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Factors affecting recurrence after trimodal treatment in invasive bladder cancer

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Abstract

Background: In this study, we aimed to determine which patients will benefit most from TMT treatment, and to evaluate the factors affecting relapse, survival and response to treatment separately.

Methods: For the study, patients who presented to our hospital's outpatient clinic between 2010 and 2020 and were diagnosed with locally advanced (T2-G3) invasive urothelial bladder cancer and treated with gemcitabine concomitantly with radiotherapy following complete TUR were identified. A total of 112 patients with transitional cell bladder cancer invading the muscle were enrolled in the study including 88 (78.6%) males and 24 (21.4%) females.

Results: Tumor location was significantly associated with tumor recurrence ($p=0.003$). Recurrence at follow-up was significantly associated with the number of tumor foci ($p=0.008$). Median duration of follow-up and median progression-free survival were 41.50 months and 65 ± 4.21 (95% CI, 56.74-73.25) months, respectively. Progression-free survival was not statistically significantly associated with neutrophil/lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR) or BMI ($p=0.32$, $p=0.47$, $p=0.39$, respectively), but muscle invasion during follow-up was significantly associated with progression-free survival ($p=0.009$).

Conclusions: Tumor location, the number of tumor foci, history of multiple transurethral resection surgeries and a NLR ≥ 2.56 were significantly associated with recurrence following Trimodal therapy (TMT). A lower rate of recurrence was observed among patients undergoing early TMT after initial diagnosis. None of the patients treated with trimodal therapy experienced severe adverse effects. Therefore, trimodal therapy is a safe, effective and tolerable therapeutic option with a low rate of recurrence in selected eligible patients.

Keywords: Bladder cancer, Protection of bladder, Recurrence, Progression-free survival, Trimodal treatment

1 Background

Currently, bladder cancer ranks the ninth most frequently occurring cancer worldwide [1]. It is the second most common cancer of the genitourinary tract after prostate cancer. In general, men are 3 to 4 times more likely than women to be diagnosed with bladder cancer. Muscle-invasive bladder cancer accounts for nearly %25 of all bladder cancers [2].

About %90 of all bladder cancers start in the urothelium also known as the transitional epithelium. At the time of diagnosis, %75 of the patients are diagnosed with superficial (noninvasive) bladder cancer and muscle-invasive bladder cancer (MIBC) is diagnosed in %25 (2). Among patients with an initial diagnosis of high-grade noninvasive bladder cancer, 15 to %30 of them may develop invasive bladder cancer during follow-up. Radical cystectomy and bilateral pelvic lymph node dissection are considered as standard treatment in advanced muscle bladder cancers invading the muscle. Good results have been achieved in terms of local tumor control and overall

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survival with 5-year and 10-year recurrence-free survival rates of %68 and %66, respectively [3].

TMT consisting of transurethral resection (TUR), chemotherapy (CT) and radiotherapy (RT) is a therapeutic approach that allows for preservation of the urinary bladder. Gemcitabine, cisplatin and 5-fluorouracil are used for chemoradiotherapy (CRT). Gemcitabine is preferred due to its acceptable toxicity and occurrence of few adverse effects. Preclinical studies have demonstrated that gemcitabine radiosensitizes a variety of tumor cells even at non-cytotoxic doses prior to administration of RT [4]. TMT provided effective and favorable local tumor control in muscle-invasive bladder cancer with complete response rates varying from 50 to %80 [5].

Bladder-sparing multimodal therapies seem to achieve highly successful results. However, residual tumor is detected by follow-up TUR in approximately 20–30% of the patients as well as recurrent tumor in 20–30% of the patients. Prognosis is particularly poor for patients with tumors that are unresponsive to treatment or patients with recurrent tumor, and salvage cystectomy is used for treatment of such patients [6]. While salvage cystectomy may be offered to patients eligible for radical surgery in the case of failed trimodal therapy, geriatric patients are not suitable for radical surgery for whom definitive non-surgical methods should be employed at every stage of the treatment. Bladder preservation strategies should be investigated and standard protocols for non-surgical radical treatment developed for geriatric patients for both initial therapy and following treatment.

There are several clinical factors affecting the natural history of the disease including age, gender and performance status of the patient, pathological type, depth of invasion of the tumor, grade, lymph node involvement and the number of lymph nodes involved, treatment-related factors and timing of treatment and experience level of the surgeon [7].

