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ORIGINAL ARTICLE

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Survival outcomes of patients diagnosed with muscle-invasive bladder cancer who showed a response after neoadjuvant chemotherapy and refused radical cystectomy, and patients who had radical cystectomy or received chemoradiotherapy

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ABSTRACT

Introduction. We aimed to compare the survival results of patients with muscle-invasive bladder cancer who responded after neoadjuvant chemotherapy (NAC) and did not accept further treatment and those who underwent radical cystectomy or received chemoradiotherapy (CRT).

Material and methods. The study included 53 patients with non-metastatic muscle-invasive bladder cancer who received NAC between 2009 and 2020. Clinical findings and post-NAC survival analysis were evaluated. Survival analyses of patients who underwent radical cystectomy (RC) after NAC, received CRT, and refused treatment were compared.

Results. The median age at diagnosis was 61 (33–80) years. After NAC, 18 patients (34%) received CRT, 9 patients (17%) underwent RC, and 18 patients (34%) refused further treatment. Complete response (CR) was present in 10 (18.4%) patients, partial response (PR) in 35 (66%) patients, stable disease (SD) in 1 (1.9%) patient, and progression in 7 (13.2%) patients. Median overall survival (OS) was 78 months. Median OS was not reached in the RC arm; it was 97 months in the CRT arm and 78 months in the declined-treatment arm. There was no statistical difference between the arms ($p = 0.94$). Median disease-free survival (DFS) was 32 months. Median DFS in the RC arm was 30 months, in the CRT arm — 34 months, and 28 months in the declined-treatment arm after NAC. There was no statistically significant difference between the arms ($p = 0.74$).

Conclusions. We did not find any difference in terms of OS and DFS between patients who after NAC underwent RC, CRT, or refused treatment.

Key words: chemoradiotherapy, neoadjuvant chemotherapy, muscle-invasive bladder cancer, radical cystectomy, refused treatment

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Introduction

Approximately 20–30% of patients with bladder cancer are diagnosed in the muscle-invasive stage [1]. Even after radical cystectomy (RC), more than 50% of muscle-invasive bladder cancer patients relapse, usually within 2 years [2]. Currently, the standard treatment for muscle-invasive bladder cancer is considered to be RC and bilateral pelvic lymph node dissection (PLND) after cisplatin-based neoadjuvant chemotherapy (NAC), which is specified in most clinical guidelines worldwide [3]. RC after NAC for patients with good performance, and chemoradiotherapy (CRT) after NAC as an alternative for selected, well-informed and compliant patients, especially those for whom radical cystectomy is not an option or is not acceptable, is recommended by the European Association of Urology [4]. Gemcitabine, cisplatin (GC) and methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) are given as NAC regimens [5–7]. Trimodality therapy (TMT) is an organ-sparing method that includes concurrent CRT after transurethral resection of the bladder (TUR-B). NAC is an important part of TMT, which has shown that CRT provides better survival than radiotherapy (RT) alone [8]. Although the effect of NAC on TMT is not fully known, there are increasing reports that adding NAC to TMT may improve survival for these patients [9, 10]. In this study, we aimed to compare the survival outcomes of patients who underwent RC or CRT after NAC and patients who showed a partial response (PR) or complete response (CR) after NAC and were followed up without treatment because they refused it.

