

Improving the outcome of patients with muscle invasive urothelial carcinoma of the bladder with neoadjuvant gemcitabine/cisplatin chemotherapy: A single institution experience

Faraj El-Gehani, MD;* Scott North, MD, FRCPC;† Sunita Ghosh, PhD;† Peter Venner, MD, FRCPC*

*Department of Oncology, University of Calgary, Calgary, AB; †Department of Oncology, University of Alberta; and Cross Cancer Institute, Edmonton, AB

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Abstract

Introduction: Neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy (RC) for muscle invasive urothelial carcinoma of the bladder improves survival. This study was undertaken to determine the rate of neoadjuvant gemcitabine and cisplatin use prior to RC and to assess its effect on the pathologic response rates and cancer-specific survival (CSS) and overall survival (OS).

Methods: This retrospective chart review examined all patients having a RC between January 1, 2007 and June 30, 2011. We collected patient demographics, pre-treatment clinical stage, type of chemotherapy, post-RC pathologic data and survival data.

Results: A total of 251 RC were performed of which 160 were for stage cT2-T4 urothelial carcinoma of the bladder. Of the 160 patients, 91 (57%) received neoadjuvant gemcitabine and cisplatin (GC) and 69 (43%) went straight to RC. Patients receiving neoadjuvant GC had a greater chance of achieving a pathologically lower stage compared to the untreated population: pT0 at 21% vs. 3%; non-invasive cancer at 37% vs. 10%; and organ-confined cancer at 60% vs. 33% ($p < 0.001$). Survival correlated with pathological stage: \leq pT3a patients had a median OS and CSS of 48.8 and 51.2 months compared to an OS and a CSS in \geq pT3b patients of 21.8 and 28.1 months, respectively ($p < 0.0001$).

Conclusions: Neoadjuvant chemotherapy for urothelial carcinoma of the bladder is more frequently administered at our institution compared to the published literature. We have found that neoadjuvant chemotherapy increases the rate of down-staging, which is associated with a reduced risk of death from urothelial carcinoma of the bladder.

Introduction

Radical cystectomy (RC) represents the primary therapeutic modality for muscle-invasive (T2-T4) urothelial carcinoma of the bladder. However, it has a 30% to 50% recurrence rate if treated with RC alone, which is likely related to the presence of gross or micro-metastases.¹

Several studies have shown that neoadjuvant chemotherapy (NAC) increases the probability of eliminating all local disease (pT0) at the time of cystectomy. The frequency of pT0 ranges from 23% to 38% in the NAC plus RC group compared to only 12% to 15% for RC only.^{2,3} This pathologic down-staging translates into improved survival.⁴ Clinical trials and subsequent meta-analyses have shown that NAC prior to RC is associated with 5% to 8% improvement in overall survival compared to RC alone.⁴⁻⁶ A meta-analysis of individual patient data from 11 trials involving 3005 urothelial carcinoma of the bladder patients found a significant survival benefit associated with platinum-based NAC, with a 14% reduction in the risk of death and a 5% absolute improvement in survival at 5 years.⁶

Despite strong evidence and clinical practice guidelines recommending NAC prior to RC, it remains low at <20% in North America regardless of whether the patient is treated in an academic or community centre.^{7,8} Although there may be medical contraindications for cisplatin-based NAC, the decision regarding its appropriateness should be made in consultation with a medical oncologist even though referrals to a medical oncologist are too low.⁹

Traditionally, the NAC regimen for urothelial carcinoma of the bladder is a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), which was the regimen used in the SWOG phase III randomized trial NAC.⁴ MVAC is an effective regimen in this setting in terms of pathologic down-staging and survival; however, it has an unfavourable toxicity profile, producing significant (grade ≥ 3) hematologic and non-hematologic toxicities.⁴ In contrast, a combination of gemcitabine and cisplatin (GC) has an improved side effect profile compared to MVAC.¹⁰ Currently, GC in the neoadjuvant setting is based on data extrapolated from the metastatic setting, as only few retrospective series have reported on administering neoadjuvant chemotherapy GC.^{2,11}

To further define the role of neoadjuvant chemotherapy GC, we conducted a single-institution, retrospective study to determine its referral rates, the proportion of patients receiv-

ing it and its effect on pathologic down-staging at time of RC and on overall survival (OS) and cancer-specific survival (CSS).