In the present study, the efficacy of the trimodal therapy as a bladder-preserving option and clinic-pathological prognostic factors affecting progression-free survival were investigated.

2 Methods

For the study, patients who presented to Urology and Medical Oncology outpatient clinic between 2010 and 2020 and were diagnosed with muscle invasive urothelial bladder cancer (T2-G3) as confirmed histopathologically with transurethral resection of bladder tumor (TURBT). Approval was obtained for this research with the decision of Medical Local Ethics Committee (2019 /201-02). All patients were treated with gemcitabine concomitantly with RT following complete TUR were performed. Patient files were reviewed retrospectively to obtain demographic and clinical data including age, gender, histopathological subtype, radiological imaging results, stage of the tumor, development of recurrence during follow-up, survival status and comorbid conditions.Patients with a diagnosis of locally advanced bladder cancer, a Karnofsky Performance Status score of 80, adequate bone marrow reserve (pretreatment leucocyte count > 3000/mm, hemoglobin > 11.0 g/dL and platelet count > 100,000/mm), alkaline phosphatase and alanine aminotransferase levels less than 3 times upper limit of normal, total bilirubin 3,0 mg/dL and serum creatinine level < 1.3 mg/dL who received gemcitabine in combination with radiotherapy were included in the study. Radiotherapy was administered to cover primary tumor and pelvic lymph nodes. RT dose consisted of 45 Gray (Gy) delivered in 1.8 fractions (fx) for five days a week and an additional boost dose of 21.6 Gy. Patients receiving the target RT dose of 66.6 Gy were enrolled in the study. All study patients were given standard premedication with gemcitabine (200 mg / m^2) by intravenous infusion over 30 min once a week just before RT.

Patients with a diagnosis of metastatic bladder cancer or any cancer apart from bladder cancer, patients previously treated with other forms of therapy other than radiotherapy, patients who have not undergone complete TUR prior to RT, patients given chemotherapy other than gemcitabine and pregnant patients, patients other than T_2G_3, patients with pathology other than transitional cell carcinoma, and patients with the presence of CIS were excluded from the study. During and after radiotherapy, whole blood count and serum urea and creatinine values were obtained and physical examinations were performed on a weekly basis. Patients were then called for monthly routine controls. Cystoscopy was performed every 3 months (for 2 years, then every 6 months). Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria, and response to treatment was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 2) criteria retrospectively [8].

The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated from whole blood count data of the patients obtained at their initial presentation to the medical oncology clinic before receiving chemotherapy or radiotherapy and recorded. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Patients with a NLR less than 2.56 were considered as systemic inflammatory response (SIR) negative and those with a NLR ≥ 2.56 were considered as SIR positive (14). PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. Patients with PLRs of < 160 and ≥ 160 were accepted as SIR negative and positive, respectively (15). Patients with a body mass index (BMI) between

20 and 24.9 kg/m^2 were considered as having a normal body weight and those with a BMI between 25–29 kg/m^2 or above 30 were considered as overweight and obese, respectively.

2.1 Statistical analysis

Statistical analyses were performed using SPSS 22 for Windows software package. Mean and standard deviation or median and minimum–maximum values were provided for metric continuous variables and frequency and percentage for qualitative variables. In group comparisons, the test for significance of the difference between two means or one-way analysis of variance (ANOVA) was used for metric continuous variables when assumptions for the parametric tests were met and Mann–Whitney U test or Kruskal–Wallis test were used when assumptions for the parametric tests were not met. The Chi-square test was used for between-group comparison of qualitative data. Survival analysis was performed using Kaplan–Meier curves and the log-rank test. A p value less than 0.05 was considered statistically significant.

3 Results

A total of 112 patients with the muscle invasive bladder cancer were enrolled in the study 88 (78.6%) males and 24 (21.4%) females). Median age of the patients was 68 years (range: 42–85). Comorbidity assessment showed essential hypertension and type 2 diabetes mellitus in 26 (23.2%) patients, coronary artery disease (CAD) in 24 (21.4%) patients and chronic obstructive pulmonary disease (COPD) in 4 (3.6%) patients (Table 1). Diabetes, hypertension, COPD and CAD did not show statistically significant association with tumor recurrence ($p=0.98$, $p=0.54$, $p=0.2$ and $p=0.7$, respectively) (Table 1).