Material and methods

The files of 469 patients diagnosed with bladder cancer who applied to the Dicle University Medical Oncology Department between 2009–2020 were scanned. Patients who were metastatic at diagnosis and did not receive NAC and those whose records could not be accessed were excluded from the study. Patients who were eligible for platinum (cisplatin or carboplatin) for neoadjuvant chemotherapy, aged ≥ 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and at least 1 cycle of chemotherapy were included in the study. Fifty-three patients who were diagnosed with non-metastatic muscle-invasive bladder cancer at the time of diagnosis and given NAC were included in the study. Age, sex, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node status (cN), tumor location in the bladder, additional comorbid disease status, renal failure status, neoadjuvant treatment regimen, type of treatment applied after neoadjuvant chemotherapy, and post-relapse progression treatments were examined. NAC was given as either cisplatin and gemcitabine or carboplatin and gemcitabine. Cisplatin 75 mg/m^2 or carboplatin at an area under the curve (AUC) dose of 4–6 mg/mL per minute on the 1st day; gemcitabine 1000 mg/m^2 was given on the 1st and 8th days at 21-day intervals. After NAC, external radiotherapy (60–66 Gy) to the bladder and pelvic lymph nodes was given for 6 weeks at 25–40 mg/m^2 weekly with concomitant cisplatin or carboplatin (AUC 2). Patients with a diagnosis of low and high-grade urothelial cell carcinoma were included in the study, while patients with a diagnosis of bladder cancer with variant histology were excluded. Pathological T2-4, clinical N0-3, and M0 patients were included in the study. Response status after NAC was evaluated with control TUR-B, chest-whole abdomen computed tomography (CT), and/or FDG positron emission tomography (PET-CT) scans.

Statistics

Statistical analyzes were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, USA). Supplementary statistics were used to evaluate patient characteristics and parameter frequency, and Kaplan-Meier survival analysis was used for survival analysis. Based on the log-rank P value. Cox regression analysis and Enter method were used for univariate analysis in survival analysis. The confidence interval was accepted as 95%, with significance $p < 0.05$.

RESULTS

Fifty-three patients diagnosed with non-metastatic muscle-invasive bladder cancer were included in our study. Forty-eight patients (90.6%) were male and 5 patients (9.4%) were female. The median age was 61 (33–80) years. Twenty-five patients (47.2%) were < 65 years old and 28 patients (52.8%) were ≥ 65 years old. The ECOG performance score of 12 patients (22.6%) was 0 and the ECOG performance score of 41 patients (77.4%) was 1–2. The characteristic features of the patients are presented in Table 1.

Considering the NAC responses; there was CR in 10 (18.4%) patients, PR in 35 (66%) patients, SD in 1 (1.9%) patient, and progression in 7 (13.2%) patients (Tab. 2). After NAC, CR was achieved in 10 patients, RC was performed in 1 of these patients, CRT was given to 2 patients, and 7 patients were followed up because they refused treatment. After NAC, PR was achieved in 32 patients. RC was performed in 8 of the patients who showed PR, CRT was given to the other 14 patients, and the remaining 10 patients were followed up because they refused treatment. While recurrence did not develop in 1 patient who had CR after NAC

Table 1. Baseline characteristics of the patients

Parameters	n (%)
Median age (range)	61 (33–80)
Age [years]	
< 65	25 (47.2)
≥ 65	28 (52.8)
Sex	
Male	48 (90.6)
Female	5 (9.4)
ECOG PS	
0	12 (22.6)
1–2	41 (77.4)
Tumor grade	
Low	6 (11.3)
High	47 (88.7)
Tumor (pT)	
T2	38 (71.7)
T3	8 (15.1)
T4	7 (13.2)
Lymph node (cN)	
N0	20 (37.7)
N1	13 (24.5)
N2	18 (34)
N3	2 (3.8)
Tumor location in the bladder	
Left lateral	13 (24.5)
Anterior	12 (22.6)
Tumor location in the bladder	**n (%)**
Diffuse	11 (20.8)
Posterior	8 (15.1)
Right lateral	7 (13.2)
Trigon	2 (3.8)
Co-morbidities	
No	19 (35.8)
Yes	34 (64.2)
Renal failure	
No	42 (79.2)
Yes	11 (20.8)
Neoadjuvant treatment regimens	
Cisplatin + gemcitabine	45 (84.9)
Carboplatin + gemcitabine	8 (15.1)
Modality after neoadjuvant therapy	
Cystectomy	9 (17)
Chemoradiotherapy	18 (34)
Refused treatment	18 (34)
Chemotherapy	2 (3.7)
Radiotherapy	1 (1.9)
Exitus	5 (9.4)
Metastatic first-line therapy	
Cisplatin and gemcitabine	8 (15.1)
Carboplatin and gemcitabine	1 (1.9)
Carboplatin and paclitaxel	3 (5.7)
Treatment Denied	9 (17)

