Original Article

Oncological outcomes of neoadjuvant chemotherapy in muscle-invasive bladder cancer in Rajavithi Hospital

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Abstract

Objective: Neoadjuvant chemotherapy (NAC) can provide better survival benefits than radical cystectomy (RC) alone in patients with muscle-invasive bladder cancer (MIBC). At Rajavithi Hospital neoadjuvant chemotherapy has been used with some patients diagnosed with MIBC and in this study the oncologic outcomes have been evaluated. The precise objectives of this study are to assess the outcomes, overall survival, and factors which show a correlation with a downstaging of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer before radical cystectomy at Rajavithi Hospital.

Materials and Methods: This is a single-center, retrospective case control study conducted at this large public hospital in Thailand. Forty patients (31 males, 9 females) were enrolled onto the study and had been diagnosed with MIBC. All had received neoadjuvant chemotherapy before undergoing radical cystectomy from January 2012 to December 2020. The primary endpoint was to assess the pathologic complete response (pCR) rate in MIBC after treatment with neoadjuvant chemotherapy. The secondary endpoints were overall survival (OS), tumor downstaging, and factors correlated with downstaging following NAC.

Results: The overall complete response rate for all patients was 7.50%. Tumor downstaging occurred in 47.50% of patients, upstaging in 22.50%, and no change in 30.00%. At a median follow-up period of 35 months, the overall survival (OS) rate was 52.80%.

Conclusion: The complete response rate and overall survival were lower than those reported in previous studies. This may be due to the primary regimen being gemcitabine and carboplatin rather than one of the other pharmaceutical combinations, and also patients not completing the full course of neoadjuvant chemotherapy. We found a correlation between non-response and chronic kidney disease (CKD), positive lymphovascular invasion (LVI), and positive pelvic lymph nodes. A correlation between non-response and mortality was also found.

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Introduction

Radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer (MIBC). However, surgery alone is associated with suboptimal disease control and survival, partly due to micrometastases. Approximately 30.00% of patients treated with surgery alone experience disease recurrence. Due to the positive improvement in overall survival in randomized trials, cisplatin-based combination chemotherapy administered before cystectomy is recommended for patients with MIBC who are eligible to receive cisplatin.[1,2]

The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have published guidelines recommending the use of neoadjuvant chemotherapy (NAC) before RC. These guidelines are rooted in meta-analyses which indicated a significant 5.00% absolute survival benefit in favor of NAC with cisplatin-based combination chemotherapy.[3-5]

Although cisplatin-based chemotherapy is effective, its nephrotoxic properties make it unsuitable for patients with renal dysfunction. It has been reported that carboplatin-containing chemotherapy has a potential role in advanced bladder cancer patients with renal impairment as carboplatin is an alkylating anti-cancer agent which is less nephrotoxic than cisplatin.[6-8] Despite these promising results, NAC remains underused worldwide. The reasons most frequently reported for this underuse include a potential delay to definitive surgery and associated toxicity.[9-10]

A previous study in Thailand showed that a group of patients treated with neoadjuvant chemotherapy had longer survival than those treated with adjuvant chemotherapy.[11]

This study analyzed patients at Rajavithi Hospital diagnosed with MIBC and treated with NAC followed by RC. At this center the neoadjuvant treatment regimen consists of three options: gemcitabine/carboplatin, gemcitabine/cisplatin, and paclitaxel. The primary objective of this study was to describe the oncologic outcomes of NAC in a neoadjuvant setting for MIBC at Rajavithi Hospital.

Materials and Methods

This is a single-center, retrospective case-controlled study. Patients included in the study had measurable and histologically proven, predominantly urothelial, muscle-invasive bladder cancer (cT2-T4, N any, M0) and had received neoadjuvant chemotherapy (regimens: gemcitabine/carboplatin, gemcitabine/cisplatin, or paclitaxel) followed by RC at Rajavithi Hospital between January 1, 2012, and December 31, 2020.

Institutional research ethics board approval was obtained prior to data collection (IRB number: 64254). Patients were excluded from the study if the pathology was not urothelial carcinoma or if there was missing data.

