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Research Article

Treatment Approach for Muscle-Invasive Bladder Cancer: Real-Life Data From a Single Center

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Abstract

Objectives: We aimed to reveal the treatments of patients with muscle-invasive bladder cancer and the results of treatments in our center. We also evaluated factors affecting progression-free survival and overall survival.

Methods: The patients are divided into 5 categories based on the treatment types: (i) only surgery, (ii) surgery + adjuvant chemotherapy, (iii) neoadjuvant chemotherapy + surgery, (iv) neoadjuvant chemotherapy + chemoradiotherapy, (v) definitive chemoradiotherapy.

Results: A total of 118 patients were included in this study. 3-year progression-free survival rate was 34% in only surgery group (n=42), 53% in surgery + adjuvant chemotherapy (n=40), 45% in neoadjuvant chemotherapy + surgery (n=8), 0% in neoadjuvant chemotherapy + chemoradiotherapy (n=6) and 26% in definitive chemoradiotherapy (n=21). 5-year survival rate was respectively 31%, 44%, 53%, 25%, and 19% in these groups. ECOG performance status of 1-3, pathological T stage 3-4, surgical margin positivity, and not receiving adjuvant chemotherapy were independent risk factors for disease progression. Pathological T stage 3-4 (HR:8.2 CI 2.4-27.4, p<0.01) and receiving incomplete chemotherapy (HR:3.9 CI 1.9-8, p<0.01) in adjuvant/neoadjuvant setting were independent risk factors for mortality.

Conclusion: Adjuvant chemotherapy and neoadjuvant chemotherapy were not used sufficiently in muscle-invasive bladder cancer. Surgery + adjuvant chemotherapy showed a survival advantage over only surgery and chemoradiotherapy. The pathological T stage is the best prognostic factor. Receiving complete systemic treatment in an adjuvant / neoadjuvant setting is related to overall survival.

Keywords: Bladder cancer, muscle-invasive, neoadjuvant chemotherapy, survival, treatment

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Bladder cancer (BC) is the ninth most common cancer and is still a serious health problem worldwide. It is three to four times more prevalent in men than in women and usually occurs mainly in the older age group, with a median age at diagnosis of 69 years in men and 71 years in women. [1] Urothelial cancer has been reported as the predominant histologic type in the United States and Europe. A tumor that invades the detrusor muscle is referred to as muscle-invasive bladder cancer (MIBC) and has a higher propensity to spread to lymph nodes and other organs. MIBC represents approximately 20% of newly diagnosed cases of BC, and non-muscle-invasive bladder cancer (NMIBC) accounts

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for approximately 70% of new cases approximately 15% to 20% of NMIBC progress to MIBC.[2]

Radical cystectomy (RC) and pelvic lymph node dissection is the gold standard treatment for MIBC. Despite RC and pelvic lymph node dissection, approximately 50% of patients ultimately develop the disease at distant sites because of disseminated micrometastases. Therefore, systemic therapy in combination with local therapy plays a key role to reduce recurrence rates.[3]

The role of postoperative adjuvant chemotherapy in BC remains unclear. The most comprehensive prospective randomized study conducted so far showed its contribution to progression-free survival (PFS) in patients postoperatively receiving cisplatin-based adjuvant chemotherapy (CT) compared to those receiving CT in recurrence, but this was not reflected in overall survival.[4] A comprehensive retrospective database study demonstrated the benefit of adjuvant CT to overall survival.[5] In light of these data, international guidelines recommend cisplatin-based adjuvant CT for the high-risk group (pathological T3-4 or lymph node +) among bladder cancer patients who do not receive neoadjuvant CT and are operated on.

The overall survival (OS) benefit of neoadjuvant chemotherapy (NAC) was demonstrated in a phase III randomized study and has been the standard of care for MIBC since 2003. NAC including methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and subsequent RC has been demonstrated to provide an OS advantage in locally advanced bladder cancer compared to RC alone.[6] Moreover, other studies have shown that the downstaging achieved with NAC secured a survival benefit in patients with a complete pathological response.[7] Patients who underwent only RC have a 5-year survival rate of 50%, while platinum-based NAC increases this rate by 5-10% in the relevant population and the 5-year survival rate is 80-90% in responders to NAC, which remains at 30-40% in non-responders.[8] Despite the documented survival benefit conferred by neoadjuvant and adjuvant CT, there has been a slow adoption of guideline recommendations for the use of perioperative CT on patients with MIBC.[9]

Since BC is a disease of advanced age, many patients may not be eligible for standard treatments due to poor performance or multiple comorbid diseases. In addition, non-preference for radical cystectomy by the patient is one of the frequently encountered conditions in clinical practice. For these reasons, some patients with MIBC can be given alternative treatments such as definitive chemoradiotherapy (CRT) or non-standard treatments such as only surgery and only radiotherapy (RT).