ECOG — Eastern Cooperative Oncology Group; PS — performance score

Table 2. Response rates after neoadjuvant chemotherapy

Responses	n (%)
Complete response	10 (18.4)
Partial response	35 (66)
Stable disease	1 (1.9)
Progression	7 (13.2)

and underwent RC, progression developed in 4 (50%) of 8 patients who underwent RC after PR was achieved. Since CR was achieved after NAC and the patients did not accept RC, 2 patients who were given CRT did not relapse, but progression developed in 6 (42%) of 14 patients who received CRT after PR was achieved. Recurrence and progression developed in 2 (28%) of 7 patients who showed CR after NAC and were followed up because of treatment refusal. Progression developed in 6 (60%) of the 10 patients who were followed up after NAC with PR because they refused treatment.

In the overall survival (OS) and disease-free survival (DFS) analysis, 5 patients who died during or immediately after NAC, 2 patients who were given chemotherapy due to progression after NAC, and 1 patient who received radiotherapy were not included. Survival analysis was performed for the remaining 45 patients. Median OS was 78 months (Fig. 1). While median OS could not be reached in the RC arm, in the CRT arm, median OS was 97 months [hazard ratio (HR) = 0.88; 95% confidence interval (CI) 0.21–3.8; p = 0.88), and 78 months in the declined-treatment arm of patients who were followed up without treatment because of response after NAC (HR = 1.1; 95% CI 0.27–4.4; p = 0.88). No statistically significant difference was found between the three arms (p = 0.94) (Tab. 3, 4). Median DFS of all patients was 32 months (Fig. 2). In the RC arm, median DFS was 30 months (p = 0.75), in the CRT arm — 34 months (HR = 0.79; 95% CI 0.23–2.7; p = 0.70), and in the declined-treatment arm — 28 months (HR = 1.1; 95% CI 0.35–3.76; p = 0.80).

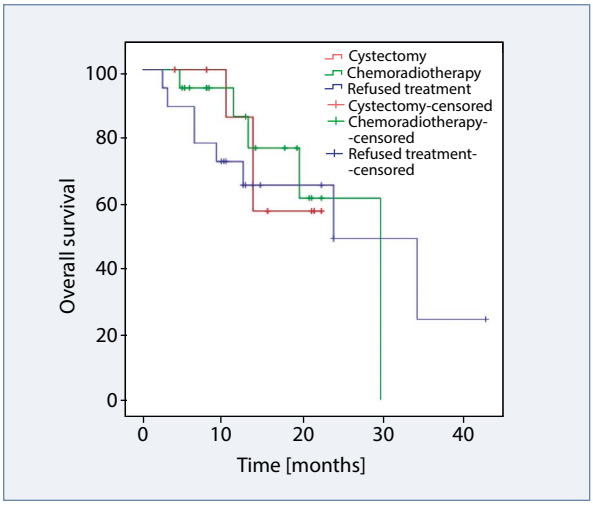

Figure 1. Overall survival of the three groups after neoadjuvant chemotherapy

Table 3. Overall survival according to treatment choice after Neoadjuvant chemotherapy

Variables	HR	95% CI	p value*
Cystectomy	Reference		0.94
Chemoradiotherapy	0.88	0.21–3.8	0.88
Refused treatment	1.1	0.27–4.4	0.88

*p significance value < 0.05; CI — confidence interval; HR — hazard ratio

Table 4. Disease-free survival according to treatment choice after neoadjuvant chemotherapy

Variables	HR	95% CI	p value*
Cystectomy	Reference		0.75
Chemoradiotherapy	0.79	0.23–2.7	0.70
Refused treatment	1.1	0.35–3.7	0.80

