, were observed with a rate of 84.6% and 38.4%, respectively. Muscle invasion was detected in the TUR-BT specimen in all patients (96.1%) except for signet ring cell adenocarcinoma containing osteoclast-like giant cells. While smoking history was a risk factor in half of our patients, 8 (88.8%) of 9 patients with squamous cell carcinoma had a history of clean intermittent catheterization. In 5 patients, no history that could constitute a risk factor was found.

The majority of patients with non-bilharzial squamous cell carcinoma (62.7%) are seen at younger ages compared to transitional cell carcinoma and they are in stage 3-4 at the time of

diagnosis, while the rate of distant metastasis is 8-34%. Five-year survival rate is 25.1-57% in patients who have undergone radical cystectomy (5,11,12,13,14). The most recommended chemotherapeutic agents in adjuvant therapy are gemcitabine and cisplatin (4). While radical cystectomy was performed in 8 of our 9 patients with squamous cell carcinoma, who were at the clinically localized stage at the time of diagnosis, 6 of them were given adjuvant CT and 1 adjuvant RT. In one patient who did not want radical surgery, complete TUR-BT + CT was applied. It was seen that CT protocols used were gemcitabine + cisplatin in 4 patients and MVAC in 3 patients. In the median 17-month (9-42) follow-up of these 9 patients, the overall survival rate was found to be 77.7%.

While patients with adenocarcinoma reported in the literature are mostly diagnosed in the sixth decade and the male/female ratio is 4.8/1 (15). If non-urachal adenocarcinoma, which has a worse prognosis and constitutes approximately 90% of bladder adenocarcinomas, is suspected, other primary tumors in the anatomical regions (colon, prostate, endometrium, cervix, breast, lung, etc.) that are likely to develop adenocarcinoma should be excluded (16,17). Standard treatment in primary, localized non-urachal adenocarcinomas is radical cystectomy + bilateral pelvic LND (18). While adjuvant CT/RT is recommended in advanced stage adenocarcinomas, it is known that the prognosis is worse in patients without radical cystectomy (3). In non-urachal adenocarcinomas, approximately 45.7% of the patients are in stage 4, while the rate of distant metastasis is 16.7-25% (5,15). The five-year survival rate was reported as 13-

Table 2. Demographic and clinical characteristics of patients with and without mortality		
Parameters	Surviving patients (n=12, 46.2%)	Patients with mortality (n=14, 53.8%)
Age	60.67±7.47	60.86±9.61
<b>Gender (n, %)</b>		
-Male	5 (41.7)	14 (100.0)
-Female	7 (58.3)	0 (0.0)
<b>Histopathological tumor types (n, %)</b>		
Squamous cell carcinoma	7 (58.3)	2 (14.3)
Adenocarcinoma	2 (16.7)	6 (42.9)
Neuroendocrine tumors	1 (8.3)	4 (28.6)
Sarcomas	2 (16.7)	2 (14.3)
<b>Pathological tumor stage (n, %)</b>		
-1	1 (8.3)	0 (0.0)
-2	7 (58.3)	0 (0.0)
-3	1 (8.3)	2 (14.3)
-4	3 (25.0)	12 (85.7)
<b>Status of undergoing cystectomy (n, %)</b>		
-Yes	9 (75.0)	6 (42.9)
-No	3 (25.0)	8 (57.1)
<b>Charlson comorbidity index (n, %)</b>		
≤2	5 (41.7)	0 (0.0)
3-4	5 (41.7)	7 (50.0)
≥5	2 (16.6)	7 (50.0)
<b>ECOG score (n, %)</b>		
≤1	11 (91.7)	3 (21.4)
≥2	1 (8.3)	11 (78.6)
<b>Presence of up-staging in patients undergoing cystectomy (n, %)</b>		
-Yes	3 (33.3)	6 (100.0)
-No	6 (66.7)	0 (0.0)
ECOG: Eastern cooperative oncology group		

35% in patients who underwent radical cystectomy (5,8,14). In the median 11-month (4-22 months) follow-up of 8 patients with adenocarcinoma including different histological variants in our study, the progression rate was 37.5% and the overall survival rate was 25%. Although one patient was detected in clinical stage 1 and 2 patients were in clinical stage 2 at the time of diagnosis, up-staging to stage 4 was observed in both patients who underwent cystectomy. Intravesical treatments have no role in the treatment of bladder adenocarcinomas (19). As a matter of fact, no recurrence or progression was detected in the 14-month follow-up of our patient of singlet ring cell adenocarcinoma with osteoclast-like giant cells at T1 stage who underwent only complete TUR-BT.