Methods

Following research ethics board approval, we retrospectively reviewed charts from the Alberta Urology Institute Radical Cystectomy Database (a prospectively collected surgical database)¹² for all patients undergoing a RC between January 1, 2007 and June 30, 2011. Patients with T2-T4 urothelial carcinoma of the bladder were considered eligible to receive NAC. Patients with cN+ disease were not included. Data collected included patient demographics, indications for RC, clinical stage (based on clinical exam and computed tomography imaging), use of NAC, pathological stage at time of RC, surgeon performing RC, overall survival, reason why NAC was not administered and the type and dose of chemotherapy administered.

The primary exposure variable was NAC use (either patients had it or not). The primary outcome was the incidence of down-staging as defined as RC pathologic stage compared to the clinical stage using the TNM Classification of Malignant Tumours (version 7). The degree of down-staging at the time of RC was categorized using 3 thresholds: complete down-staging (i.e., pT0N0); non-invasive down-staging (i.e., residual cancer of pTis/pTa/pT1 and pN0); and organ-confined disease (\leq pT3a and pN0). Patients with pT3b to pT4b and any patients with pN+ disease were classified as having non-organ confined disease.^{3,13} The secondary outcome determined was OS and CSS stratified by treatment (NAC vs. no NAC) and pathological stage.

The chemotherapy treatment plan consisted of 4 cycles of gemcitabine combined with cisplatin over a 21-day cycle, with gemcitabine administered on days 1 and 8 (1250 mg/m²) and cisplatin administered on day 1 (70 mg/m²).

Descriptive statistics were obtained for categorical and continuous variables. The mean and standard deviation were reported for continuous variables and frequencies for categorical variables. Chi-square test statistics were used to compare the categorical variables. OS and CSS were defined as the time from pathologic confirmation of disease until death; patients who were alive at the end of the follow-up were considered censored. OS and CSS survival were calculated using the Kaplan-Meier estimator. Log-rank test statistics were used to compare the survival outcomes among different groups. Hazard ratio and the corresponding 95% confidence interval for survival were obtained using Cox's proportional hazard model. All statistical analyses were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC) and a p value ≤ 0.05 was considered statistically significant.

Results

During the study period, a total of 251 RCs were performed. Of these, 160 patients had muscle-invasive, non-metastatic urothelial carcinoma of the bladder and considered potential NAC candidates. Of the 160 patients, 69 (43%) went straight to RC (i.e., they were untreated with NAC) and the remaining 91 (57%) received NAC (i.e., the treated group). Patients did not receive NAC for the following reasons: 13% patient choice, 33% no referral to medical oncology and in 55% there was a medical contraindication (Fig. 1). These included 46% with inadequate renal function, 16% poor performance status, 16% heart disease, 14% large urinary bladder mass with ureteral obstruction, 5% fistula formation and 3% due to rapidly progressing disease.

Baseline demographics

The characteristics of the NAC candidates are described in Table 1. The untreated group was older with a mean age of 72 years compared to 65 years for the treated group ($p < 0.0001$). The male to female patient ratio was not different between the treated and untreated groups ($p = 0.6449$). The pre-treatment clinical stage was different in the 2 groups: 45% in the treated group were \geq cT3 compared to only 22% of patients in the untreated group ($p = 0.0003$).

In total, 91 patients received NAC. Cisplatin-based NAC was delivered to 82 (90%), carboplatin-based NAC to 7 (8%) and 2 (2%) started on cisplatin and then switched to carboplatin due to toxicities. Initially, the protocol called for 3 cycles of chemotherapy instead of the now standard 4; 16 patients received only 3 cycles. Twelve patients had the chemotherapy stopped because of toxicity; 5 patients had fewer than 4 cycles of chemotherapy because of progressive disease on interim imaging and ultimately they proceeded to RC.

The time between the transurethral resection of the bladder tumour and the RC was significantly longer in the treated group compared to the untreated group (159 days vs. 78 days, $p < 0.0001$).

Patients underwent an extended pelvic lymph node dissection in association with RC. The median number of lymph nodes removed was 12.

