Canadian experience of neoadjuvant chemotherapy on bladder recurrences in patients managed with trimodal therapy for muscle-invasive bladder cancer

Khaled Ajib, MD[1]; Michael C. Tjong, MD[2]; Guan Hee Tan, MD[1]; Gregory J. Nason, MD[1]; Mohamad Baker Berjaoui, MD[1]; Annette Erlich, MD[3]; Manjula Maganti, MD[4]; Srikala S. Sridhar, MD[5]; Neil E. Fleshner, MD[1]; Alexandre R. Zlotta, MD[3]; Charles Catton, MD[2]; Alejandro Berlin, MD[2]; Peter Chung, MD[2]; Girish S. Kulkarni, MD[1]

[1]Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [2]Department of Radiation Oncology of Urology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [3]Division of Urology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [4]Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [5]Division of Medical Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

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Abstract

Introduction: Bladder preservation with trimodal therapy (TMT) has emerged as a feasible alternative to radical cystectomy in patients with muscle-invasive bladder cancer. Neoadjuvant chemotherapy (NAC) was proven to cause pathological downstaging. For this reason, we evaluated whether receipt of NAC decreases local bladder recurrences in TMT patients.

Methods: We retrospectively analyzed our TMT database for all patients treated between 2003 and 2017. Patients were treated with maximal transurethral resection of bladder tumor (TURBT) followed by chemotherapy/radiotherapy with or without NAC. Baseline demographic and tumor characteristics were recorded. Rates of local and systemic recurrence were analyzed per receipt of NAC. Overall recurrence-free survival (RFS) and bladder (b)RFS were analyzed using the Kaplan-Meier method and Cox proportional hazards modelling.

Results: Median age and followup periods were 72 years and 3.6 years, respectively. Fifty-four patients had NAC and concurrent chemoradiation (NAC-TMT) vs. 70 patients who had concurrent chemoradiation only (TMT). Carcinoma in situ (CIS) was present in 31% of the patients in NAC-TMT group compared to 24% in TMT group (p=0.40). After treatment, 24 (44%) and 31 (44%) patients in NAC-TMT and TMT groups, respectively, had bladder tumor recurrence. Overall RFS at three years was 46% and 50% in NAC-TMT and TMT groups, respectively (p=0.70). BRFS at three years was 55% and 69% in NAC-TMT and TMT groups, respectively (p=0.27). Multivariable analyses found that the presence of concomitant CIS (hazard ratio [HR] 2.13; 95% confidence interval CI 1.06–4.27; p=0.0036) was the primary factor associated with local bladder recurrence.

Conclusions: Receipt of NAC does not obviate the risk of bladder recurrence post-TMT. Patients with CIS should be monitored especially closely for local recurrence.

Introduction

Bladder cancer is the eleventh most commonly diagnosed cancer worldwide, and the fourth most common cancer in men in the U.S..[1] An estimated 17 240 deaths per year occur due to bladder cancer in the U.S.[2] Radical cystectomy (RC) is considered the mainstay of treatment in patients with localized non-metastatic muscle invasive bladder cancer (MIBC).[3] All national and international guidelines recommend neoadjuvant chemotherapy (NAC) in addition to radical cystectomy with pelvic lymph node dissection in the management of localized MIBC.[3-5]

The addition of NAC has shown a significant advantage to overall survival (OS), with a 5% absolute benefit at five years.[6] A meta-analysis demonstrated that the rate of downstaging to ≤pT1 at RC was 29.1%, which increased the five-year OS to 75.7% in these patients.[7] However, RC is associated with a substantial risk of morbidity and impaired quality of life.[8] To obviate these risks, organ preservation has been recognized as an alternative therapy to radical surgery. Several bladder preservation studies have demonstrated an improved quality of life compared to surgery without compromising the oncological outcome.[9] In the U.K., for example, 60% of MIBC cases are managed with organ-preserving strategies.[10]

The most accepted form of bladder preservation is trimodal therapy (TMT; aggressive transurethral resection of bladder tumor [TURBT], radiotherapy, and concomitant che-

motherapy). Although NAC already has an established and proven role in the treatment of MIBC, the benefit of NAC in a TMT has not been robustly studied. In addition to treating micrometaststic disease, NAC can cause pathological downstaging.[11] As a corollary, it is possible that NAC may impact long-term local bladder control by decreasing the risk of intravesical recurrences in the TMT-preserved bladder.