Pløeg et al. (10) reported that the survival time was significantly lower in squamous cell carcinoma than adenocarcinoma (10 months vs 31.6 months), while Arslan et al. (20) could not find a significant difference (21 months vs 22 months) between the two histological types. On the other hand, in our limited

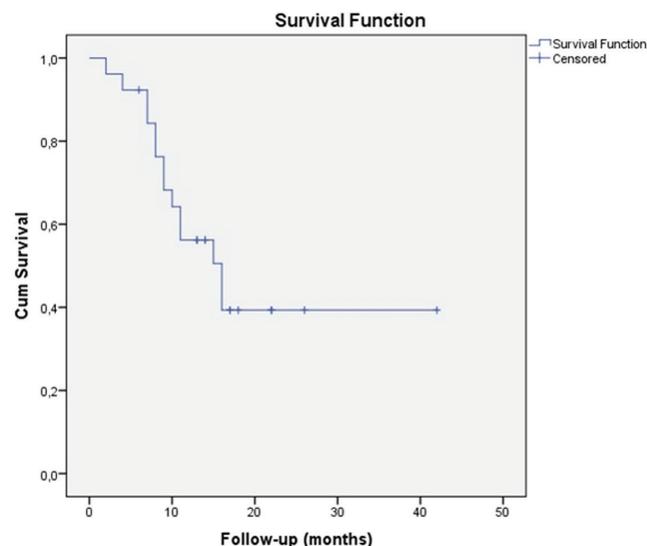


Figure 1. Overall survival plot of all patients

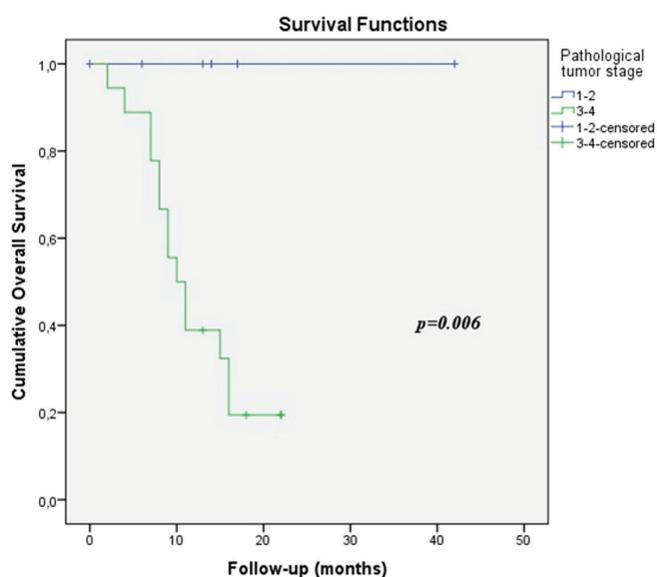
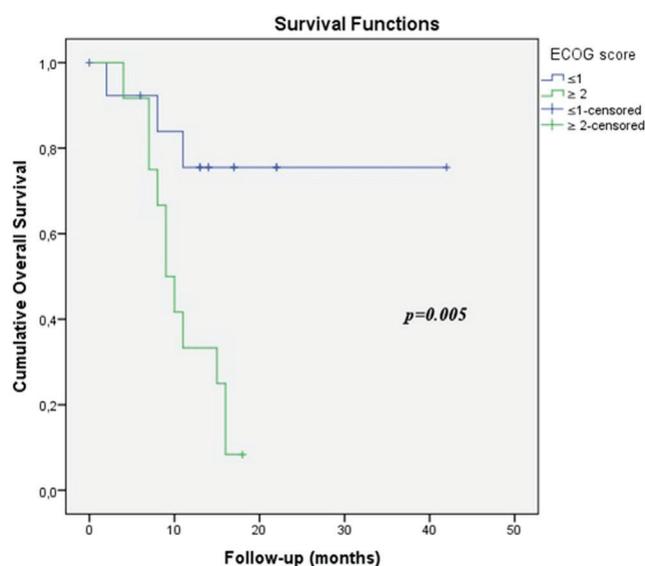


Figure 2. Overall survival plot according to pathological tumor stage

number of patients, we could not find a significant difference between the two groups in terms of overall survival (17 months vs 11.5 months,  $p=0.149$ ).