Down-staging

The proportion of patients completely down-staged at RC (pT0) was higher in the treated group compared with untreated group, 21% (19/91) vs. 3% (2/69) ($p = 0.001$) (Table 2). In addition, in the treated group the proportion of patients with $<$ pT2 disease was 37% compared to 10% in the untreated group ($p = 0.0001$) and the proportion of patients down-staged to organ-confined disease was also greater in the NAC group (60% vs. 33%, $p = 0.0006$).

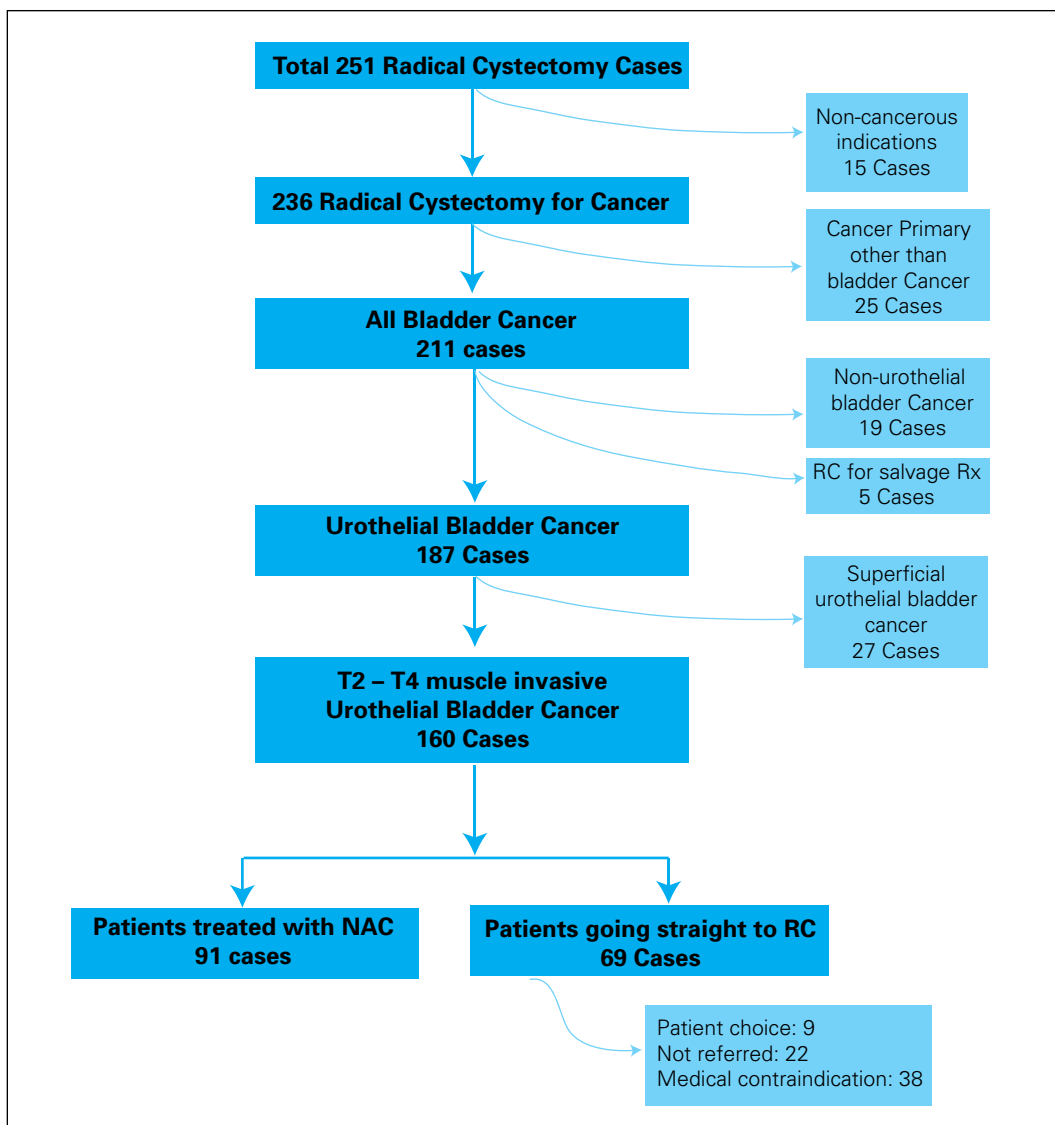


Fig. 1. Consort diagram shows the study cohort of 251 patients undergoing radical cystectomy between January 1, 2007 and June 30, 2011.