The primary endpoint of the study was the pathologic complete response rate (tumor downstaging to pT0 from any cT stage) after neoadjuvant chemotherapy at the time of cystectomy. The initial clinical stage and nodal status at diagnosis were assessed using computerized tomography (CT) scans and pathology after transurethral resection of the bladder tumor (TURBT). Data pertinent to the pathological stage at the time of cystectomy was also collected. The protocol for neoadjuvant chemotherapy was determined based on the advice from the medical oncologist after the urologist decided to transfer patients for NAC.

Secondary endpoints included tumor downstaging (downstage from initial clinical stage), tumor downstaging <T2, tumor non-response (tumor upstage from initial clinical stage or no change in stage), overall survival, and factors related to tumor downstaging (age, underlying conditions such as diabetes mellitus (DM), Hypertension (HT), chronic kidney disease (CKD), regimen, number of NAC cycles, body mass index (BMI), nodal status, performance status (ECOG), smoking history, and lymphovascular invasion (LVI).

Tumor downstaging was defined as a pathological T stage (ypT) at the time of cystectomy that was lower than the initial clinical T stage (cT. Tumor non-response was defined as a more invasive stage of disease or no change in the clinical T stage. Pathologic N stage (ypN) positive at the time of cystectomy was considered non-response for patients with an initial clinical stage of N0. Overall survival was assessed based on the updated patient data available in the medical records at the conclusion of the study.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences v.26.0

(SPSS Inc, Chicago, IL, USA). The percentage, mean, mode, and standard deviation (SD) were used for descriptive data. Comparisons between the two groups were carried out using the Student's T-test, Mann-Whitney U test, Chi-square test, and Fisher's Exact test. Overall survival (OS) was analyzed using the log-rank test to compare OS. For all statistical tests, a p-value of less than 0.05 was considered to indicate a significant difference.

Results

A total of 484 patients underwent radical cystectomy. Of these, 42 patients received neoadjuvant chemotherapy before the procedure. Two patients were excluded due to pathology that was not urothelial carcinoma: one had adenocarcinoma, and one had small cell carcinoma (Fig. 1).

Of the 40 patients included, 30 received NAC at Rajavithi Hospital, and 10 received it from other hospitals. The mean age was 65 years (range: 50 to 85), and 77.50% were male. Sixty percent of the patients received fewer than 3 cycles of NAC and did not complete the full course because surgery was scheduled. Baseline characteristics are listed in Table 1.

Overall, the pathological complete response rate to pT0 was 7.50% (n = 3). Tumor downstaging occurred in 47.50% of patients (n = 19). Tumor downstaging to < pT2 was 22.50%. Tumor upstaging at cystectomy compared to before NAC occurred in 22.50% of patients (n = 9). Twelve patients (30.00%) had no change in their staging following chemotherapy at the time of cystectomy. Overall, the non-response rate was 52.50% (n = 21), (Table 2).

The secondary endpoint, overall patient survival rates were 87.20%, 52.80%, and 39.60% at 12, 35, and 49 months, respectively (Fig. 2).

When the subgroup analysis was performed, overall survival was compared between the downstaging and non-response groups. The overall survival rates at 17 months were 88.90% for the downstaging group and 57.10% for the non-response group. A statistically significant difference was found in the survival curves (Fig. 3).

The overall median follow-up time was 27.6 months. The median follow-up times were 30.47 months in the downstaging group and 25 months in the non-response group.

The comparisons between the downstaging group and non-response group with regard to other factors (age, DM, HT, CKD, regimen, number of cycles of NAC, BMI, ECOG, and smoking history) did not show any statistically significant differences. However, we found that CKD, nodal status, and LVI were significantly associated with the non-response group and showed a correlation with a higher mortality rate (Table 3.).

Complications occurred during NAC in two patients: one had neutropenia and the other had anemia. Both patients had received the gemcitabine and carboplatin regimen.

A total of 18 patients died in this study, with the majority of deaths (15 patients) attributed to bladder cancer.