Neuroendocrine bladder carcinomas generally constitute 0.45-1.2% of all bladder tumors. In this group, small cell carcinomas, which are the more common subtypes, often have muscle invasion, distant organ metastasis and paraneoplastic syndromes at the time of diagnosis (21). Of the patients, 53% are at pT3-4 stage at the time of diagnosis (22). It is necessary to differentiate bladder urothelial carcinoma from small cell carcinoma of prostate origin, and primary small cell carcinoma of the lung, and screening for another primary focus is important (23). Although there is no agreed clear treatment strategy, since micrometastatic involvement may occur at the time of diagnosis, following radical cystectomy/RT and adjuvant CT (cisplatin +



**Figure 3.** Overall survival plot according to ECOG score  
ECOG: Eastern cooperative oncology group

etoposide)/RT is the most recommended scheme (3,4). Despite these combinations of therapy, the five-year survival rate has been reported as 10% (24). In patients in whom radical cystectomy cannot be performed, adjuvant CT+RT combination is required in addition to TUR-BT (25,26). Our patient, who was diagnosed at clinical stage 2 and underwent radical cystectomy following neoadjuvant cisplatin + etoposide in accordance with the information in the literature, was still alive at the 6-month follow-up, and death was observed in a median 10-month (9-11 months) follow-up in 2 patients who were found in the metastatic stage and underwent CT.

Large cell carcinomas of the bladder are another less common subtype of neuroendocrine carcinoma (3). As in small cell carcinoma, it is recommended to investigate the presence of another primary focus for differential diagnosis (27). The most common treatment approach reported for this carcinoma with poor prognosis, which is usually detected at an advanced stage, is the combination of adjuvant cisplatin/carboplatin and etoposide following radical cystectomy. Adjuvant cisplatin and etoposide were administered following TUR-BT in 2 patients who were evaluated as having clinical stage 3 disease at the time of diagnosis and did not want radical cystectomy; however, at a median 12.5-month (10-15 months) follow-up, death due to cancer was observed following progression.

Extra-gastrointestinal stromal tumors originating from the bladder are extremely rare mesenchymal tumors (28). Clinical presentation symptoms are generally non-specific, but patients presenting with macroscopic hematuria have also been reported. There is no specific tumor marker and radiological appearance (29). Complete surgical resection is the most curative treatment approach in this tumor, which is resistant to CT and RT. In our patient, who presented with macroscopic hematuria and abdominal distention without clot, partial cystectomy + ileal resection + partial omentectomy was applied to the mass that originated from the bladder dome and spread to the right

adnexal area adjacent to the bladder and invaded the ileum. Our patient, who did not receive any additional treatment other than surgery, was in remission during a follow-up of 22 months. Sarcomas of the bladder and malignant undifferentiated mesenchymal tumors constitute less than 0.5% of all bladder carcinomas. The most common histopathological type among non-epithelial malignant bladder tumors is leiomyosarcoma (3). In these patients, who mostly present with macroscopic hematuria, the tumor is large and often in advanced stage at the time of diagnosis. While radical cystectomy is recommended in the localized stage, adjuvant CT/RT should be combined in advanced stages. The most commonly used CT protocol is doxorubicin and ifosfamide. Nevertheless, since the number of patients reported in the literature is very low, standardization of treatment has not been achieved and mortality rates are quite high (3,30). Although radical cystectomy + adjuvant CT was applied in our patient with malignant undifferentiated mesenchymal tumor diagnosed at clinical stage 2, mortality was observed within 8 months. While one of our two patients with leiomyosarcoma who underwent radical cystectomy died in the second month postoperatively, in our other patient, no recurrence or progression was observed in the 13-month follow-up after adjuvant RT+CT.