This study aimed to reveal the treatments of patients with MIBC who were treated in our center and the results of these treatments with survival data. Moreover, it was aimed to evaluate patient and treatment-related factors affecting PFS and OS.

Methods

Patients treated in our clinic between January 2010 and December 2021 for MIBC were retrospectively reviewed. Patient data were obtained from patient files and electronic medical records of the hospital system. The study included patients older than 18 years of age, with a pathologically confirmed diagnosis of bladder cancer. All histological types were included. Patients with clinical stages 2 and 3 were included in this study. Patients with NMIBC and those with metastatic disease were excluded from the study. Additionally, patients with stages 2 and 3 who did not receive any treatment and were lost to follow-up and whose treatment results were unknown were excluded.

Age at diagnosis, number of comorbid diseases, histological features of the tumor, Eastern Cooperative Oncology Group (ECOG) performance status (PS), stage of bladder cancer, history of cancer except for BC, presence of secondary urinary system malignancy, treatments administered including neoadjuvant CT, surgery, adjuvant CT, adjuvant RT, definitive chemoradiotherapy (CRT), and treatment results were recorded. The patients were divided into 5 categories based on their treatment type. These were as follows: (i) those who were only operated on, (ii) those who underwent an operation and received adjuvant CT, (iii) those who received neoadjuvant CT and underwent an operation, and (iv) those who were not operated on but received CRT after receiving neoadjuvant CT, (v) those who received definitive CRT/RT.

Tumor stages were evaluated according to the 8th edition American Joint Committee on Cancer (AJCC) staging manual (2017). Outcomes were recorded as relapsed or not and as survived or dead. PFS was defined as the time from the operation to disease relapse in operated patients, and as the time from the diagnosis of muscle-invasive disease to relapse in patients receiving CRT.

When comparing the patients in terms of survival data as those who received the full dose of systemic CT and those who did not, patients who received a combined (platinum + gemcitabine) regimen of 4 cycles or more in adjuvant or neoadjuvant settings were defined as those who received the full dose of planned systemic CT, while those who received 3 cycles or less were defined as those who did not receive full systemic treatment. Patients who received CRT and those who only underwent surgery were included in the group that did not receive full systemic treatment.

Statistical analysis was performed using SPPS version 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 considered statistically significant.

Results

The data of 176 patients followed up with the diagnosis of bladder cancer between January 2010 and December 2021 were retrospectively analyzed. Forty-eight patients with stage 4 disease at the time of diagnosis were excluded. The remaining 128 patients were those who presented at the muscle invasion stage. Of these, 5 patients were excluded because they did not receive any treatment, including surgery, and 5 patients were excluded because they were lost to follow-up and their results were unknown. The analysis included 118 patients.

The mean age was 66.28±8.67 (range, 41-86), and 56.8% of the patients were 65 years and older. Of the patients, 102 (86.4%) were male and 16 (13.6%) were female. While 37.3% of the whole group did not have comorbid diseases, 26.3% had 1 comorbid disease and 36.4% had 2 or more comorbid diseases. Of the patients, 50% had an ECOG PS of 0, 42.4% had an ECOG PS of 1, 5.1% had an ECOG PS of 2, and 2.5% had an ECOG PS of 3. Ninety-four percent of the patients had a smoking history. Four patients had a history of cancer except for bladder cancer. Of these patients, one had gynecological cancer, two had head and neck cancer, and one had ureteral cancer. The initial clinical stage was 2 in 25% of the patients, while the remaining 75% had stage 3 diseases.

The histological type was urothelial carcinoma in 114 patients (96.6%), squamous cell carcinoma in 2 patients, small cell carcinoma in 1 patient, and bladder carcinosarcoma in 1 patient. In 71.2% of the patients, muscle-invasive disease (pathological T2) was demonstrated by transurethral resection. The other 28.8% of the patients were clinically and radiologically diagnosed with the muscle-invasive disease. The pathological examination confirmed early-stage prostate cancer in 22 (27.5%) of 80 men patients who underwent radical cystoprostatectomy.

Eighty-two (69.5%) of the patients underwent RC + pelvic lymph node dissection without NAC. Forty-two patients (35.6%) did not receive adjuvant CT after surgery, while 40 patients (33.9%) received adjuvant CT. As adjuvant therapy, 87.5% of the patients received a cisplatin + gemcitabine regimen and 12.5% of them received a carboplatin + gemcitabine regimen. The median number of cycles was 4 (range, 1-6). Fifteen patients received NAC. Of these patients, 80% received cisplatin + gemcitabine and 20% received carboplatin + gemcitabine. One of these patients died from urosepsis while receiving NAC. Six patients refused the operation after NAC and underwent CRT. Of the 8 patients who were operated on, 3 (37.5%) achieved pathological complete response (pT0N0), while 5 (62.5%) achieved other bad responses (≥ pT2N0). All 8 patients who were operated on after NAC received cisplatin + gemcitabine. The total number of patients who were operated on was 90. The surgical margin was positive in 10 (11.1%) patients. Twenty-one of the patients, who were not eligible for surgery or did not accept it, received CRT/RT for definitive purposes. The comparison of the patient characteristics and treatment groups is summarized in Table 1.