Overall, 28% of the patients were pN+ and although there was a trend to a reduction in pN+ disease in the NAC group, there was no statistically significant difference in the frequency of lymph node metastases between the treated group and the untreated group (24% vs. 33%, $p = 0.09$).

In the untreated group, 13/69 (19%) subsequently received adjuvant GC chemotherapy after the RC.

Survival and pathological stage

The median follow-up was 34 months (range: 6.4-84.6) for the treated group and 22.1 months (range: 1.7-74.6) for the untreated group. For all 160 patients, the median OS was 41.1 months and the median CSS was not reached (Fig. 2). The median OS of the NAC group was 51.2 months,

compared to 24.1 months for the untreated group (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.44-1.04, $p = 0.07$). The median duration of CSS of the NAC treated group was not reached compared to 39.3 months for the untreated patients (Fig. 3) (HR 0.70; 95% CI 0.43-1.14, $p = 0.15$).

Patients with organ-confined urothelial carcinoma of the bladder had a longer median OS compared to those with non-organ confined disease (48.8 vs. 21.7 months; HR 0.55; 95% CI 0.32-0.94, $p = 0.03$). They also had a longer CSS (51.2 vs. 28.1 months; HR 0.60; 95% CI 0.34-1.07, $p = 0.08$) (Fig. 4). The outcome of patients more specifically correlated with the actual pathological stage; in patients with pT0 and pT1 disease, the median OS has not been reached, compared to 48.8 months for pT2/pT3a patients

Table 1. Baseline characteristics of all 160 neoadjuvant chemotherapy candidates			
	Neoadjuvant chemotherapy n=91	No neoadjuvant chemotherapy n=69	p value
Age (yr)			
Mean/Range	65 (48-89)	72 (50-89)	<0.0001
Gender, no. (%)			
Male	67 (74%)	53 (77%)	0.6449
Female	24 (26%)	16 (23%)	
Clinical stage, no. (%)			
T2	50 (55%)	54 (78%)	0.0003
T3	38 (42%)	9 (13%)	
T4	3 (3%)	6 (9%)	

and 21.7 months for \geq pT3b and or N+ disease (Table 3) (Fig. 5). This was similar for CSS with the median survival not being reached in the patients with pT0 and pT1 cancers compared to a median survival of 51.2 months in the pT2/pT3a group and 28.1 months in the \geq pT3b and or N+ group (Table 4) (Fig 5).

The outcome for patients with pathological involvement of the lymph nodes was similar whether or not they received NAC (Fig. 6). The OS for patients with ypN0 and pN0 was not reached and was not significantly different ($p = 0.13$). The OS for patients with ypN+ or pN+ disease was, respectively, 20.8 and 17.8 months ($p = 0.57$); CSS was 23.7 and 22.1 months ($p = 0.85$), respectively. The median OS for patients with pN0, pN1, pN2 and pN3 disease was 55.8, 21.2, 19.0 and 16.6 months, respectively ($p < 0.0001$).

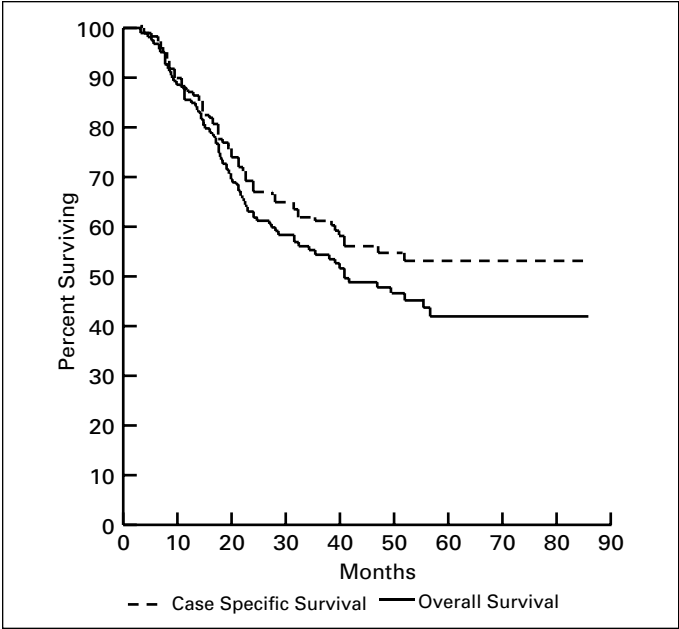


Fig. 2. Kaplan-Meier curve of overall survival and cancer specific survival estimates for all 160 patients undergoing a radical cystectomy for muscle invasive bladder cancer.