Muscle invasion was present in 78 (69.6%) patients at the time of diagnosis and remaining 34 (30.4%) patients developed muscle invasion during follow-up (these patients were previously NMIBC). While TURBT surgery was performed once in 78 (69.6%) patients, one patient underwent 14 TURBT operations.

Considering the tumor location, tumor involved right lateral wall of the bladder in 34%, left lateral wall of the bladder in 21.4%, posterior wall of the bladder in 9%, trigone in 5.3%, dome of the bladder in 1.8% of the patients and 28.5% had multiple foci. Single-focus tumors were predominantly identified in the patients (62.5%). The median largest tumor diameter was 4 cm (2–8), and the median total tumor diameter was 5 cm (2–13) (Table 2). Tumor location was also statistically significantly associated with recurrence ($p=0.003$), and recurrence was more common particularly in tumors with multiple foci (Table 2).

Table 1 Patient demographics

	Recurrence (+) patients ($n=52$)	**Recurrence (−) patients ($n=60$)**	***P***
Gender (%)			0.78
Female	12 (23%)	12 (%20)	
Male	40 (76.9%)	48 (%80)	
Age (years)	67 (42–85)	69 (43–85)	0.24
BMI (kg/m^2)			0.19
Normal	22 (42.3%)	20 (%33.3)	
Overweight	18 (34,6%)	34 (%56.6)	
Obese	12 (23%)	6 (%10)	
Comorbidity			
Hypertension (%)	14 (26.9%)	12 (%20)	0.54
Diabetes mellitus (%)	12 (23%)	14 (%23.3)	0.98
Coronary artery disease (%)	10(19.2%)	14 (%23.3)	0.7
COPD (%)	4 (7.6%)	–	0.2

* BMI (kg/m^2): Body mass index

* COPD: Chronic obstructive pulmonary disease

Table 2 Pre-treatment and post-treatment clinical characteristics of the patients

	Recurrence (+) patients ($n=52$)	**Recurrence (−) patients ($n=60$)**	***P***
Duration of follow-up (months)	53 ± 22,4	51,07 ± 14,80	0.104
Number of tumor foci (*n*)			0.008
Single focus	22 (42.3%)	48 (80%)	
Two foci	4 (7.7%)	4(6.6%)	
3 or more	26 (50%)	8 (13.3%)	
Tumor diameter (cm)	5.69 ± 2.55	4.20 ± 1.44	0.08
Tumor location (n)			0.003
Right lateral wall	10 (19.2%)	28 (46.6%)	
Left lateral wall	10 (19.2%)	14 (23.3%)	
Posterior wall	2 (3.8%)	8 (13.3%)	
Trigone	2 (3.8%)	4 (6.6%)	
Multiple foci	26 (50%)	6 (10%)	
Dome	2 (3.8%)	–	
History of TUR			
Primary	20 (38.4%)	50 (83.3%)	< 0,001
Secondary (2 or more)	32 (61.5%)	10 (16.6%)	
NLR	3.37 ± 1.87	2.225 ± 0.95	0.01
PLR	116.8 ± 60.7	113.8 ± 51.6	0.8
General condition			< 0.001
Deceased	32 (61.5%)	2 (3.3%)	

* TUR: Transurethral resection

* NLR: Neutrophil/lymphocyte ratio

* PLR: Platelet/ lymphocyte ratio

Follow-up cystoscopy demonstrated tumor recurrence in 45.5% of the males and 50% of the females (a total of 52 patients %46.4). Salvage cystectomy was performed in these patients (38 patients %34). However, since metastasis developed in 14 patients, chemotherapy was started for these patients. Tumor recurrence occurred in 12.3% of the patients with single-focus tumor, 37.7% of the patients with two-foci tumor and 50% of the patients with multiple foci. Recurrence at follow-up was statistically significantly associated with the number of tumor foci ($p=0.008$) but not with tumor diameter ($p=0.08$) (Table 2).

Median duration of follow-up was 41.50 months (15–99). Median progression-free survival of the patients was 65 ± 4.21 months (95% confidence interval (CI) 56.74-73.25) (Fig. 1).