The median follow-up time in the study was 30 (range, 5.2-144.5) months. At the end of the follow-up period, 69 (58.5%) of the patients developed recurrence, while 49 (41.5%) were in remission. Seventy-two patients (61%) died at the end of the follow-up period. The median OS was 39 months and the median PFS was 26.8 months.

According to the treatment types, the median PFS was 12.1 months in those who only underwent surgery, 15.7 months in those who had NAC + surgery, 12.6 months in those who had NAC+CRT, 10.6 months in those who received definitive CRT/RT, while those who had surgery + adjuvant CT did not achieve the median PFS ($p<0.05$). Three-year PFS rate was 34% in those who only underwent surgery, 53% in those who had surgery +adjuvant CT, 45% in those who had NAC + surgery, 26% in those who received definitive CRT/RT, and 0% in those who had NAC+CRT (Fig. 1a). Pairwise comparisons between groups were shown in Figure 1b.

The OS was 34.4 months in those who only underwent surgery, 53.6 months in those who had surgery + adjuvant CT, 15.3 months in those who received NAC+CRT, 17.6 months in those who received definitive CRT/RT, while those who had NAC + surgery did not achieve the median OS yet ($p=0.02$). The five-year survival rate was respectively 31% in the only surgery group, 44% in the surgery + adjuvant CT group, 25% in the NAC+CRT group, 19% in the CRT/RT group, and 53% in NAC + surgery group (Fig. 2a). Pairwise comparisons between groups were shown in Figure 2b.

Of the patients treated with adjuvant CT, patients receiving

Table 1. Characteristics of patients by the treatment types

Variable	Treatment Type					p
	Only surgery (n=42)	Surgery + Adjuvant CT (n=40)	NAC + surgery (n=8)	NAC + CRT (n=6)	CRT/RT (n=21)	
Age group (year)						
<65	16 (38.1%)	21 (52.5%)	7 (87.5%)	5 (83.3%)	2 (9.5%)	<0.01
≥65	26 (61.9%)	19 (47.5%)	1 (12.5%)	1 (16.7%)	19 (90.5%)	
ECOG PS						
0	21 (50.0%)	23 (57.5%)	8 (100.0%)	4 (66.7%)	3 (14.3%)	<0.01
1-3	21 (50.0%)	17 (42.5%)	0 (0.0%)	2 (33.3%)	18 (85.7%)	
Number of comorbid diseases						
0-1	25 (59.5%)	27 (67.5%)	6 (75.0%)	6 (100.0%)	10 (47.6%)	0.15
≥2	17 (40.5%)	13 (32.5%)	2 (25.0%)	0 (0.0%)	11 (52.4%)	
Pathological T stage*						
pT0	1 (2.4%)	0 (0.0%)	3 (42.9%)			<0.01
pT2	12 (29.3%)	3 (7.5%)	1 (12.5%)			
pT3	17 (41.5%)	27 (67.5%)	4 (50.0%)			
pT4	11 (26.8%)	10 (25.0%)	0 (0.0%)			
Pathological N stage*						
pN0	34 (85.0%)	14 (35%)	6 (75.0%)			<0.01
pN1	1 (2.5%)	10 (25.0%)	2 (25.0%)			
pN2	4 (10.0%)	16 (40.0%)	0 (0.0%)			
pN3	1 (2.5%)	0 (0.0%)	0 (0.0%)			

ECOG: Eastern Cooperative Oncology Group; PS: Performance score; CT: Chemotherapy; RT: Radiotherapy; NAC: Neoadjuvant chemotherapy; CRT: Chemoradiotherapy; p: Pathological; T: Tumor; N: Node; *pT stage and pN stage are given for the only operated patient.

cisplatin + gemcitabine (n=35) could not achieve median PFS, while the median PFS was 10.7 months in patients receiving carboplatin + gemcitabine (n=5) (p<0.01). The OS was 53.6 months in those receiving cisplatin + gemcitabine and 53.8 months in those receiving carboplatin + gemcitabine (p=0.70).