Table 2. Pathologic stage of all 160 patients undergoing a radical cystectomy			
Pre-cystectomy clinical stage	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	p value
Complete down-staging			
T2	12/50 (24%)	2/54 (4%)	0.002
T3	7/38 (18%)	0/9 (0%)	0.163
T4	0/3 (0%)	0/6 (0%)	-
ALL	19/91 (21%)	2/69 (3%)	0.001
Non-invasive cancer			
T2	22/50 (44%)	7/54 (13%)	0.0004
T3	11/38 (29%)	0/9 (0%)	0.065
T4	1/3 (33%)	0/6 (0%)	0.133
ALL	34/91 (37%)	7/69 (10%)	0.0001
Organ confined cancer			
T2	33/50 (66%)	20/54 (37%)	0.003
T3	20/38 (53%)	2/9 (22%)	0.100
T4	2/3 (67%)	1/6 (17%)	0.134
ALL	55/91 (60%)	23/69 (33%)	0.0006

The CSS for patients with pN0 and pN1 disease was not reached; for pN2 and pN3, the CSS was 19.2 and 19.7 months, respectively (Fig. 7).

Influence of urological surgeon

The 160 radical cystectomies were performed by 6 urologists. Analyses based on the individual surgeons for referral rates for NAC and outcomes based on OS did not reveal any significant difference between the surgeons (data not shown).

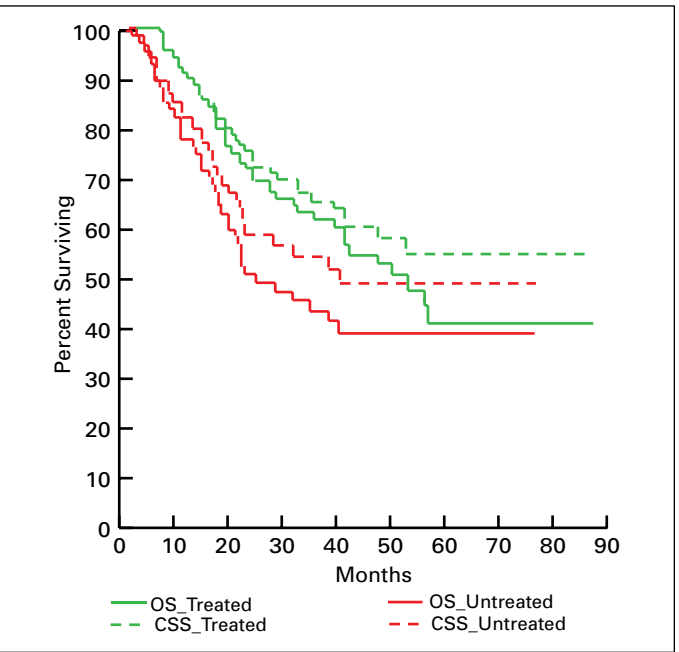


Fig. 3. Kaplan-Meier curve of overall survival and cancer specific survival estimates of patients receiving or not receiving neo-adjuvant chemotherapy.