After neoadjuvant chemotherapy followed by radical cystectomy, most patients received

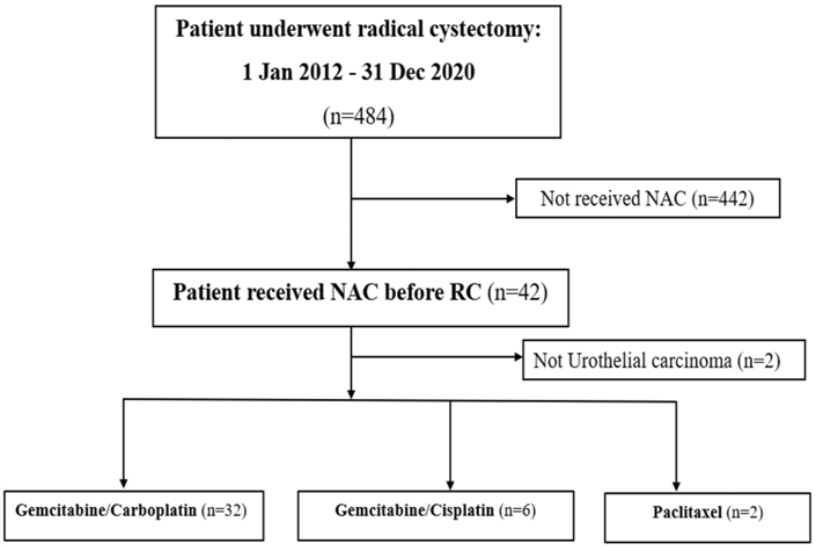

Figure 1. Study cohort selection process

Table 1. Baseline characteristics

Factors	n (%)
Age (years) Mean±SD	65.30±8.71
BMI (kg/m^2) Mean±SD	22.83±5.33
GFR (120 ml/min/1.73m^2) Mean±SD	67.60±26.19
Gender	
Male	
Female	
Smoking history	31 (77.50)
ECOG	
0	
1	
2	
Diabetes mellitus	12 (30.00)
Chronic kidney disease (GFR <40 ml/min/1.73m^2)	17 (42.50)
Hypertension	18 (45.00)
Clinical T stage	
T2	13 (32.50)
T3	20 (50.00)
T4	7 (17.50)
M stage	
M0	40 (100.00)
High grade of pathology	37 (92.50)
Lymphovascular invasion (positive)	21 (52.50)
Positive pelvic nodes at time of surgery	11 (27.50)
Place patients received NAC	
Rajavithi Hospital	30 (75.00)
Other hospitals	10 (25.00)
Regimen NAC	
Gemcitabine/carboplatin	32 (80.00)
Gemcitabine/cisplatin	6 (15.00)
Paclitaxel	2 (5.00)
Cycles of NAC	
≤3	24 (60.00)
>3	16 (40.00)

SD = standard deviation, GFR = glomerular filtration rate, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, BMI = body mass index

adjuvant chemotherapy, while others received chemoradiotherapy or no adjuvant treatment. Distributions are shown in Figure 2.

Discussion

The results of this retrospective analysis pertinent to neoadjuvant chemotherapy at Rajavithi Hospital showed an overall pathological complete response (pCR) rate to pT0 of 7.50%, which is lower than that reported in previous studies. Meleis et al[12] reported a pCR rate of 14.00% in

Table 2. Tumor upstaging, downstaging and nonresponse

Factors	n (%)
Overall tumor downstaging	19 (47.50)
Pathologic complete response rate	3 (7.50)
Gemcitabine/carboplatin	1 (2.50)
Gemcitabine/cisplatin	2 (5.00)
Paclitaxel	0 (0.00)
Down staging < pT2	9 (22.50)
Gemcitabine/carboplatin	8 (20.00)
Gemcitabine/cisplatin	1 (2.50)
Paclitaxel	0 (0.00)
Tumor downstaging to T2 (cT3-4 to pT2)	7 (17.50)
Overall tumor non-response	21 (52.50)
No change	12 (30.00)
Upstaging	9 (22.50)
- cT2 to pT3-4	3 (7.50)
- cT3 to pT4	6 (15.00)

MIBC patients who received four cycles of neoadjuvant gemcitabine and cisplatin. Peyton et al[13] reported a pCR of 9.40% in MIBC patients who received a mean regimen of 4.4 cycles of gemcitabine and carboplatin.

However, the pCR in this study was higher than the pCR observed in patients who underwent radical cystectomy alone (2.70%), similar results to those reported by Murasawa et al[14]

There was a comparable response rate between our analysis and prior studies using gemcitabine and carboplatin for NAC. Murasawa et al[14] reported a downstaging to <pT2 after the completion of 2 cycles of NAC of 24.50%. In our study, downstaging to <pT2 was 22.50%.