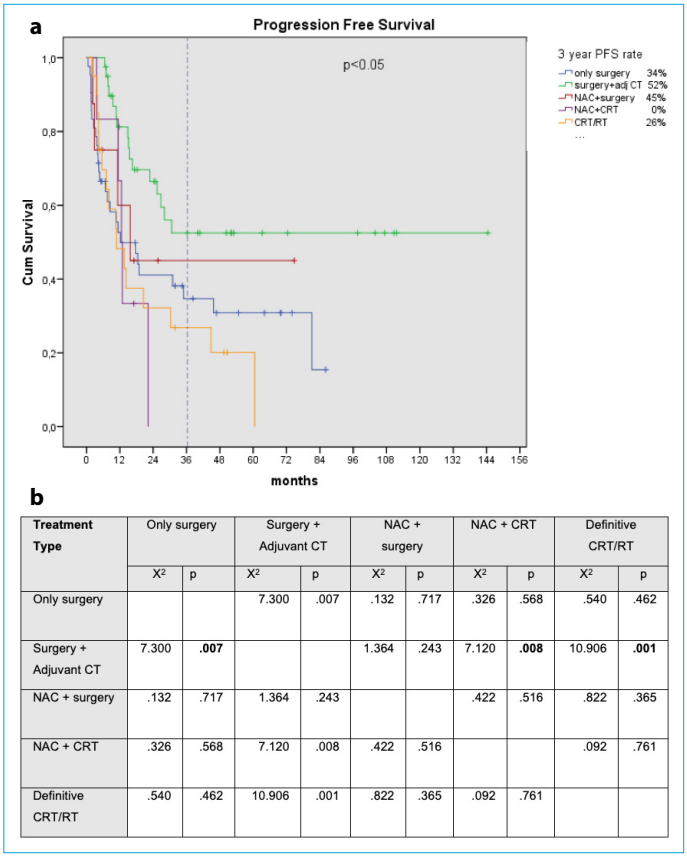
Clinical, pathological, and treatment-related factors affecting PFS and OS were evaluated by univariate and multivariate analyses and presented in Table 2. While an ECOG PS of 1-3, pathological T stage 3-4, surgical margin positivity, and not receiving adjuvant CT were independent risk factors for disease progression, pathological stage 3-4 and receiving incomplete CT in an adjuvant/neoadjuvant setting were independent factors for mortality. The survival chart by the pathological stages of the operated patients is shown in Figure 3.

Discussion

Managing MIBC contains difficulties for clinicians because it is a disease that requires major surgery such as RC and severe treatments such as cisplatin-based CT, but it is also a cancer of geriatric individuals with multiple comorbid diseases. In the present study which we evaluate our approach and results in these patients, the mean age was 66.2 years, 86.4% of the patients were male, 94% of the patients had a history of smoking, and two-thirds of the patients had at least 1 comorbid disease which is in line with the literature.[1-3]

Of the patients, 69.5% underwent surgery as the first treatment without NAC. On the other hand, 17.8% of the patients received definitive CRT/RT. Patients treated with definitive CRT received this treatment because they were not eligible for or did not accept surgery. Moreover, given the characteristics of these patients in Table 1, it is seen that 90.5% of them are over 65 years of age, the rate of patients with an ECOG PS of 0 is only 14.5%, and 52.4% of the patients have 2 or more comorbid diseases. This information reveals the reasons for preferring CRT for patients, which seem reasonable.

Although RC + pelvic lymph node dissection following NAC has been the standard treatment that provides OS advantage and has been reported as a category I recommendation in the guidelines, only 12.7% of the patients were treated with NAC. Such a low rate of preferring NAC was notable. Moreover, considering Table 1, it is seen that the patients selected for NAC are younger, have better perfor-