The aim of this paper, thus, is to test the hypothesis that NAC can impact intravesical recurrences in patients who have opted for bladder preservation.

Methods

Patient characteristics

In this single-institution, retrospective study, data was collected for 124 patients who had cT2–T4 MIBC treated with curative intent between 2003 and 2017. All patients had TMT that included maximal TURBT with combined chemotherapy and radiotherapy with or without NAC. Early in our TMT experience, patients did not receive NAC; however, as the benefits of NAC in the RC population became better understood, we began to adopt NAC as part of our definitive bladder-sparing TMT protocol.

Inclusion criteria

Patients who received TMT had the following tumor characteristics: 1) tumor <5 cm; 2) solitary tumors; 3) minimal to no hydronephrosis on cross-sectional imaging; 4) good bladder function; 5) no multifocal carcinoma in situ (CIS); and 6) adequate bladder function. Patients who were candidates for both RC and TMT had an extensive discussion that included possible outcomes and complications of both procedures.

TMT

TMT included TURBT, chemotherapy, and radiation. In most cases, extensive resection was performed during the TURBTs to clear all macroscopic tumor. Chemotherapy mainly comprised of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); cisplatin, methotrexate, and vinblastine (CMV); gemcitabine and cisplatin (GC); or gemcitabine alone. In our series, GC was the most common regimen used. Cisplatin-based chemotherapy criteria included an Eastern Cooperative Oncology Group (ECOG) status <2, creatinine clearance >60 ml/min, no grade 2 or worse hearing loss or neuropathy, and adequate cardiac function.[12] Daily image-guided, intensity-modulated radiotherapy was delivered to the bladder and pelvic nodes to a dose of 46 Gy in 23 fractions, with a sequential tumor boost of 20 Gy in 10 fractions (total 64–66 Gy). The tumor boost was guided with localizing lipidol injections around the TURBT scar prior to commencement of radiotherapy. Patients received concurrent cisplatin chemotherapy at a dose of 40 mg/m^2 weekly during radiation treatments (concurrent chemoradiation).

Study design

In this non-randomized, retrospective study, we compared outcomes of TMT patients based on their receipt of NAC. Fifty-four patients in the NAC-TMT group had NAC followed by concomitant chemoradiation (TMT), while 70 patients in TMT group only had TMT. Baseline demographics and tumor characteristics were collected, including age, smoking history, bladder cancer history, comorbidities, ECOG score, presence of CIS, cTNM staging, and tumor grade. Outcomes assessed were recurrence-free survival (RFS) (locoregional), bladder recurrence-free survival (bRFS), cystectomy-free survival, and OS.

Statistical analysis

Data on categorical variables were reported as frequencies and percentages. Continuous variables were described as means ± standard deviations, along with median values and ranges. Summary statistics were reported on the whole cohort and by type of chemo. Statistical significance was reported using Chi-squared or the Fisher exact test for categorical variables, and t-test for continuous data.

The Kaplan-Meier method was used to estimate the probability of OS, disease-free survival, bladder recurrence, and cystectomy free survival, while the log-rank test was used for significance testing between groups. Cox regression modelling was used to identify significant independent predictors of the aforementioned time to event outcomes. Competing risks approach was used to estimate the probability of cause-specific death, and Gray's test was used to report significance between groups. Competing risks regression was used to report independent predictors of cause-specific survival.

Results

Table 1 summarizes the baseline characteristics of the patients in both groups. The median followup period was 3.6 years. Median age was 70.5 and 75.0 years in the NAC-TMT and TMT groups, respectively (p=0.038). The distribution of clinical staging was as follows: 76% (n= 41), 11% (n=6), and 13% (n=7) of the patients in the NAC-TMT group had cT2, cT3, and cT4, respectively, compared to 77% (n=54), 21% (n=15), and 1% (n=1) in the TMT group (p= 0.51). Concomitant CIS was present in 31% (n=15) of the patients in the TMT-NAC group compared to 24% (n=16) in the TMT group (p=0.40). There was no difference in clinical node status between the two groups, with 69% (n=37) and