*p significance value < 0.05; CI — confidence interval; HR — hazard ratio

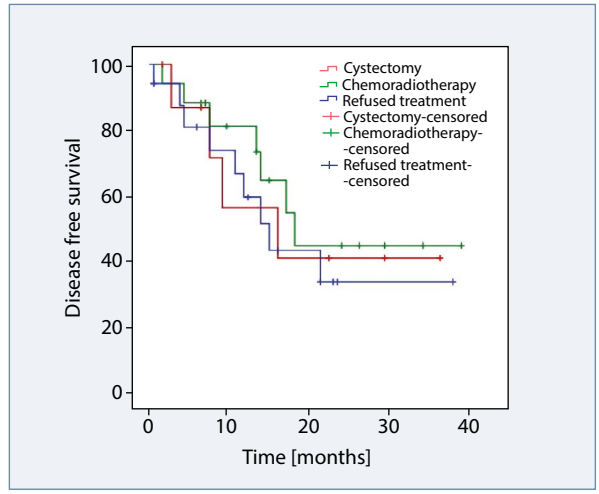

Figure 2. Disease-free survival of the three groups after neoadjuvant chemotherapy

Table 5. Survival outcomes according to treatment choice after neoadjuvant chemotherapy

	Overall survival [months]			Disease-free survival [months]		
	Median	95% CI	p value*	Median	95% CI	p value*
All patients	78		0.94	32		0.74
Cystectomy	NR	NR		30		
Chemoradiotherapy	97	0.21–3.8		34	0.23–2.7	
Refused treatment	78	0.27–4.4		28	0.35–3.7	

*p significance value < 0.05; CI — confidence interval; HR — hazard ratio; NR — not reached

There was no statistically significant difference between the arms (p = 0.74) (Tab. 4, 5).

Median OS was 78 months in patients receiving neoadjuvant cisplatin plus gemcitabine, and 43 months in patients receiving carboplatin plus gemcitabine. Median OS was higher in the cisplatin-treated arm, but no statistically significant difference was found between the two groups (p = 0.82) (Fig. 3). Median DFS was 28 months in 45 patients receiving neoadjuvant cisplatin plus gemcitabine and 14 months in 8 patients receiving carboplatin plus gemcitabine. Median DFS was numerically higher in the cisplatin-treated arm, but there was no statistically significant difference between the two groups (p = 0.31) (Fig. 4).

Parameters that may affect both OS and DFS, such as age (<65 or ≥65), ECOG performance score (0 or 1–2), renal failure status, pT (2 or 3–4), lymph node status, and comorbid diseases evaluated with univariate

