

RESEARCH ARTICLE

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Neoadjuvant versus Adjuvant Chemotherapy in Patients with Resectable Muscle-Invasive Bladder Cancer

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Abstract

Introduction: In regards to resectable muscle-invasive bladder cancer (MIBC) patients, contemporary guidelines recommend treatment with radical cystectomy and perioperative chemotherapy (neoadjuvant or adjuvant). In addition, the 5-year survival rate ranges from 36% to 48% in connection to T3 or T4 staged tumors or lymph node metastatic tumors. Perioperative treatment can improve overall survival, and the most robust evidence are in favor of neoadjuvant chemotherapy. The purpose of this study was to assess the impact of perioperative chemotherapy on the survival of patients with muscle-invasive bladder cancer (MIBC) who underwent radical cystectomy (RC). **Methods:** The medical records of ninety-four patients with muscle-invasive bladder cancer (MIBC) that were treated with radical cystectomy and perioperative chemotherapy from 2008 to 2018 were retrospectively analyzed at Songklanagarind hospital. Neoadjuvant and adjuvant chemotherapy groups were classified. Univariable and multivariable regression analyses were used to predict overall survival (OS) after treatment. The survival rates for each group were estimated and compared using long-rank testing. **Results:** Overall, we identified 94 eligible patients of whom 20 patients (21.2%) received neoadjuvant and 74 patients (78.8%) received adjuvant chemotherapy. The 5-year survival rate of the neoadjuvant group was 55.7%, and in regards to the adjuvant group it was 30.4%. A multivariable analysis yielded that, patients treated with neoadjuvant chemotherapy had longer survival than those treated with adjuvant chemotherapy ($p=0.039$). The median survival here as log rank compares median survival. **Conclusion:** The overall survival of neoadjuvant chemotherapy (NAC) was better than adjuvant chemotherapy (AC) in regards to muscle-invasive bladder cancer. These data could support the use of neoadjuvant chemotherapy in MIBC prior to radical cystectomy.

Keywords: Neoadjuvant chemotherapy- radical cystectomy- adjuvant chemotherapy- overall survival

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Introduction

Bladder cancer is one of the most common malignancies of the urinary tract, with an estimated 80,470 new diagnoses during the year 2019 in the USA (Seigel et al., 2019). In 2020, it was reported in Thailand that 5,021 new cases of bladder cancer were diagnosed (Bejrananda et al., 2017). Especially, muscle-invasive bladder cancer (MIBC) was known as an aggressive disease with developed metastasis and increased risk of mortality. Currently, the mainstay treatment for localized and locally advanced bladder cancer, is radical cystectomy. Furthermore, when chemotherapy is not used then the 5-year cancer-specific survival for patients with clinical T1, T2, T3, and T4 is at 89%, 32%, 30%, and 11.6%, respectively. Patients with lymph node metastasis have a 5-year survival rate of 12.9% (Kim et al., 2017). The use of perioperative chemotherapy significantly improves survival, particularly when there is a high risk of developing recurrent disease (Grossman et al., 2003; Keegan et al., 2014). Although there is evidence that neoadjuvant chemotherapy (NAC)

improves survival rates in connection to MIBC (Keegan et al.; Fedeli et al., 2011), there have been restrictions to its administration.

The benefit of neoadjuvant chemotherapy reduces the release and implantation of malignant cells while radical cystectomy can eradicate the micrometastasis. A National Cancer Data Base analysis yielded that only 16% of MIBC patients received NAC before radical cystectomy (Zaid et al., 2014). The limitation of NAC in routine practice might be due to toxicity concerns and delays in regards to curative-intent surgery. Nevertheless, the management of MIBC remains a subject of debate with an ongoing controversy in connection to overusing NAC or adjuvant chemotherapy (AC) in combination with radical cystectomy. Moreover, the variety of adjuvant checkpoint inhibitors in muscle-invasive urothelial carcinoma provide (Bellmunt et al., 2021; Rizzo et al., 2022).

We aimed to analyze the outcome of NAC and AC treatment is regards to radical cystectomy patients and to examine factors associated with overall survival. Understanding demographic and clinical factors

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associated with its use will help develop strategies to improve survival in patients with muscle-invasive bladder cancer.