When NLR was used as a predictor of SIR, 54(48.2%) patients were SIR-negative and 58 (51.8%) patients were SIR-positive. NLR was not significantly associated with progression-free survival ($p=0.32$) (Fig. 2). The use of PLR to predict SIR identified 96 (85.7%) SIR-negative and 16 (14.3%) SIR-positive patients. PLR was not significantly associated with progression-free survival ($p=0.47$) (Fig. 3).

Stratification of the patients according to BMI showed that 37.5% of the patients had normal body weight, 46.4% were overweight, and 16.1% were obese and no significant differences in progression-free survival were observed across BMI categories ($p=0.39$) (Fig. 4). Progression-free survival was not significantly different among tumors with single, two or multiple foci ($p=0.47$) (Fig. 5). There was a significant difference in progression-free survival between 78 (69.6%) patients with muscle invasion at diagnosis and 34 (30.4%) patients developing muscle invasion during follow-up ($p=0.009$) (Fig. 6).

4 DISCUSSION

Despite the small sample size and short follow-up used in the present study, treatment of locally advanced bladder cancer with postoperative radiotherapy and concomitant gemcitabine was found to be an effective and safe therapeutic option in a selected group of geriatric patients. In the current study, progression-free survival was 65 ± 4.21 months for bladder cancer patients treated with trimodal therapy. Tumor recurrence was significantly associated with tumor location, number of tumor foci at initial diagnosis and NLR.