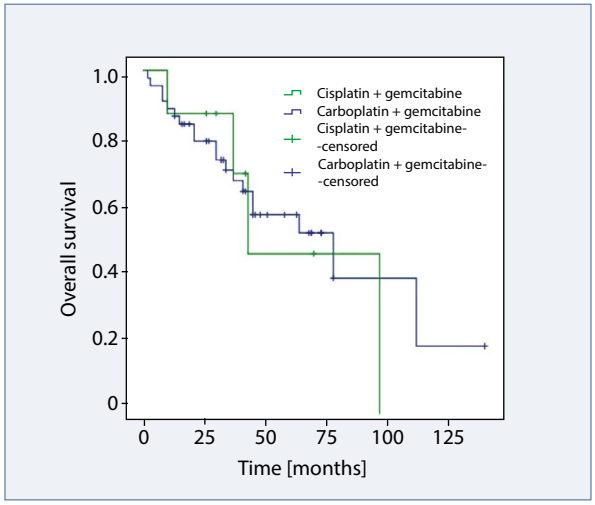

Figure 3. Overall survival with neoadjuvant chemotherapy regimens

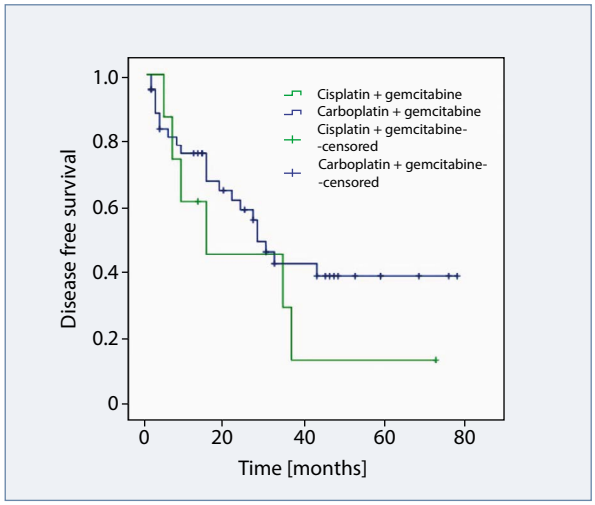

Figure 4. Disease-free survival with neoadjuvant chemotherapy regimens

and multivariate analysis, no statistically significant difference was found.

Discussion

Bladder cancer is the 6th most common cancer in the USA and is usually diagnosed in the elderly. Approximately 20–30% of patients have muscle-invasive bladder cancer at diagnosis. Since most of the patients are in the 6th and 7th decades at diagnosis, these patients have additional comorbidities. The general approach accepted worldwide in the treatment of muscle-invasive bladder cancer is RC and PLND after NAC. In patients with muscle-invasive bladder cancer who do not accept RC, TMT is the treatment option recommended by professional community guidelines. In TMT, after TUR-B, definitive CRT is given, and the bladder is thus protected. However, even in the case of a complete response after TMT, recurrences may occur in bladder cancer. There are no prospective randomized studies on active follow-up or CRT in patients who have a complete or partial response after neoadjuvant chemotherapy and do not accept radical cystectomy.

In the past, RC alone was performed by urologists before NAC treatment, and high recurrence rates were encountered. Considering previous studies on this subject; five-year recurrence-free survival (RFS) for pT2, pT3a, pT3b, pT4, and node-positive disease in patients who underwent RC without NAC was found to be 89%, 78%, 62%, 50%, and 35%, respectively [11]. It was assumed that NAC therapy could improve outcomes, and this view was also supported by randomized phase III studies [12–15]. Randomized controlled studies and meta-analyses have shown that administering NAC before RC has an additional 5% OS benefit [13, 15, 16]. In another study, it was shown that RC after platinum-based NAC was associated with a 5% OS and 9% DFS increase compared to pre-determined RC [17]. In a study by Grossman et al., which followed patients for over 11 years, 154 patients were assigned to the RC alone group and 153 to the NAC after RC group. Median OS was 46 months in patients who underwent RC alone, compared to 77 months in patients who underwent RC after NAC ($p = 0.06$). The group of patients who underwent RC after NAC had significantly less residual disease compared to the group of patients who underwent RC alone (38% *vs.* 15%; $p < 0.001$) [13].

In studies, high objective response rates were obtained after NAC. For example, in a study by Nowak-Sadzikowska et al. [18] on muscle-invasive bladder cancer, after NAC CR was obtained in 8 patients (30%), PR was obtained in 13 patients (48%), and SD was obtained in 6 patients (22%). In that study, response assessment after NAC was performed with control TUR-B and pelvic CT [18]. In a study by Hafez et al. on non-metastatic muscle-invasive bladder cancer, the rate of patients who achieved CR after NAC was found to be 60%. In that study, response evaluation was performed 3 weeks after NAC with repeat cystoscopy and, if possible, tumor biopsy, while radiological evaluation (CT and/or MRI) was also performed to support clinical decision-making. The study defined CR as the absence of residual tumor. If no disease was visible on endoscopic biopsy, this was considered a CR. PR was defined as pathologically downstaging to pTa, pT1, pTis, or evidence of radiological response [19]. In another study, CR was achieved in 78% of patients after NAC [20]. In our study, after NAC,

CR was obtained in 10 (18.4%) patients, PR in 35 (66%) patients, and SD in 1 patient (1.9%). We applied control TUR-B to all patients after neoadjuvant chemotherapy. It was accepted that CR was present in 10 patients with no signs of disease on TUR-B, FDG/PET-CT, or CT. Thirty-five patients with < T2 pathology in the control TUR-B and with a response on their imaging were considered as PR.