Cohen et al. (4) found that the rate of up-staging was higher in non-urothelial carcinomas compared to urothelial carcinomas after radical cystectomy + bilateral expanded pelvic LND. They also stated that in patients with non-urothelial carcinoma with up-staging, overall survival was lower (32.4% vs 46%), and the highest up-staging rate was observed in patients with squamous cell carcinoma (61.8%). On the other hand, unlike the results of the study by Cohen et al. (4), we observed that the rate of up-staging in adenocarcinomas and sarcomas was higher than in squamous cell carcinomas.

When all non-urothelial carcinomas were evaluated, advanced tumor stage, lymph node involvement, advanced age (>70), poor ECOG score, histological types other than squamous cell carcinoma, presence of positive surgical margins, detection of local recurrence during follow-up were found to be significant factors in predicting overall survival (5,12,13,20). We could not evaluate the effects of these factors on survival, since the number of patients was not sufficient to perform multivariate regression analysis. On the other hand, according to Kaplan-Meier analysis; we observed that overall survival times were shorter as expected in the presence of advanced (stages 3-4) pathological stage and high ( $\geq 2$ ) ECOG score.

### Study Limitations

Although we shared the results of 3 centers in our study, the retrospective design of our study, the limited number of patients, not being able to make randomization, not being able to perform multivariate regression analysis due to the inadequate number of patients, short follow-up periods, and non-standard CT regimens were the main limiting factors.

### Conclusion

When multimodal treatments including radical cystectomy were applied to non-urothelial carcinomas of the bladder, which

were rare and had very heterogeneous subtypes, as observed in our patients, overall survival rates increased compared to the bladder-sparing approach. According to our results, while survival rates were higher in squamous cell carcinomas, the rate of metastasis at the time of diagnosis was higher in adenocarcinoma and neuroendocrine tumors. We found higher up-staging rates in adenocarcinomas, sarcomas and squamous cell carcinomas after cystectomy. However, since neoadjuvant or adjuvant treatment protocols standardized according to tumor subtype are still not established; there is a need for better determination of prognostic factors that have an impact on survival. Prospective, randomized, controlled and multi-center studies with a large number of patients and longer follow-up periods are needed.

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**Contribution:** There is not any contributors who may not be listed as authors.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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### Ethics

**Ethics Committee Approval:** All procedures in our study were conducted in accordance with the ethical standards of the institutional and national research committee including human participants and the principles of the Helsinki Declaration, and since it was a retrospective study, no ethics committee approval was made.

**Informed Consent:** Each patient was informed before the surgery that oncological follow-up information such as recurrence, metastasis development, and survival analysis can be used in various oncological studies to be performed in the clinic without specifying the patient names and identity information, and the data of patients who did not consent were not used.

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

### Authorship Contributions

Concept: E.O.G., Design: İ.S., Data Collection or Processing: İ.S., M.U.K., Y.Ü., Analysis or Interpretation: İ.S., E.O.G., Y.Ü., İ.T., Literature Search: İ.S., Writing: İ.S.