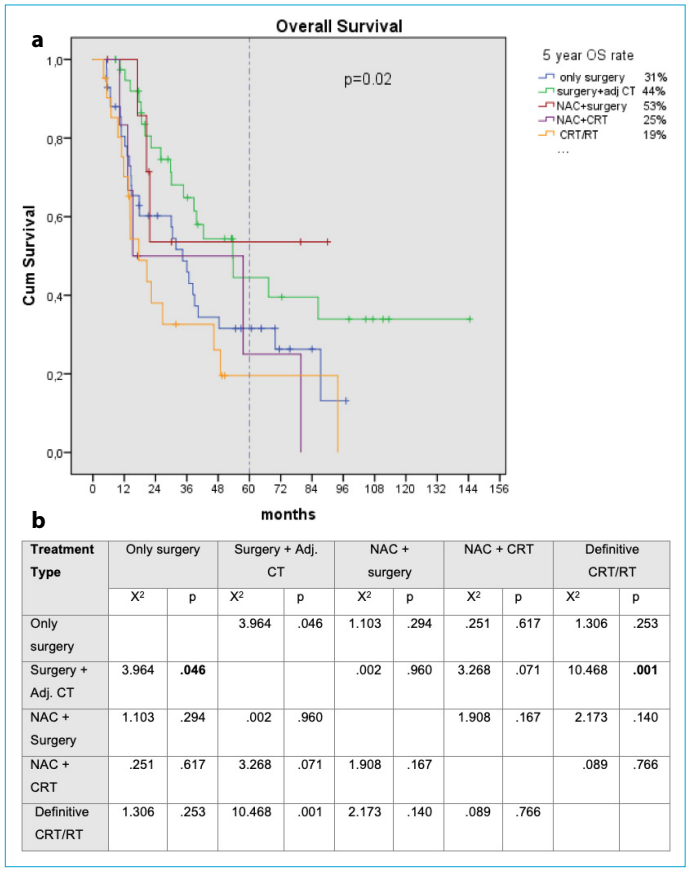


b

Treatment Type	Only surgery		Surgery + Adjuvant CT		NAC + surgery		NAC + CRT		Definitive CRT/RT	
	X^2	p	X^2	p	X^2	p	X^2	p	X^2	p
Only surgery			7.300	.007	.132	.717	.326	.568	.540	.462
Surgery + Adjuvant CT	7.300	**.007**			1.364	.243	7.120	**.008**	10.906	**.001**
NAC + surgery	.132	.717	1.364	.243			.422	.516	.822	.365
NAC + CRT	.326	.568	7.120	.008	.422	.516			.092	.761
Definitive CRT/RT	.540	.462	10.906	.001	.822	.365	.092	.761		

Figure 1. (a) Three-year progression-free survival of treatment groups. **(b)** Pairwise comparisons of treatment groups for PFS.

CT: Chemotherapy; RT: Radiotherapy; CRT: Chemoradiotherapy; NAC: Neoadjuvant chemotherapy.



b

Treatment Type	Only surgery		Surgery + Adj. CT		NAC + surgery		NAC + CRT		Definitive CRT/RT	
	X^2	p	X^2	p	X^2	p	X^2	p	X^2	p
Only surgery			3.964	.046	1.103	.294	.251	.617	1.306	.253
Surgery + Adj. CT	3.964	**.046**			.002	.960	3.268	.071	10.468	**.001**
NAC + Surgery	1.103	.294	.002	.960			1.908	.167	2.173	.140
NAC + CRT	.251	.617	3.268	.071	1.908	.167			.089	.766
Definitive CRT/RT	1.306	.253	10.468	.001	2.173	.140	.089	.766		

Figure 2. (a) Five-year overall survival of treatment groups. **(b)** Pairwise comparisons of treatment groups for OS.

CT: Chemotherapy; RT: Radiotherapy; CRT: Chemoradiotherapy; NAC: Neoadjuvant chemotherapy.

mance status, and have fewer comorbid diseases compared to other treatment groups, with a statistically significant difference in age and PS. This information shows that NAC is avoided for older and more fragile patients. It is known that about 50% of patients with MIBC are ineligible for cisplatin-based NAC because of age-related and/or disease-related risks.[3] Galsky et al. established a consensus definition of cisplatin ineligibility as meeting one of the following criteria: an ECOG PS ≥2, impaired renal function with creatinine clearance ≤60 mg per minute 1.73 m^2, New York Heart Association class III heart failure, grade ≥2 hearing loss, and grade ≥2 neuropathy.[10] Apart from this, it has been shown that clinicians both in the world and in our country avoid NAC due to concerns about intolerance to NAC, delaying surgery which is a curative therapy, or disease progression during NAC, and completely losing the chance of surgery.[9,11] We think that such concerns may have led to the selection of the fittest patients for NAC, resulting in a low patient rate. Furthermore, approximately 30% of the patients in our study were clinically and radiologically diagnosed with muscle-invasive bladder cancer (pT2), while the disease was not pathologically confirmed by transurethral resection (TUR). Considering overtreatment with NAC, surgery may have been preferred in the first place for these

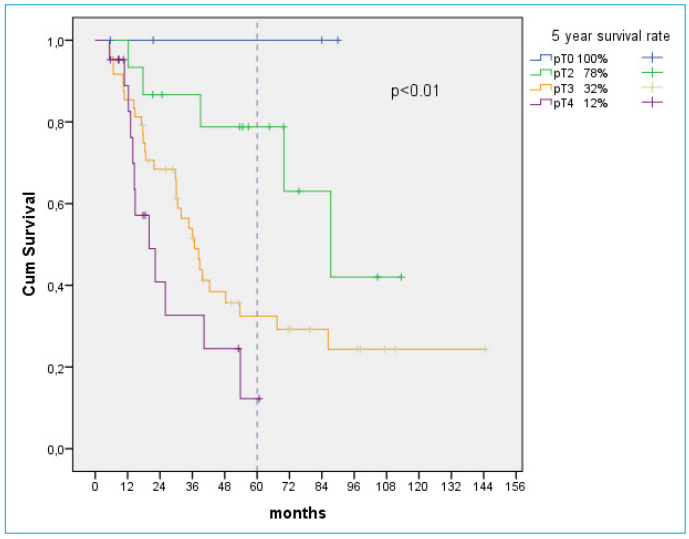


Figure 3. Five-year survival rates of the operated patients by the pathological stages.