Methods and Materials

Study population

This was a retrospective study. We enrolled 94 MIBC patients who underwent radical cystectomy (RC) and received perioperative chemotherapy (NAC or AC) at Songklanagarind hospital from July 2008 to June 2018. We excluded patients with non-muscle invasive disease and those with a concomitant diagnosis of a nonurothelial malignancy, including prostate cancer, if diagnosed before cystectomy as this could potentially impact treatment selection and survival.

Study outcomes

The main objective outcome of the study was to explore the overall survival rate of patients who underwent radical cystectomy with perioperative chemotherapy. The main treatment was categorized as neoadjuvant chemotherapy (NAC), received chemotherapy before radical cystectomy within 6 months; and adjuvant chemotherapy (AC), received chemotherapy after radical cystectomy within 4 months. The chemotherapy regimen in both treatments was gemcitabine plus cisplatin. After surgery, patients underwent a follow-up protocol including a CT abdomen /pelvis with intravenous contrast, and pathologic identification included tumor grade and stage based on the American Joint Committee on Cancer, 6th edition.

Statistical analysis

All patients were classified into 2 groups: radical cystectomy treatment with neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC). Variables collected included patient demographics, clinical-stage, pathological features, and oncological outcomes.

Means and medians were used for continuous variables. Proportions and frequencies were used for categorical variables. For variables with non-normal distribution, data was reported as the median and interquartile range (IQR). Means were compared by using a 'Student's T-test'. Proportions were compared by using Chi-squared tests including continuity correction in regards to Fisher's exact test, as and when appropriate. For variables with non-normal distribution, the Mann-Whitney U test and the Kruskal-Wallis test were used for comparisons in connection to two groups or more than three groups, respectively. In regards to univariable analysis, focusing on the examined factors associated with survival in regards to each factor, and in connection to the multivariable model examining the association of patient factors with treatment outcome; cox regression models were used to examine the effect of important variables on overall survival. The Kaplan-Meier method was used to display OS as per the treatment in our cohort settings. OS was used from the time of RC until the date of death or the last follow-up. All the statistical analyses were calculated using R (R project, Vienna, Austria, version 3.6.1), reported p values are two-sided and a p-value ≤ 0.05 was considered statistically significant.

Results

Patient demographics and clinical features

Patient demographic data are described in Table 1. A total of 94 patients were enrolled for the study. The median age was 65.1 years (± 9.5) and 90% of cases are male. The pathologically reported lymph node-positive is 47 (50%) patients. Overall, 20 (21.3%) cases were treated with NAC, and 74 (78.7%) cases were treated with AC.

The demographic data of patients were compared between 2 groups, and there were no differences in regards to age, gender, ECOG, N stage, lymph node status, and surgical margin. However, the AC group had a more advanced cT stage (T3-4: 86.5% vs 50% in the NAC

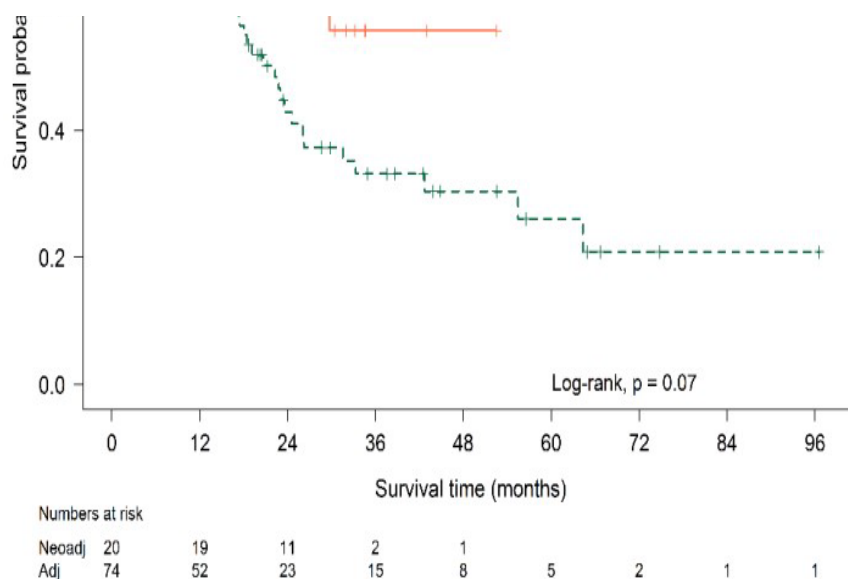


Figure 1. Kaplan Meier Survival Curve of 94 Muscle-Invasive Bladder Cancer Patients Treated with Radical Cystectomy with Perioperative Chemotherapy

Table 1. Demographic, Clinical Features of Muscle-Invasive Bladder Cancer (MIBC) Treated Radical Cystectomy with Perioperative Chemotherapy.