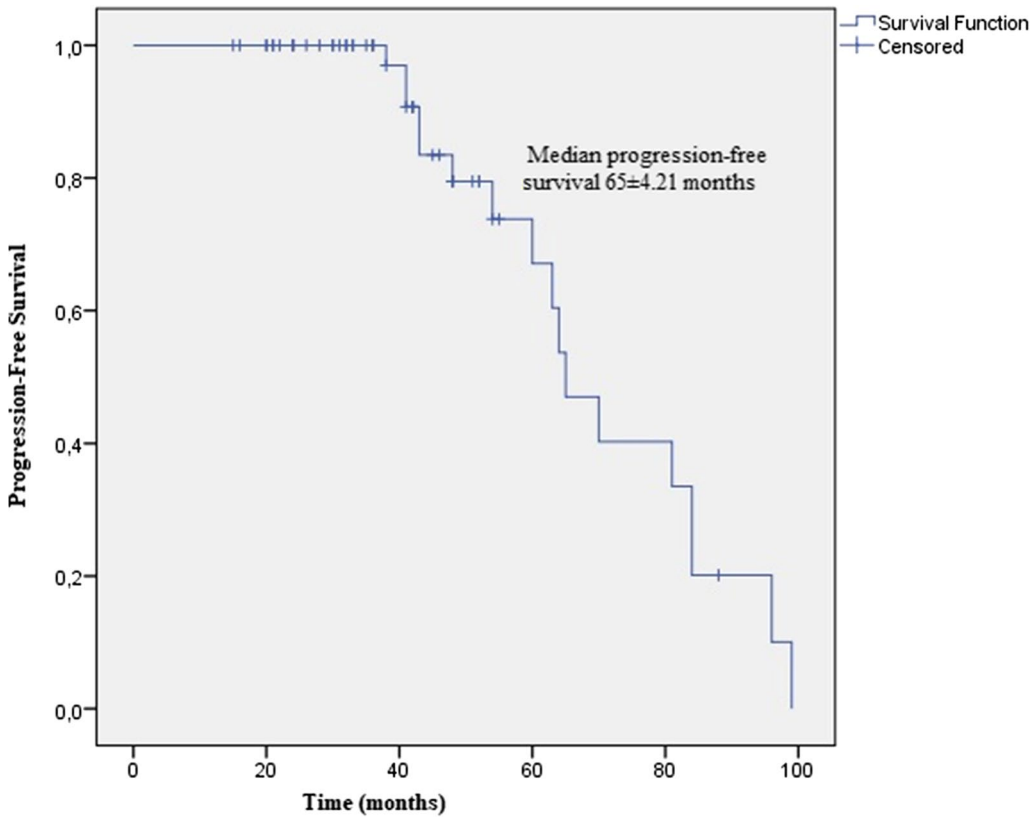

Fig. 1 Median progression-free survival

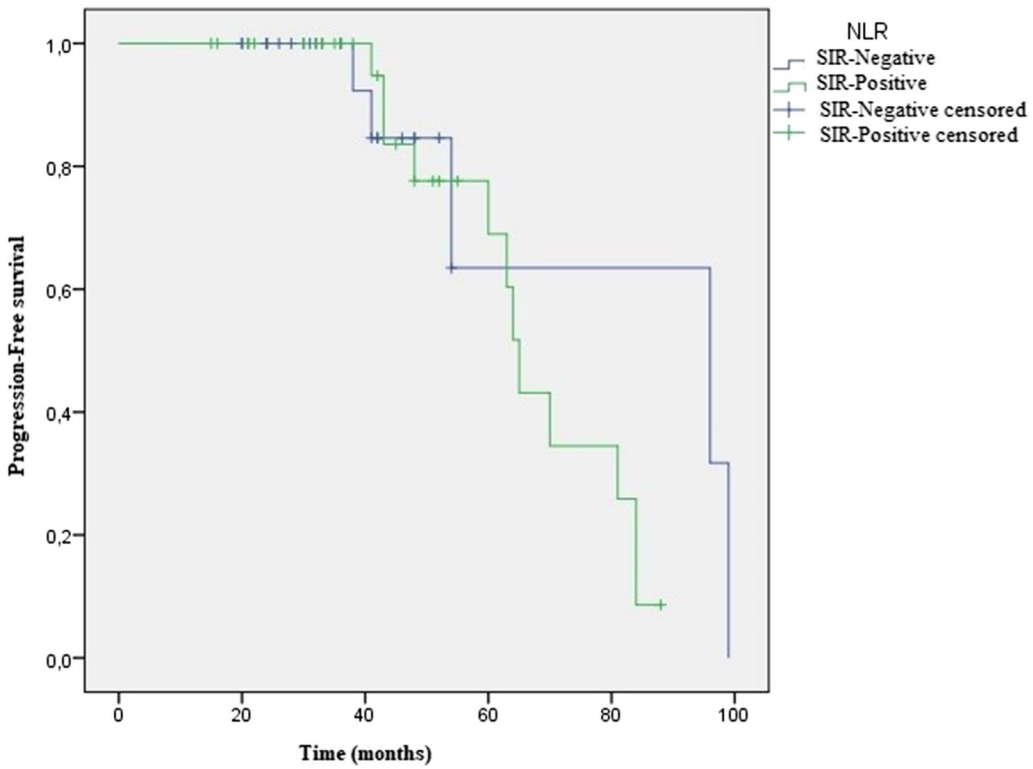

Fig. 2 Neutrophil/lymphocyte ratio (NLR)–progression-free survival: SIR (systemic inflammatory response)—negative, SIR (systemic inflammatory response)—positive