### References

1. Kaur S, Gupta A, Gulwani HV. A clinicopathological and immunohistochemical study of non-urothelial bladder tumours. *Indian J Cancer* 2019;56:254-260.
2. Cıtegez S, Erözenci A, Yörükoğlu K. Non-ürotelyal mesane kanserleri. *Bull Urooncol* 2007;4:9-14.
3. Alanee S, Alvarado-Cabrero I, Murugan P, et al. Update of the International Consultation on Urological Diseases on bladder cancer 2018: non-urothelial cancers of the urinary bladder. *World J Urol* 2019;37:107-114.
4. Cohen AJ, Packiam V, Nottingham C, et al. Upstaging of nonurothelial histology in bladder cancer at the time of surgical treatment in the National Cancer Data Base. *Urol Oncol* 2017;35:34.e1-34.e8. doi: 10.1016/j.urolonc.2016.08.002.
5. Erdem GU, Dogan M, Sakin A, et al. Non-urothelial bladder cancer: comparison of clinicopathological and prognostic characteristics in pure adenocarcinoma and non-bilharzial squamous cell carcinoma of the bladder. *Oncol Res Treat* 2018;41:220-225.
6. AJCC Cancer Staging Manual. 7<sup>th</sup> edition. 2010. p. 497-502.
7. Ravi K, Kumar T, Bakshi H, et al. Non urothelial bladder cancers: a case series. *Indian J Surg Oncol* 2013;4:2-8.
8. Abdollah F, Sun M, Jeldres C, et al. Survival after radical cystectomy of non-bilharzial squamous cell carcinoma vs urothelial carcinoma: a competing-risks analysis. *BJU Int* 2012;109:564-569.
9. Manunta A, Vincendeau S, Kiriakou G, et al. Non-transitional cell bladder carcinomas. *BJU Int* 2005;95:497-502.
10. Ploeg M, Aben KK, Hulsbergen-van de Kaa CA, et al. Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer Registry. *J Urol* 2010;183:915-920.
11. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. *Eur Urol* 2003;44:672-681.
12. Izzard JP, Siemens DR, Mackillop WJ, et al. Outcomes of squamous histology in bladder cancer: a populationbased study. *Urol Oncol* 2015;33:425.e7-13. doi: 10.1016/j.urolonc.2015.06.011.
13. Lagwinski N, Thomas A, Stephenson AJ, et al. Squamous cell carcinoma of the bladder: a clinicopathologic analysis of 45 cases. *Am J Surg Pathol* 2007;31:1777-1787.
14. Rogers CG, Palapattu GS, Shariat SF, et al. Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. *J Urol* 2006;175:2048-2053; discussion 2053.
15. Zaghoul MS, Nouh A, Nazmy M, et al. Long-term results of primary adenocarcinoma of the urinary bladder: a report on 192 patients. *Urol Oncol* 2006;24:13-20.
16. Grignon DJ, Ro JY, Ayala AG, et al. Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases. *Cancer* 1991;67:2165-2172.
17. Wright JL, Porter MP, Li CI, et al. Differences in survival among patients with urachal and nonurachal adenocarcinomas of the bladder. *Cancer* 2006;107:721-728.
18. Zafuto E, Gazdovich S, Leyh-Bannurah SR, et al. Contemporary rates of pathological features and mortality for adenocarcinoma of the urinary bladder in the USA. *Int J Urol* 2017;24:117-123.
19. Roy S, Pradhan D, Ernst WL, et al. Next-generation sequencing-based molecular characterization of primary urinary bladder adenocarcinoma. *Mod Pathol* 2017;30:1133-1143.
20. Arslan B, Bozkurt IH, Yonguc T, et al. Clinical features and outcomes of nontransitional cell carcinomas of the urinary bladder: analysis of 125 cases. *Urol Ann* 2015;7:177-182.
21. Vincendeau S, de Lajarte-Thirouard AS, Bensalah K, et al. Neuroendocrine differentiation of bladder tumors. *Prog Urol* 2003;13:375-384.
22. Williams HA, Punjani N, Khan O, Power NE. The oncological outcomes of small cell carcinoma of the bladder. *Can Urol Assoc J* 2018;13:260-265.
23. Ou WT, Liang QL, Huang X, et al. Small cell carcinoma of the urinary bladder: a case report and review of the literature. *Oncol Lett* 2015;9:488-490.
24. Quek ML, Nichols PW, Yamzon J, et al. Radical cystectomy for primary neuroendocrine tumors of the bladder: the university of southern california experience. *J Urol* 2005;174:93-96.
25. Church DN, Bahl A. Clinical review - small cell carcinoma of the bladder. *Cancer Treat Rev* 2006;32:588-593.

26. Lohrisch C, Murray N, Pickles T, Sullivan L. Small cell carcinoma of the bladder: long term outcome with integrated chemoradiation. *Cancer* 1999;86:2346-2352.
27. Coelho HM, Pereira BA, Caetano PA. Large cell neuroendocrine carcinoma of the urinary bladder: case report and review. *Curr Urol* 2013;7:155-159.
28. Ayık E, Elpek Ö. Extragastrointestinal stromal tumors: localization and clinicopathological features. *Turkiye Klinikleri J Med Pathol-Special Topics* 2017;2:173-183.
29. He F, Fang Z, Zhu P, et al. Bladder extragastrointestinal stromal tumor in an adolescent patient: A case-based review. *Mol Clin Oncol* 2014;2:960-962.
30. Lee TK, Miyamoto H, Osunkoya AO, et al. Smooth muscle neoplasms of the urinary bladder: a clinicopathologic study of 51 cases. *Am J Surg Pathol* 2010;34:502-509.