Variables	Neoadjuvant chemotherapy (n=20)	Adjuvant chemotherapy (n=74)	Total population (n=94)	P value
Total	20	74	94	
Age at surgery, years				0.134
Mean(SD)	62.2 (8.4)	65.9 (9.7)	65.1 (9.5)	
Gender				0.197
Male	20 (100)	65 (87.8)	85 (90.4)	
Female	0 (0)	9 (12.2)	9 (9.6)	
ECOG				0.214
0	8 (40)	17 (23)	25 (26.6)	
1	12 (60)	57 (77)	69 (73.4)	
Diversion				< 0.001
Conduit	11 (55)	70 (94.6)	81 (86.2)	
Neobladder	9 (45)	4 (5.4)	13 (13.8)	
Time to radical cystectomy (days)				< 0.001
Median (IQR)	127 (105.8,202.8)	49 (22.2,77.8)	61.5 (29,113.8)	
Clinical T stage				0.001
1	0 (0)	2 (2.7)	2 (2.1)	
2	10 (50)	8 (10.8)	18 (19.1)	
3	2 (10)	26 (35.1)	28 (29.8)	
4	8 (40)	38 (51.4)	46 (48.9)	
Clinical N stage				0.773
0	11 (55)	36 (48.6)	47 (50)	
1	3 (15)	19 (25.7)	22 (23.4)	
2	6 (30)	17 (23)	23 (24.5)	
3	0 (0)	2 (2.7)	2 (2.1)	
Lymph node status				0.801
Negative	11 (55)	36 (48.6)	47 (50)	
Positive	9 (45)	38 (51.4)	47 (50)	
Surgical margin				0.487
Negative	16 (80)	64 (86.5)	80 (85.1)	
Positive	4 (20)	10 (13.5)	14 (14.9)	
Lymphovascular invasion (LVI)				0.008
Negative	13 (65)	22 (29.7)	35 (37.2)	
Positive	7 (35)	52 (70.3)	59 (62.8)	
Time to surgery 90 days				< 0.001
≤90	4 (20)	59 (79.7)	63 (67)	
>90	16 (80)	15 (20.3)	31 (33)	
Status				0.101
Alive	12 (60)	27 (36.5)	39 (41.5)	
Death	8 (40)	47 (63.5)	55 (58.5)	

LVI, lymphovascular invasion; SD, standard deviations; IQR, interquartile range

group) and had a shorter time to surgery ($p \leq 0.001$). Instead, the patients treated with NAC had a lower number in regards to lymphovascular invasion (LVI) ($p=0.008$).

Overall survival

A total of 94 MIBC patients underwent radical cystectomy with perioperative chemotherapy, the median OS time was 22 months and the median follow-up period was 24 months (4-96). Figure 1 outlines the Kaplan–

Meier 5-year overall survival (OS) curves and the overall survival of MIBC patients treated with radical cystectomy, stratified by neoadjuvant chemotherapy versus adjuvant chemotherapy, as per Figure 2.

Patients receiving NAC had better OS outcomes than the AC group, approaching the borderline of significance. ($p=0.07$). In regards to clinical T stage, Figure 3 outlines that the Kaplan Meier curves for OS of the two groups between neoadjuvant and adjuvant chemotherapy on