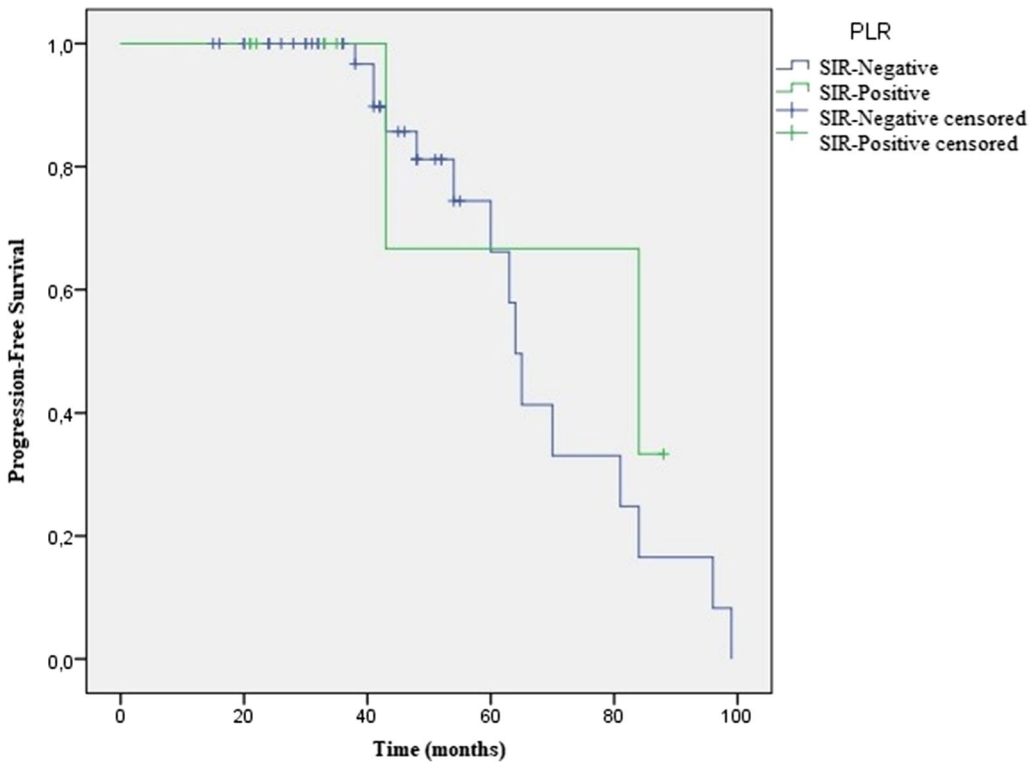

Fig. 3 Platelet/lymphocyte ratio (PLT)–progression-free survival: SIR (systemic inflammatory response)—negative, SIR (systemic inflammatory response)—positive

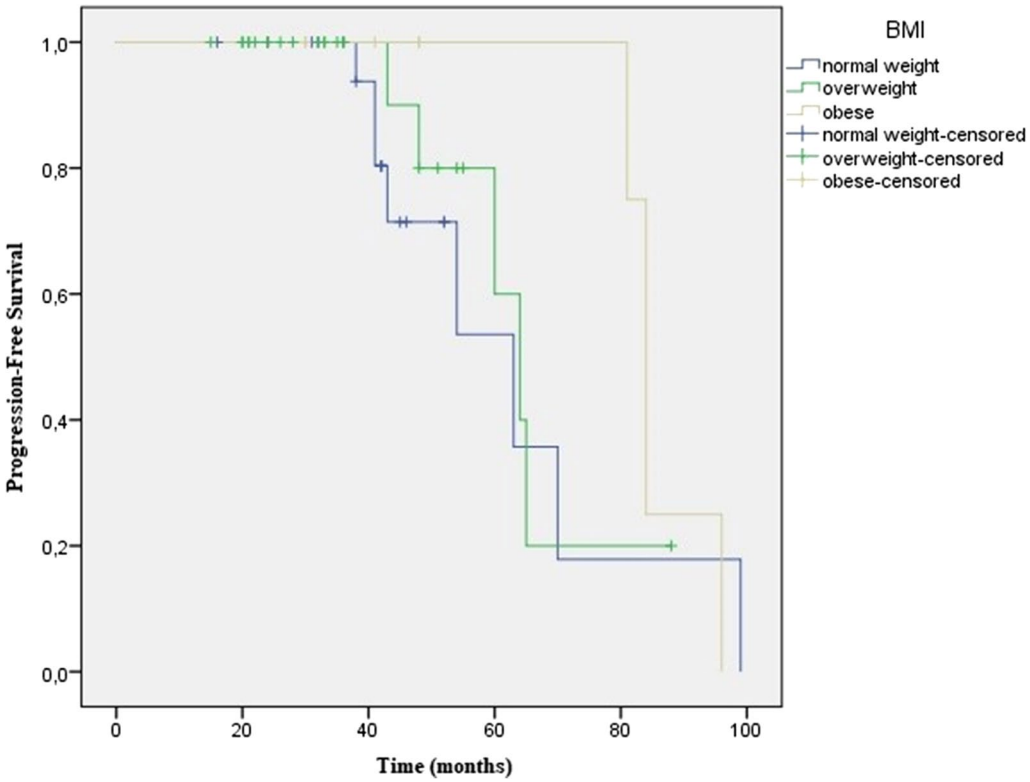

Fig. 4 Body mass index (BKI)–progression-free survival

Bladder cancer is prevalent among elderly adults. Only 21% of patients with muscle-invasive bladder cancer are under 65 years of age. Therefore, it is often not possible to perform radical cystectomy in this patient group due to high morbidity and mortality associated with surgery in the elderly population [9]. In our study, median age of the patients was 68 years (range 42–85).

Comorbidities were identified in most of our elderly patients including hypertension in 23.2%, diabetes mellitus in 23.2%, CAD in 21.4% and COPD in 3.6%.