As is practice at our hospital, patients received various regimens and cycles of NAC before surgery. The main regimen in this study was gemcitabine and carboplatin, which showed a lower outcome compared to cisplatin-based NAC. Additionally, the majority of the population in previous studies had tumors at pT2, whereas in this study, most patients had tumors classified as pT3. Therefore, the pCR and downstaging rates in this study are lower than those reported in other studies.

Regarding overall survival, Lee et al[15] reported a 3 year overall survival (OS) of 89.00% of patients who had received 3 complete cycles of gemcitabine and cisplatin before radical cystectomy. Koie et al[16] reported a 41-month OS of 89.70% in patients who received gemcitabine and

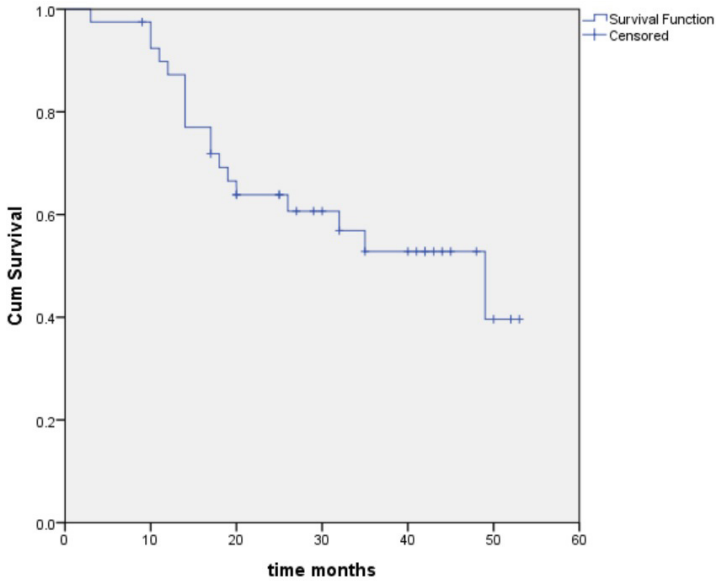

Figure 2. Overall survival

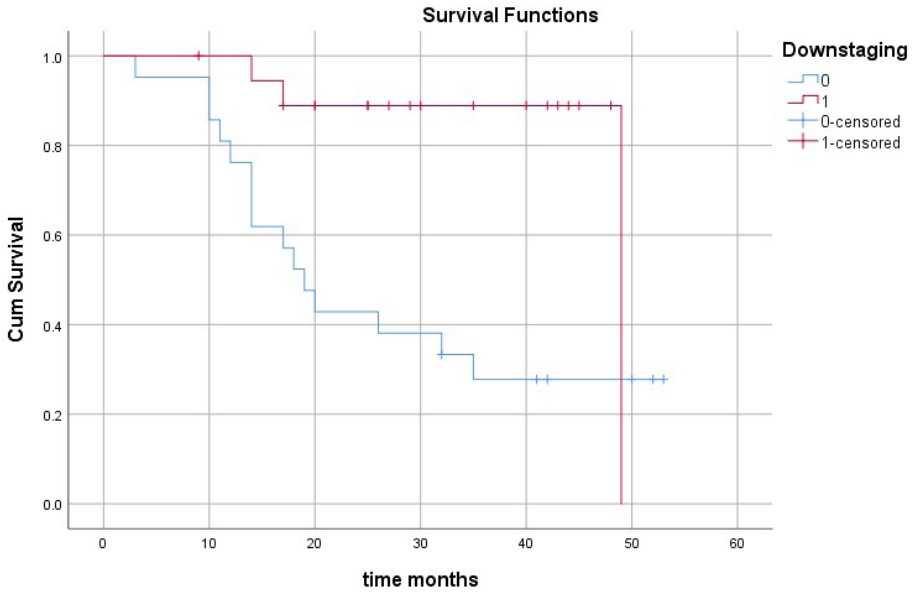

Figure 3. Overall survival between the response group (red) and non-response (blue)

carboplatin. In this study, the overall survival rates were 87.20%, 52.80%, and 39.60% at 12, 35, and 49 months, respectively. These rates are lower than those reported in previous studies[1,14,16,18]. The results could potentially be due to disease staging, regimen, and the number cycles of NAC. However, the overall survival in this study does not solely reflect the effect of NAC, as 60.00% of patients received adjuvant therapy.