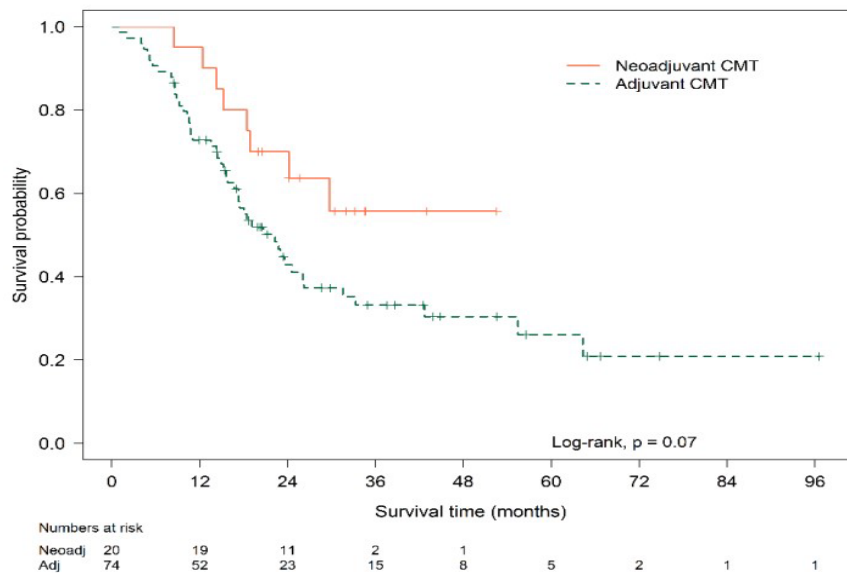


Figure 2. Kaplan Meier Curve for Overall Survival of Muscle Invasive Bladder Cancer Patient Treated with Radical Cystectomy Stratified by Neoadjuvant Chemotherapy versus adjuvant Chemotherapy

clinical T3-4 stage had a comparable outcome. (p =0.9) and in N0, N1, N2-3 stage MIBC patient and no difference overall survival in both NAC and AC group (p =0.09) as in Figure 4, Figure 5 and Figure 6, respectively.

Cox regression analyses and survival estimates

A univariable and multivariable analysis in the Cox proportional hazards regression model in Table 2 yielded that the type of chemotherapy between adjuvant chemotherapy was associated with increased overall mortality (OM) compared to neoadjuvant chemotherapy (HR 1.98, 95% CI 0.93-4.2) (P < 0.039). Furthermore, node-positive patients with N2-3 were significantly associated to increased mortality compared to N0-1 patients (HR 2.05; 95% CI 1.17 –3.61, p = 0.017).

Whereas a higher T stage T3-4 vs T1-2 (HR 1.61, 95% CI 0.78–3.3, p =0.172), the cN2-3 vs cN0-1 status (HR 1.97, 95% CI 1.12–3.46, p=0.007), age; >70 vs <=70 (HR: 1.2, 95% CI 0.68-2.11) and gender; female vs. male (HR 1.00, 95% CI 0.40–2.53) were not significantly associated

with overall mortality.

Discussion

In this real-world data study, we found that NAC had improved more 5-year OS in comparison to AC for patients with MIBC, approaching the borderline of significance (55.7% vs 30.4%, p =0.07) and it was confirmed via multivariable analysis that AC was associated with an increase overall mortality (OM) compared to NAC. (HR 1.98, 95% CI 0.93-4.2) (P <0.039). Furthermore, there is concordance with a previous meta-analytic study that there was a significant overall survival (OS) benefit associated with cisplatin-based neoadjuvant chemotherapy (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.79-0.96) (Yin et al., 2016).

It is suggested that when treating MIBC patients with radical cystectomy, perioperative chemotherapy using NAC leads to longer OS than AC regardless of the clinical or pathological nodal status. However, a

Table 2. Univariable and Multivariable Cox Regression Analysis Predicting Overall Survival (OS) in 94 Patients MIBC Treated with Neoadjuvant (NAC) or Adjuvant (AC) Chemotherapy

Variables	Univariable analysis		Multivariable analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Type of chemotherapy				0.039
Adjuvant vs Neoadjuvant	1.98 (0.93-4.2)	0.07	2.08 (0.98,4-43)	
Tstage:				
T3-T4 vs T1-T2	1.61 (0.78-3.3)	0.172		
N stage				0.017
N2-N3 vs N0-N1	1.97 (1.12-3.46)	0.024	2.05 (1.17-3.61)	
Age (years)				
>70 vs <=70	1.2 (0.68-2.11)	0.53		
Gender				
Female vs Male	1.00 (0.40-2.53)	0.986		

HR, hazard ratio; CI, confidence interval; cT, clinical T stage; cN, clinical N stage