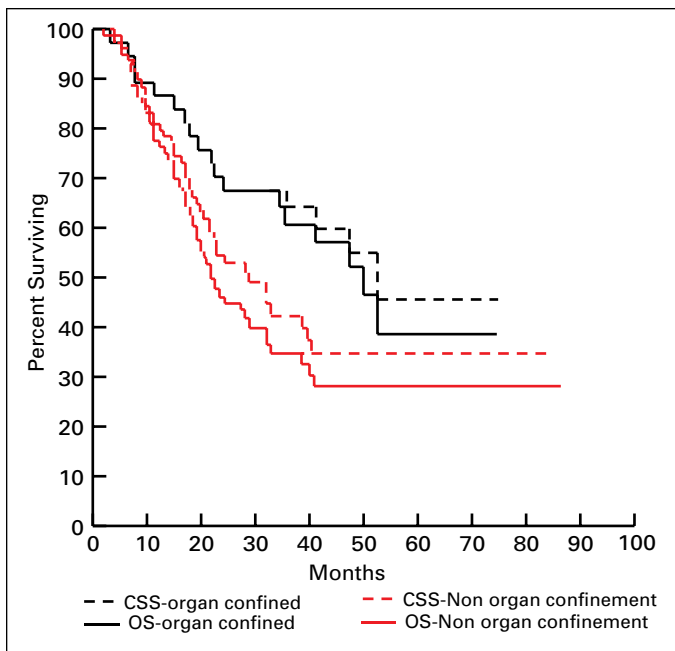


Fig. 4. Kaplan-Meier curve of overall survival and cancer specific survival estimates of patients based on organ confinement or not at the time of radical cystectomy.

Discussion

In North America, RC is the standard treatment for muscle-invasive (T2-T4) urothelial carcinoma of the bladder; alone it is only associated with 5-year survival rates of 57% to 68%.^{7,8} Studies have shown that cisplatin-based NAC followed by RC is associated with a 5% to 8% improved survival and a 14% to 16% reduction in risk of death compared to RC alone.^{4-6,14} Despite strong evidence to support the use of NAC in urothelial carcinoma of the bladder, its use remains dismal.⁴ While earlier studies have shown that only 1% to 5% of bladder cancer patients received NAC, there does appear to be a small increase in the use of NAC since 2003, with rates increasing to 12% to 19%.^{9,15,16}

In this series, 91/113 (80%) of potentially eligible patients received NAC (Fig. 1). The high rate of NAC may be due to the increased awareness of the urological oncology community of the importance of NAC in urothelial carcinoma of the

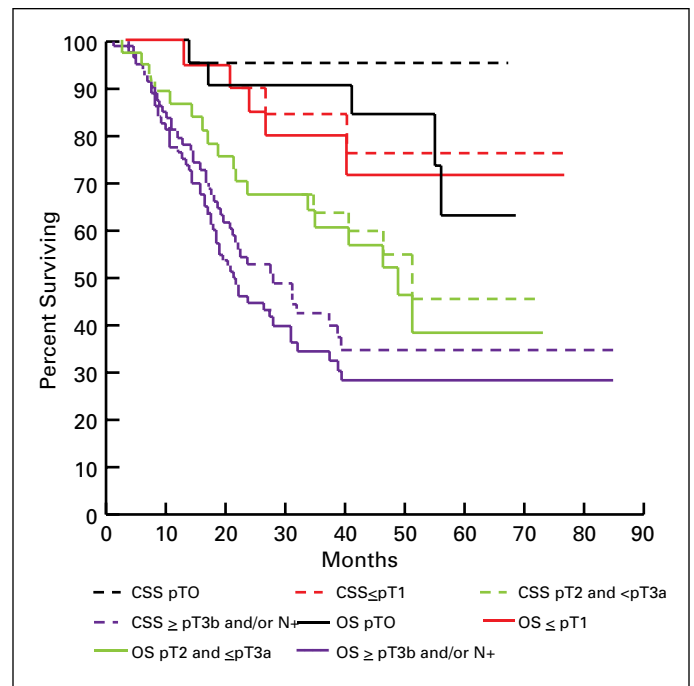


Fig. 5. Kaplan-Meier curve of overall survival and cancer specific survival estimates of patients based on pathological stage at the time of radical cystectomy.

bladder, a centralized referral system with excellent communication between specialties, recognition that chemotherapy can be given safely to properly selected patients, and a commitment from medical oncologists to ensure rapid time to consultation, chemotherapy delivery and referral back for RC. A multidisciplinary care approach and implementation of the clinical practice guidelines have helped to change the practice.⁹

The time to RC for the NAC group was 81 days longer, which is only slightly longer than the time needed to deliver a 10-week NAC program. Therefore, there does not appear to be undue delays in time to RC due to medical oncology referral or recovery from NAC toxicities.