Comparable results have been obtained with trimodal therapy and radical cystectomy in selected eligible patients. In a study involving 475 patients undergoing trimodal therapy, 5- and 10-year disease-specific survival (DSS) rates were 66% and 59%, respectively. In that study, a multivariate analysis showed that clinical *T* stage, complete response to chemotherapy and presence of hydronephrosis predicted overall survival (OS) response [10].

In the present study, a significant association was found between the number of TUR surgeries and progression-free survival. Muscle invasion was present in 69.6% of patients at the time of diagnosis and 30.4% patients developed muscle invasion during follow-up. Muscle invasion was significantly associated with progression-free survival ($p=0.009$) (Fig. 6), and all 34 patients developing muscle invasion had undergone multiple TUR operations, of whom 24 died during follow-up. The mean time to relapse in patients with recurrence was found to be 16.4 ± 6.3 months.

In the current study, we showed that the number of tumor foci was an important predictor of recurrence. Rodel et al. found that tumor diameter, the number of foci and absence of hydronephrosis predicted the response to TMT [11]. In our study, data on hydronephrosis were unavailable for most of the patients and thus hydronephrosis could not be evaluated. Tumor diameter was not associated with recurrence. In parallel with the aforementioned study, the number of tumor foci was found to be associated with disease recurrence in the present study.

Giacalone et al. from Massachusetts General Hospital reported an updated analysis of long-term outcomes after bladder-preserving TMT in patients with MIBC and showed that complete response to chemoradiation and clinical T stage were independent prognostic factors for both OS and DSS. In addition, tumor-associated carcinoma in situ and hydronephrosis were also identified as prognostic factors [12].

A recent study on the health-related quality of long-term survivors of MIBC reported that bladder-sparing TMT was associated with improved quality of life, better sexual function and body image [13]. These factors are