Table 2. Univariate and multivariate analysis for PFS and OS

Characteristics	Univariate analysis (PFS)		Multivariate analysis (PFS)		Univariate analysis (OS)		Multivariate analysis (OS)	
	m (95% CI)	p	Adjusted HR (95% CI)	p	m (95% CI)	p	Adjusted HR (95% CI)	p
Age (year)								
<65	25.4 (15.1-35.6)	0.38	36.8 (30.5-43)	0.07				
≥65	15.1 (7.8-22.4)		31.8 (13.3-50.4)					
Comorbid disease								
0-1	22.2 (11.3-33.2)	0.98	34.7 (24.6-44.7)	0.57				
≥2	18.5 (1.1-35.8)		38.7 (14.9-62.6)					
ECOG PS								
0	30.7 (7.1-54.2)	0.03	1.86 (1-3.4)	0.05	53.6 (26.9-80.3)	<0.01		
1-3	14.7 (8.0-20.4)				22.3 (8.7-35.8)			
Cancer history								
No	18.9 (9.27.8)	0.56			36.8 (27.6-45.9)	0.05		
Yes	4.3 (0-30.5)				5.3 (0-35.4)			
Initial stage								
Stage 2	15.7 (7.9-23.4)	0.96			57.6 (8.6-106.5)	0.71		
Stage 3	22.2 (11.5-32.8)				36 (27.5-44.5)			
Surgery								
Yes	26.8 (13.6-40.0)	0.02			39 (31.7-46.3)	<0.01		
No	12.6 (9.2-15.9)				17.6 (7.7-27.4)			
pT stage								
0-2	NR	0.05	3.7 (1.5-9.3)	<0.01	NR	<0.01	8.2 (2.4-27.4)	<0.01
3-4	25.4 (11.6-39.1)				34.7 (26.7-42.6)			
pN								
N -	31 (1.1-60.8)	0.52			40.3 (8.5-72.1)	0.79		
N+	26.8 (12.9-40.7)				39 (204-57.5)			
Surgical margin								
R0	34.9	0.02	2.7 (1.2-6.1)	0.01	42.3 (23.8-60.9)	0.19		
R1	12.1 (0-27.3)				22.2 (0-54.7)			
LVI								
No	45.7	0.75			36 (15.5-56.5)	0.91		
Yes	28 (13.1-42.9)				39 (33.3-44.7)			
PNI								
No	NR	0.26			NR	0.06		
Yes	30.7 (17.9-43.7)				38.7 (33.1-44.4)			
Neoadjuvant CT								
Yes	12.9 (7.6-18.1)	0.46			36.8 (28.2-45.3)	0.78		
No	22.7 (9.9-35.5)				21.8 (0-705)			

Table 2. Univariate and multivariate analysis for PFS and OS

Characteristics	Univariate analysis (PFS)		Multivariate analysis (PFS)		Univariate analysis (OS)		Multivariate analysis (OS)	
	m (95% CI)	p	Adjusted HR (95% CI)	p	m (95% CI)	p	Adjusted HR (95% CI)	p
Adjuvant CT								
No	12.9 (8.6-17.2)	<0.01	3.1 (1.6-5.9)	<0.01	30 (15.7-44.3)	<0.01		
Yes	NR				53.6 (34.5-72.6)			
Full-dose of CT								
Yes	NR	<0.01			NR	<0.01	3.9 (1.9-8)	<0.01
No	12.6 (7.5-17.6)				26.7 (12.9-40.5)			
Adjuvant RT								
No	17.7 (8.3-27)	0.26			36 (26.4-45.6)	0.85		
Yes	26.8 (8.8-44.8)				29.7 (5.7-53.6)			
Definitive CRT/RT								
Yes	12.9 (13.6-40)	0.02			20.6 (10.4-30.9)	0.01		
No	26.8 (9.6-16.2)				38.7 (33-44.4)			

HR: Hazard ratio; CI: Confidence interval; m: month; ECOG: Eastern Cooperative Oncology Group; PFS: Progression-free survival; OS: Overall survival; NR: Not reached; CT: Chemotherapy; RT: Radiotherapy; CRT: Chemoradiotherapy; LVI: Lymphovascular invasion; PNI: Perineural invasion; T: Tumor; N: Node.