A cisplatin-based regimen, which requires adequate renal function, should be the standard in the NAC setting. Initially when NAC started to be given at our institution, some patients were treated with carboplatin because of the

Table 3. Overall survival hazard ratios based on pathological stage at the time of radical cystectomy

Stage	HR	95% CI	p value
pT0 vs. pT2/pT3a	0.35	0.14-0.99	0.05
pT0 vs. >pT3b	0.20	0.08-0.50	<0.0001
pT1 vs. pT2/pT3a	0.42	0.15-1.12	0.08
pT1 vs. >pT3b and/or N+	0.23	0.10-0.57	0.002

HR: hazard ratio; CI: confidence interval.

Table 4. Cancer-specific survival hazard ratios based on pathological stage at the time of radical cystectomy

Stage	HR	95% CI	p value
pT0 vs. pT2/pT3a	0.10	0.01-0.64	0.02
pT0 vs. ≥pT3b	0.10	0.01-0.37	0.003
pT1 vs. pT2/pT3a	0.38	0.13-1.14	0.09
pT1 vs. >pT3b and/or N+	0.23	0.08-0.64	0.005

HR: hazard ratio; CI: confidence interval.

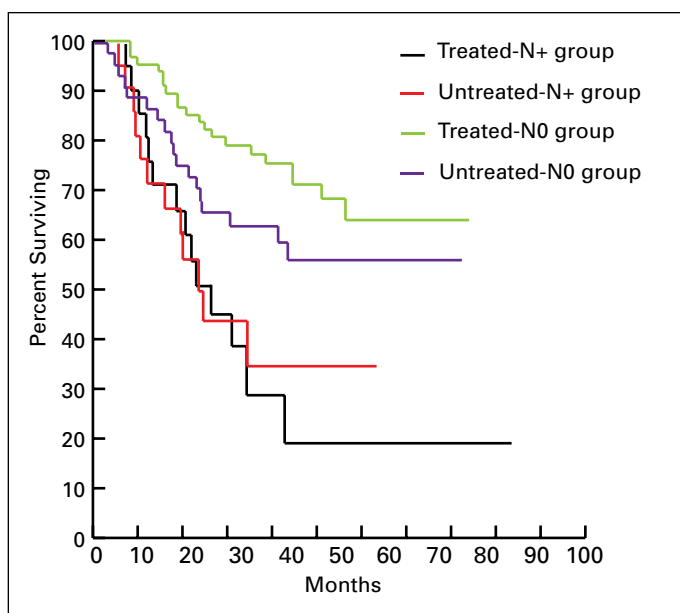


Fig. 6. Kaplan-Meier curve of cancer specific survival estimates of patients based on presence or absence of lymph node metastases receiving NAC or going straight to RC.

perceived need to administer some form of NAC. This practice was subsequently abandoned as there was no evidence from randomized studies demonstrating the equivalence of carboplatin to cisplatin in this setting. However, a recent report suggests that carboplatin combined with gemcitabine maybe a reasonable alternative to the cisplatin combination and should be considered when the latter cannot be administered.¹⁷ Generally, in both clinical trials and standard practice, cisplatin-based NAC is given only to patients with glomerular filtration rates (GFR) of at least 60 mL/min/1.73m². This is because bladder cancer patients with a lower GFR (50-59 mL/min/1.73m²) showed poorer survival rates compared to those with GFR above 60 mL/min/1.73m² when treated with NAC (cisplatin, methotrexate and vinblastine).¹⁸ Similar to previous reports,^{15,19} in the 46% of patients in this series who were ineligible for NAC, the primary reason was inadequate renal function.

This study helps define the role of GC as NAC. In our study, an average of 3.5 cycles of NA GC was delivered (88% of the planned cycles) and 21% of the treated patients achieved complete response, 37% non-invasive disease and 60% organ-confined disease. These findings, which are clinically meaningful and statistically significant, are consistent with other retrospective series that looked at using GC in the neoadjuvant setting.^{2,3,10,11}

Pathological stage is an important prognostic factor for patients undergoing RC for bladder cancer.^{4,20,21} Patients with pathologically organ-confined disease at RC (stage <pT3a, pN0) generally have a more favourable prognosis.^{4,21} Median OS for those who achieve stage pT0 was 13.6 years in the sub-analysis of SWOG87-10.²⁰ The fact that there is a greater