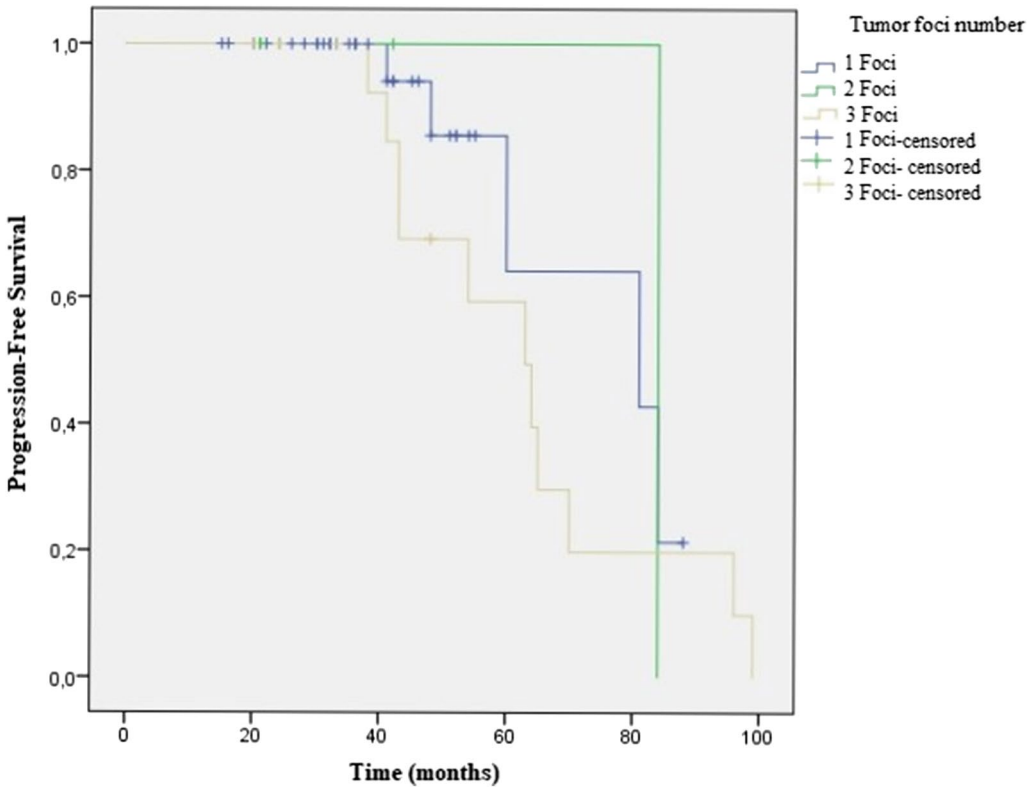

Fig. 5 Tumor foci number–progression-free survival

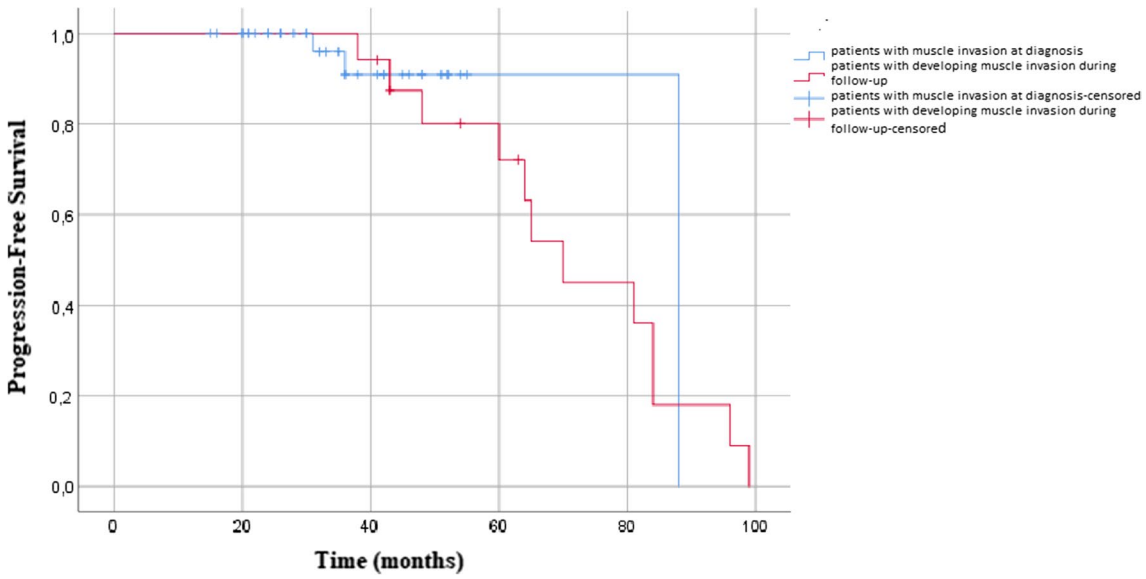

Fig. 6 Muscle invasion status at first diagnosis–progression-free survival

also taken into account by patients when making decisions about their treatment.

5 CONCLUSION

Mounting evidence supports the use of TMT in MIBC. Determining which patients will benefit from this treatment can protect elderly MIBC patients from possible

operative side effects. The patients received radiotherapy in accordance with routine organ-preserving standards. No serious adverse effects were observed in any of the patients. In the current study, we showed that clinicopathological factors including tumor location, the number of tumor foci, the number of previous TUR operations and NLR were associated with tumor recurrence. Further studies employing newer diagnostic methods are needed to corroborate these findings.

Abbreviations

TUR: Transurethral resection; PFS: Progression-free survival; NLR: Neutrophil/ lymphocyte ratio; PLR: Platelet/ lymphocyte ratio; BMI: Body mass index; CRT : Chemoradiotherapy; MIBC: Muscle-invasive bladder cancer; TMT: Trimodal therapy; RT: Radiotherapy; TURBT: Transurethral resection of bladder tumor; RECIST 2: Response evaluation criteria in solid tumors 2; SIR: Systemic inflammatory response; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; DSS: Disease-specific survival; OS: Overall survival.

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Authorship contributions

MS and MY did physical examinations and acquired the data of patients. MS, ZY,V K, NB and AIS studided on design and biochemical parameters. MY performed the statistical analysis and interpretation of data drafting of the manuscript. MS and NB worked on critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The corresponding author has full access to all of the data and takes full responsibility for the veracity of the data.

Declarations

Ethics approval and consent to participate

Approval was obtained for this research with the decision of the Gaziantep Sanko University Medical Local Ethics Committee dated 04.03.2019 /serial numbered 201-02, and the study was conducted in compliance with the Helsinki Declaration Rules. Written consents were obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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