When comparing patients between the response and non-response groups, we found that CKD, LVI, and nodal status showed a statistically significant correlation with the non-response group, and non-response was associated with a higher death rate. These findings are similar to those in previous studies.[16,17]

Our study has several limitations. The retrospective nature, the lack of randomization, and the absence of centralized radiology and pathology reviews may affect our results, and the rate of complete TUR-BT was not recorded. The use of clinical staging could be associated with understaging or overstaging. In future studies information regarding the rationale behind the choice of NAC regimen, and more detailed data regarding NAC administered to patients who received it at another hospital before being referred to our hospital for surgery could be included to add

Table 3. Correlation between factors and downstaging of tumor

	Down Staging n	Non-Response (no change + upstaging) n	OR (95%CI)	P-value
Age (years) Mean±SD	63.79±9.914	66.67±7.432	0.99 (0.91-1.08)	0.303
BMI (kg/m^2) Mean±SD	21.63±6.020	23.90±4.482	0.91 (0.78-1.06)	0.892
Smoking history	15	16	1.26 (0.22-7.22)	0.698
ECOG			0.23 (0.06-0.84)	0.051
0	11	5		
1	8	15		
2	0	1		
Diabetes mellitus	7	5	1.37 (0.29-7.26)	0.369
Hypertension	8	10	0.70 (0.16-3.16)	0.726
Chronic kidney disease (GFR <40 ml/min/ 1.73m^2)	5	12	0.38 (0.09-1.59)	0.049*
LVI	5	16	0.11 (0.02-0.78)	0.002*
Regimen NAC			7.39 (0.47-115.39)	0.075
Gemcitabine/carboplatin	14	18		
Gemcitabine/cisplatin	5	1		
Paclitaxel	0	2		
Cycle of NAC			3.38 (0.40-28.81)	0.366
≤3	24			
>3	16			
Grade of pathology (high grade)	16	21	-	0.098
Nodal status (positive pelvic lymph node)	0	11	-	<0.001*

SD = standard deviation, GFR = glomerular filtration rate, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, OR = odd ratio, BMI = body mass index, LVI = lymphovascular invasion

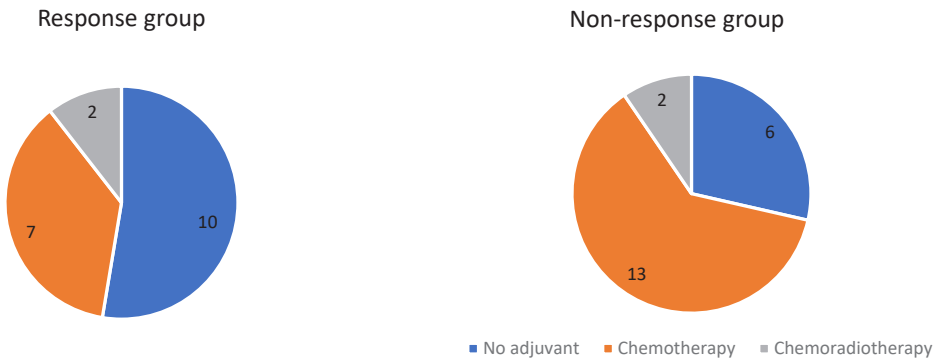

Figure 4. Adjuvant treatment

to the findings. Although treatment allocation was mostly driven by institutional preferences, selection bias cannot be confidently excluded. We were unable to assess the outcomes of patients who received NAC but did not undergo radical cystectomy due to disease progression. The relatively small number of patients enrolled in our study and the short follow-up period are additional limitations.

Conclusion

In this study, the complete response rate, response rate, and overall survival were lower than those in previous studies but higher than those observed associated with radical cystectomy alone. This may be due to the main regimen being gemcitabine and carboplatin, rather than the cisplatin-based NAC included in previous studies. Some patients did not complete the full

program of cycles of neoadjuvant chemotherapy which may have impacted response rate. Correlations between non-response and CKD, positive LVI, and positive pelvic lymph nodes were also found. There was also a correlation between non-response and a higher mortality rate. Further studies should be prospective, include the rate of complete TURBT, have longer follow-up periods, and protocols should be put in place for the completion of the full number of cycles of NAC before surgery.

Conflict of Interest

The authors declare no conflict of interest.

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