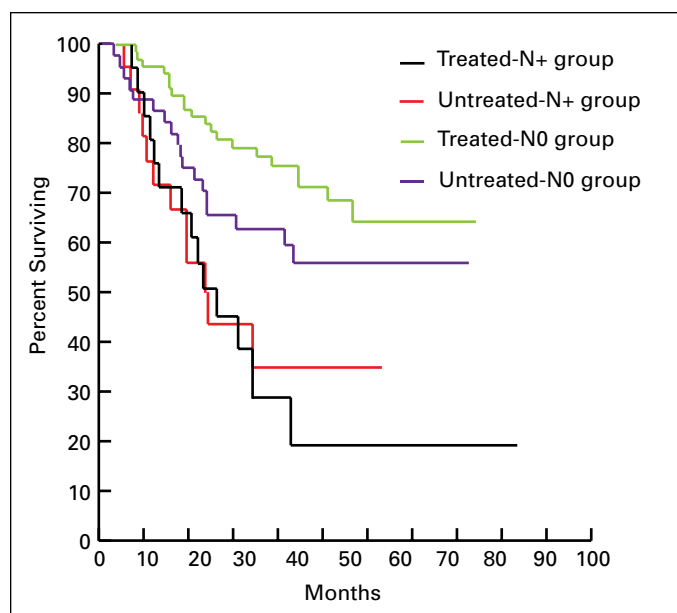


Fig. 7. Kaplan-Meier curve of cause specific survival estimates based on pathological lymph node stage for all patients.

rate of pathologic down-staging with NAC and that lower pathological stage correlates with an improvement in median survival are critical considerations in the management of muscle invasive urothelial carcinoma of the bladder.

More than 3 times as many patients in the NA GC group compared to the untreated group had non-invasive urothelial carcinoma of the bladder. This series also confirms that a pathological lower stage occurs more frequently with NAC (60% vs. 33%) and that a lower stage results in improved survivals (HR 0.54; 95% CI 0.32-93). Receiving NAC GC resulted in twice as many patients achieving a non-muscle invasive disease status compared to those that did not receive NA GC (42% vs. 87%). Based on a comparison of the survival curves for patients with non-invasive disease (pT0 and pT1) to patients with invasive cancer, but organ-confined disease (pT2 and pT3a), there is a 63% reduced risk of dying ($p = 0.01$); when the non-invasive group is compared to the non-organ confined group (pT3b and or N+), there is a 78% reduction in the risk of death ($p < 0.0001$).

The incidence of lymph node metastases is reduced in the NAC group (24% vs. 33%), although this was not statistically significant. This is similar to a recently reported single institution study examining ypN status in patients undergoing an extended pelvic lymph node dissection post-NAC.²² Survival in the present series is related to the absence or presence of lymph node metastases, which is also correlated with clinical stage. NAC did not have a meaningful impact on survival for patients with pN+ disease, but it is possible that NAC down-staged patients such that the incidence of pN+ disease is reduced which contributes to the improvement in survival observed with NAC.

Although the median survival is considerably longer in the NAC arm compared to the untreated arm (51 vs. 24 months) and NAC reduces the risk of dying by 33%, the true benefit of NAC may have been attenuated by the fact that 19% of the untreated group subsequently received adjuvant chemotherapy following their RC.

It is also worthwhile pointing out that considerably more of the patients receiving NA GC in this series had clinical T3/T4 disease compared to the patients that did not receive NA GC (45% vs. 22%) and clinical stage T3/T4 disease is associated with a worse prognosis than T2 disease.¹² Countering this imbalance of the higher risk patients in the NAC group is the fact that the average age of the NAC treated group was younger, which would be associated with longer OS but not necessarily a longer CSS.

Conclusion

The real world administration of NAC GC for muscle invasive urothelial carcinoma of the bladder has definite clinical activity with meaningful rates of pathological down-staging, which is associated with an improvement in survival. As GC is a well-tolerated chemotherapy regimen, its utilization in the neoadjuvant setting may encourage the administration of NAC compared to the uptake of MVAC, which should contribute to improved outcomes for patients with muscle invasive urothelial carcinoma of the bladder. Further studies need to be done to identify patients who would need and benefit from NAC.

Competing interests: Dr. El-Ghani, Dr. North, Dr. Ghosh and Dr. Venner all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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Correspondence: Dr. Peter Venner, Department of Oncology, University of Calgary, Calgary, AB; peter.venner@albertahealthservices.ca