patients. However, it should be stated that concerns about avoidance of NAC have decreased over time and the rates of NAC for bladder cancer tend to rise, which seems to have increased from 10% to 35% over the years.[9,12]

In our study, 1 of 15 patients who were treated with NAC died from urosepsis during NAC. Six patients refused surgery after receiving NAC and underwent CRT. For 8 patients who underwent surgery, the pathological complete response rate was 37.5%, and although the number of patients was low, these results were similar to those reported by the reference studies.[6,13] Of the 15 patients treated with NAC in our study, 80% received cisplatin + gemcitabine and 20% received carboplatin+ gemcitabine. All 8 patients who were operated on after NAC received cisplatin + gemcitabine. In the reference studies, patients received methotrexate, vinblastine, doxorubicin, cisplatin (MVAC), and dose-dense (dd) MVAC. According to data from retrospective studies and current meta-analyses, it is known that cisplatin + gemcitabine has similar efficacy with MVAC in a neoadjuvant setting.[14] However, the initial results of the study comparing ddMVAC and gemcitabine + cisplatin in a neoadjuvant setting showed that the PCR rates were higher in patients receiving ddMVAC compared with those receiving GC (42% vs. 36%; p=0.02). Both regimes are recommended in the current guidelines. Carboplatin + gemcitabine is a less effective treatment (pathological CR 20-30%) and is not recommended for neoadjuvant therapy.[3,16]

The evaluation of PFS by the 5 treatment categories revealed the success ranking (according to the 3-year PFR rate) as follows: surgery + adjuvant CT, NAC + surgery, only surgery, CRT, NAC + CRT (Fig. 1a, $p<0.05$). The pairwise comparisons showed that the significance was due to the difference between the surgery + adj CT group and other groups except for the NAC + surgery group (Fig. 1b). In other words, there was no significant difference in the PFS of the patients who underwent NAC and adjuvant CT together with surgery. So far, there has been no conducted study comparing these two treatment modalities. Considering the demonstrated survival contribution of NAC and studies on adjuvant CT that are not clear enough, it does not seem reasonable to make this comparison. However, we believe that this data is valuable in terms of demonstrating the significance of adjuvant CT in bladder cancer. The difference between the NAC + surgery group and other groups was not significant. This was attributed to the low number of patients.

Given the success ranking by median OS, which is a more valuable endpoint than PFS, it is seen that NAC + surgery ranks first with the median OS that has not yet been achieved. This is followed by surgery + adjuvant CT with a

median OS of 53.6 months. Those who only underwent surgery had a median OS of 34.4 months, those who received CRT had an OS of 17.6 months, and those who received NAC+CRT had an OS of 15.3 months (Fig. 2a, p=0.02). Moreover, given the pairwise comparisons, it is seen that the superiority of surgery + adjuvant CT over surgery alone and the superiority of surgery + adjuvant CT over CRT are significant (Fig. 2b). We think that the survival advantage in patients who underwent NAC + surgery cannot be shown statistically due to a small number of cases.

An evident superiority of patients who received adjuvant CT after surgery in both PFS and OS compared to patients who did not receive adjuvant CT is important to emphasize the significance of adjuvant therapy. In our study, 40 of 82 patients who underwent surgery initially received adjuvant CT, while 42 of them did not. As expected, LN positivity was statistically significantly higher (65% vs. 15%) in the adjuvant CT group. The rate of pT3 was also higher in this group. The rate of pT2 was higher in those who did not receive CT, while the rates of pT4 were similar (Table 1). Nevertheless, considering the patients who did not receive adjuvant CT, we see that approximately 70% of them were patients with pT3 and pT4 and were patients with an indication for adjuvant CT. The reasons for not administering CT to these patients may be poor performance, advanced age, comorbid diseases, and patient preference. Nonetheless, although the group receiving adjuvant CT had a higher risk, the significant PFS [12.9 months vs not reached (NR)] and OS (30 vs 53.6 months) benefit in this group show the value of adjuvant CT. In addition, 5 of the patients treated with adjuvant CT received carboplatin + gemcitabine, an inferior treatment that is no longer recommended in an adjuvant setting. The median PFS was not achieved in the cisplatin + gemcitabine group (n=35), while it was 10.7 months in the carboplatin + gemcitabine group (n=5) (p<0.01). The OS was 53.6 months in those receiving cisplatin + gemcitabine and 53.8 months in those receiving carboplatin + gemcitabine (p=0.70). Possibly, if the number of patients was higher, this difference could also be reflected in OS.