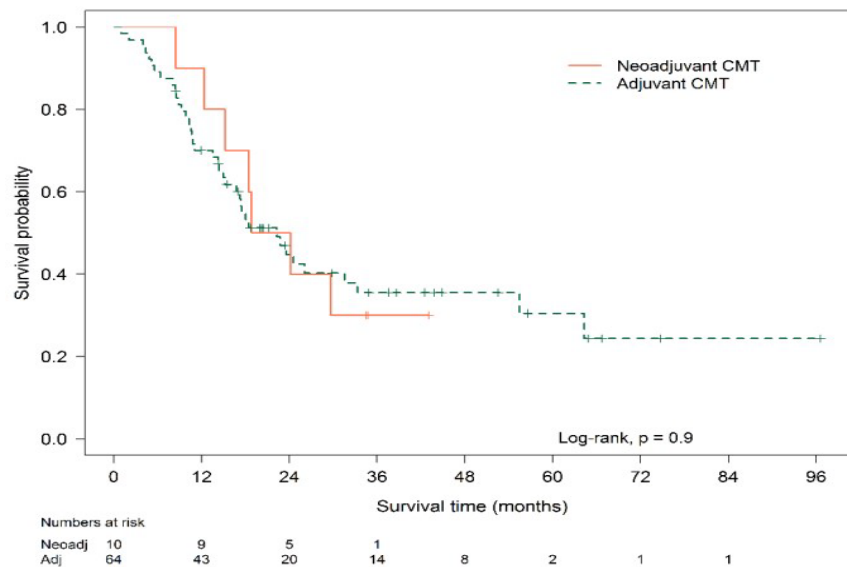


Figure 3. Kaplan Meier Survival Curve of Muscle-Invasive Bladder Cancer Patient Treated with Radical Cystectomy Compare Neoadjuvant versus adjuvant Chemotherapy Focus on T stage3-4

comprehensive interpretation of these data should be considered. Moreover, the NAC group has shown 25% improvement in the 5-year OS compared to the AC group. This difference may be related to the advantage of NAC in these patients, in which patients' baseline characteristics have lower numbers of higher clinical T stage. There are some patients with T1 with nodal metastasis included. Our cohort used only the GC chemotherapy regimen mainly with 3-4 cycles. The younger male patients, candidates for neobladder with better ECOG PS, and lower clinical T stage preferentially underwent neoadjuvant chemotherapy and also had a lower incidence of lymphovascular invasion. This could be attributed to the effect of the therapy itself as the pathological analysis followed the chemotherapy in this treatment arm. Clinical N stage and lymph node status perfectly match each other. However, we did not evaluate cases with clinically confirmed lymph node metastases

which were diagnosed from pathological examination of surgically resected specimens, or cases with a down-staged status post neoadjuvant chemotherapy. Type of chemotherapy between dose-dense MVAC and GC was not compared in our cohort but data from 1,766 patients were included in 13 retrospective studies. There was no significant difference in pathological complete response between MVAC and GC. However, GC was associated with a significantly reduced overall survival (HR, 1.26; 95% CI, 1.01-1.57). After excluding carboplatin data, GC still seemed to be inferior to MVAC in OS (HR, 1.31; 95% CI, 0.99-1.74), but the difference was no longer statistically significant.

The increase of neoadjuvant chemotherapy use could be potentially explained by several factors. Firstly, there are the standard guideline recommendations supporting the use of neoadjuvant chemotherapy with level I evidence