In previous TMT studies where the benefit of NAC was not clearly defined, NAC was generally not administered before CRT [21–25]. In six Radiation Therapy Oncology Group (RTOG) compilation studies, it was found that 32% of the patients were treated with TMT after NAC [21]. In a review by Giacalone et al. [26], it was found that 25% of patients treated with TMT received NAC. Good evaluation of tumor response after NAC may be an important selection criterion for TMT. The probability of bladder preservation is significantly lower in patients who do not respond to NAC, and direct RC should be considered [13, 19, 27]. In a study in which CRT was given after NAC, CR was obtained in 32 patients (78.04%). RC was performed in 6 (21%) of 9 patients who did not get a CR, and chemotherapy was applied in 3 patients [20]. In the study of Sadzikowska et al. CR was obtained in 18 patients (67%) treated with CRT after NAC [28]. In a review examining the bladder-sparing method, it was shown that TMT had better survival outcomes than RC or RC after NAC [29]. In a study of patients who refused cystectomy after NAC for muscle-invasive bladder cancer, the number and size of invasive tumors were strongly associated with overall survival. In the above study, restaging (second) TUR-B was performed 2–6 weeks after the first TUR-B and was intended to resect all visible or suspected muscle-invasive tumors. Only patients who had muscle-invasive cancer on the second TUR-B had received NAC. In this study, the most important treatment variable predicting better survival was the complete resection of the invasive tumor at restaging TUR-B before starting NAC [30]. In some studies, the bladder-sparing method was found to provide a better quality of life compared to RC without affecting survival [31]. Many studies currently accept the bladder-sparing method in muscle-invasive bladder cancer as an alternative approach. In our study, CR was achieved in 11 (68%) of 18 patients who received CRT after NAC.

A complete response to NAC is the main determinant of survival for patients undergoing cystectomy, but whether the complete response is permanent is unknown if cystectomy is not performed after NAC. In a collaborative study of 118 patients, 5-year cystectomy-free survival, RFS, DFS, and OS after NAC were 76%, 64%, 90%, and 86%, respectively. However, 11% of these patients relapsed with muscle-invasive bladder cancer, and only 4 of 26 patients who underwent rescue RC died due to bladder cancer [32]. It has been stated that chemotherapy alone should not be advocated in the treatment of non-metastatic muscle-invasive bladder cancer because many patients will relapse due to residual disease if RC is not performed, and chemotherapy alone is acceptable in the selected patient group [33]. NAC alone is limited to patients who are scheduled for RC after NAC but achieve a clinical complete response and do not want RC because of this complete response. In our study, recurrence and progression developed in 2 (28%) of 7 patients who had CR after NAC and were followed up because they refused treatment; progression developed in 6 (60%) of 10 patients who had PR after NAC and were followed up because of refusing treatment. Therefore, treatment response after NAC can be used as a predictor of long-term survival.

The limitations of our study were its retrospective character, inadequacy of the patient files related to treatment-related side effects, and the small number of patients.

Conclusions

In conclusion, there was no difference in OS and DFS between patients who underwent RC, received CRT, or refused treatment after NAC. These data need to be confirmed by further studies in a large population to recommend treatment-free follow-up for patients who achieved CR after NAC but refused CRT and RC.

Article Information and Declarations

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles defined in the Declaration of Helsinki (approval no: 130/2022).

Author's contribution

S.T.: conception and design of the study, writing of the article; Z.U.: data analysis and interpretation; S.E.: data analysis and interpretation; S.I.: acquisition of clinical data; Z.K.: acquisition of clinical data; Z.O.: acquisition of clinical data; M.K.: acquisition of clinical data; M.A.K.: data analysis and interpretation; A.I.: data analysis and interpretation.

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Conflict of interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Supplementary material

None.

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