For patients who are not eligible candidates for RC or who want to preserve their natural bladder, trimodal therapy (TMT), which includes maximal transurethral resection of the bladder tumor (TURBT) followed by RT with simultaneous CT, is an appropriate alternative and is recommended in the current guidelines.[17] In our study, 17.8% of the patients underwent definitive CRT or RT, which constituted the oldest and most fragile patient group. Both PFS and OS results of these patients were found to be worse than the other groups. The results of studies comparing TMT with RC in the literature are contradictory.[18,19] Based on our data, we demonstrated a serious survival disadvantage even compared to those who only underwent surgery. However, other than treatment differences, this disadvantage may be because patients receiving CRT are much older, have low performance, and have more comorbid diseases than patients who underwent surgery.

Another notable point in the study was that the patient group who did not accept surgery after receiving NAC and received CRT had similar PFS (12.6 and 10.6 months) and OS (15.3 and 17.6 months) to the patients receiving CRT. This shows that NAC before CRT has no additional benefit. Therefore the treatment plan should be discussed in detail with patients scheduled for NAC and the plan should be clarified at the beginning. The meta-analysis of 30,293 patients by Fahmi et al. reported comparable survival results for TMT and RC. Some of the patients in the study received NAC, and NAC showed survival benefits in patients who underwent RC. For those who underwent TMT, the mean 5-year OS was 58.3% in 370 patients who received NAC plus TMT and 50.4% in 2,281 patients who were treated with TMT only (p=0.078). The mean 5-year disease-specific survival was 72.4% in 217 patients treated with NAC plus TMT compared to 62.2% in 1,639 patients treated with TMT only (p=0.13). The statistically significant contribution of NAC+TMT could not be demonstrated.[20]

In our study, the effect of complete treatment on survival in an adjuvant or neoadjuvant setting was also examined. There was no relevant data in the literature; however, in a study, discontinuation of treatment was shown to be associated with mortality in patients undergoing TMT.[21] The number of cycles, which is standard in both adjuvant and neoadjuvant settings is four. In our study, at least 4 cycles of platinum + gemcitabine every 21 days were evaluated as receiving a full dose of treatment. Some of our patients, who were lymph node-positive, received 6 cycles of CT in an adjuvant setting. The reason for this was that lymph node positivity was considered stage 4 according to the old staging system. We demonstrated a significant difference in both PSF (NR vs 12.6 months) and OS (NR vs 27.6 months) in the comparison of patients who received 4-6 cycles of CT with those who received 3 cycles and less, or those who did not receive CT at all. Both median PFS and median OS were not yet achieved in patients receiving full-dose treatment, and this difference was very striking. The patients who receive incomplete treatment may have a worse survival with low PS and comorbid diseases that cause receive incomplete treatment. However, in multivariate analysis receiving incomplete systemic treatment was found to be an independent risk factor for mortality. This data showed us clearly the significance of completing the CT protocol in both adjuvant and neoadjuvant settings.

While the results of our study showed an ECOG PS ≥1, pathological T stage 3-4, surgical margin positivity, and not receiving adjuvant CT as independent risk factors for disease progression, pathological stage 3-4 and receiving incomplete CT in an adjuvant/neoadjuvant setting were found to be independent factors for mortality (Table 2). As is seen in Figure 3, the pathological T stage appears to be the most determinant prognostic factor in MIBC. Because none of our patients with pathological stage 0 died. We found that patients with a pathological stage of 3-4 had 8.2 times higher risk of mortality compared to those with pT 0-2 ($p<0.01$). This result emphasizes the significance of achieving a pathological complete response in BC and therefore administering a neoadjuvant treatment.

After demonstrating the effectiveness of immunotherapy (IO) in metastatic bladder cancer, IO was also investigated in the treatment of MIBC. For patients with high-risk (ypT2-4 or positive lymph node) muscle-invasive urothelial carcinoma who had undergone radical surgery, disease-free survival was longer with adjuvant nivolumab than with placebo in the intention-to-treat population.[22] But the patients in the present study did not receive IO due to this agent not being covered by the social healthcare system in our country. In addition, these data are quite new and our study includes patients in the last 12 years. Better results can be obtained in MIBC if IO agents are available.

The limitations of our study were being retrospectively designed and the low number of cases, especially the patients who receive NAC. The strong aspect of the study was to present real-life data and compare treatment methods.

Conclusion

In the present study, we demonstrated that adjuvant CT and especially NAC were not used sufficiently in MIBC despite the current guideline recommendations. Surgery + adjuvant CT showed a survival advantage over those who underwent only surgery and received CRT. While an ECOG PS≥1, pathological T stage 3-4, surgical margin positivity, and not receiving adjuvant CT were independent risk factors for disease progression; pathological stage 3-4 and receiving incomplete CT in an adjuvant/neoadjuvant setting were found to be independent factors for mortality.

Disclosures

Ethics Committee Approval: The Institutional Review Board of Haydarpasa Numune Training and Research Hospital approved the study (Number: 2022/33).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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