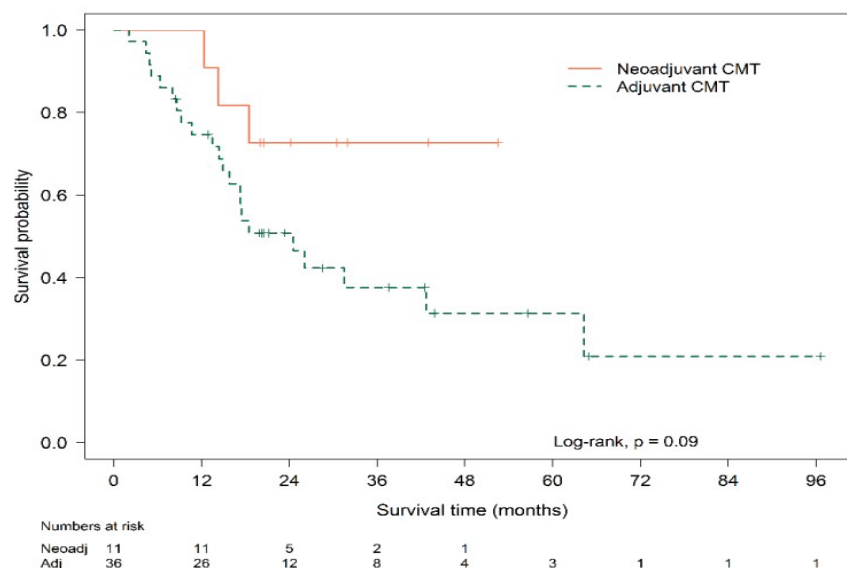


Figure 4. Kaplan Meier Survival Curve of Muscle-Invasive Bladder Cancer Patient Treated with Radical Cystectomy Compare Neoadjuvant versus adjuvant Chemotherapy Focus on the Nodal State 0 (N0)

(Grossman et al., 2003; Keegan et al., 2014; Fedeli et al., 2011; Zaid et al., 2014; Bellmunt et al., 2021, Rizzo et al., 2022; Readon et al., 2015; Green, 2002) and there are also several retrospective studies using database analysis, including as many as 656 patients and 1,342 patients, revealing promising results about NAC (Del et al., 2018; Mcleod et al., 2020). Secondly, neoadjuvant treatments have been made to be more attractive in regards to their administration due to its decreased toxicity and increased tolerability by patients as a consequence. In addition, a number of studies, about perioperative chemotherapy regimens, confirmed that the use of gemcitabine and cisplatin combination or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin has comparable efficacy (Zargar et al., 2015). Even, in our cohort, the number of NAC group has fewer than AC group due to many factors in connection to their clinical condition at presentation and the inconvenience of the impact of received neoadjuvant chemotherapy in relation to performing radical cystectomy first and then considering adjuvant chemotherapy due to the pathological reports. However, observations during this study yielded that in regards to the later period, the decrease of the number of patients who were treated with adjuvant chemotherapy might be from many potential reasons, for example after surgery many patients develop postoperative complications which can lead to unsuitability for chemotherapy. In addition, if patients receive neoadjuvant chemotherapy, resulting in a downstage at the time of cystectomy, then there is no need for further adjuvant chemotherapy (Dash et al, 2015). Since this analysis demonstrated an overall survival difference based on neoadjuvant versus adjuvant sequencing; the important consideration from a policy and quality improvement standpoint is ensuring that all patients are fully considered and evaluated for perioperative chemotherapy, in order to improve rates of guideline-concordance.

Our analysis had some limitations. Firstly, this is a retrospective study and featured multiple biases. Secondly, the type and technique of the pelvic lymph node dissection (PLND) was not described for all patients, in regards to surgical outcomes. Furthermore, it should be considered that patients in the AC group had a more advanced clinical T stage.

Finally, the clinical paradigm in relation to bladder cancer management is progressively developing and it might include genomic subtyping in regards to the relevant treatment guidelines, such as the programmed death-ligand- 1 receptor in relation to platinum ineligible patient treatment or the FGFR-3 inhibitors (Balar et al., 2017). In the future, we would have to balance evidence-based care and real-life practice about novel bladder cancer treatment ; high cost drugs and the potential need of personalized biomarkers are key in order to determine which specific patients would have the best outcomes with also unforgettable aspects with financial and social resources in real-world setting.

In conclusion, the results of this study indicate that there is a significant overall survival benefit in MIBC patients who received neoadjuvant chemotherapy. These data support the usefulness of neoadjuvant chemotherapy

administration in MIBC to improve overall survival. These findings should be interpreted within the context of a hypothesis-generating, retrospective study design. To draw further treatment conclusions, well-designed prospective evaluations of the role of various systemic therapy in muscle-invasive bladder cancer, are needed.

Author Contribution Statement

Conceptualization, AS and TB. Methodology, AS and TB. Data analysis, AS and TB. Writing-original draft preparation, AS, MT and TB. Writing-review and editing. All authors contributed to the article and approved the submitted version.

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Data availability statement

The article and supplementary material contain the original contributions discussed in the study. The associated authors can be contacted for more information.

Ethics statement

The Songklanagarind hospital Ethics Committee granted approval for this study with a waiver of informed consent, and this study was in compliance with the declaration of Helsinki's guiding principles (REC. 62-269-10-4).

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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