Table 1. Baseline characteristics

	Overall	NAC-TMT	TMT	p
Age (median)	72 (28.91)	70.5 (45.85)	75 (28.91)	0.038
Sex (%)				1.00
Female	38 (31)	17 (31)	21 (30)	
Male	86 (69)	37 (69)	49 (70)	
Smoking (%)				0.58
Current	23 (19)	12 (22)	11 (16)	
No	39 (32)	15 (28)	24 (35)	
Discontinued (>12 months)	61 (50)	27 (50)	34 (49)	
History of NMIBC (%)				0.25
No	102 (82)	47 (87)	55 (79)	
Yes	22 (18)	7 (13)	15 (21)	
ECOG (%)		0.49		0.49
0	63 (52)	26 (50)	37 (54)	
1	41 (34)	21 (40)	20 (29)	
2	14 (12)	5 (10)	9 (13)	
3	2 (2)	0 (0)	2 (3)	
Grade no (%)				1.00
G2	3 (3)	1 (2)	2 (3)	
G3	116 (97)	51 (98)	65 (97)	
Presence of CIS (%)				0.40
None	86 (74)	34 (69)	52 (76)	
Yes	31 (26)	15 (31)	16 (24)	
cT stage (%)				0.02
cT2	95 (77)	41 (76)	54 (77)	
cT3	21 (17)	6 (11)	15 (21)	
cT4	8 (6)	7 (13)	1 (1)	
cN stage (%)				0.44
cN0	93 (75)	37 (69)	56 (80)	
cN1	12 (10)	7 (13)	5 (7)	
cN2	7 (6)	4 (7)	3 (4)	
cN3	4 (3)	3 (6)	1 (1)	
cNx	8 (6)	3 (6)	5 (7)	
Surgical candidate				0.53
Yes	112 (91)	47 (89)	65 (93)	
No	11 (9)	6 (11)	5 (7)	

CIS: carcinoma in situ; ECOG: Eastern Cooperative Oncology Group; NAC: non-adjuvant chemotherapy; NMIBC: non-muscle-invasive bladder cancer; TMT: trimodal therapy.

80% (n=56) of patients in the NAC-TMT and TMT groups, respectively (p=0.44), being node-negative (cN0) at diagnosis. Out of all the patients in the NAC-TMT group, 89% (n=47) were surgical candidates vs. 93% (n=65) in the TMT group (p=0.53).

During the followup period, 44% of patients in each group had tumor recurrence after treatment (NAC-TMT group: n=24 vs. TMT group: n=31). Intravesical-only recurrence was seen in 12.9% (n=7) in the NAC-TMT group vs. 8.6% (n=6) in the TMT group. Fig. 1 illustrates the Kaplan-Meier curves of RFS, bRFS, cystectomy-free survival, and OS. The bRFS at three years was 55% and 69% in NAC-TMT and TMT groups,

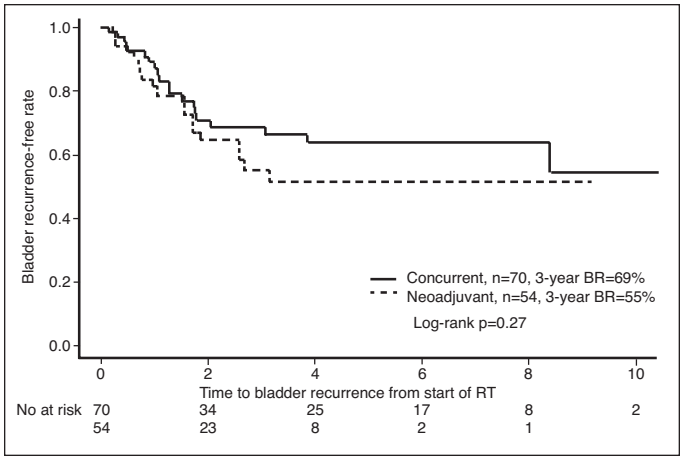

Fig. 1A. Bladder recurrence-free (BR) survival according to receipt of neoadjuvant chemotherapy. RT: radiation therapy.

respectively (p=0.27) (Fig. 1A). The overall RFS, described as locoregional or metastatic recurrence, during the same period was 46% and 50% in NAC-TMT and TMT groups, respectively (p=0.70) (Fig. 1B). A total of 22.2% (n=12) and 12.9% (n=9) of the patients in NAC-TMT and TMT groups, respectively, underwent cystectomy for tumor recurrences. The Kaplan-Meier cystectomy-free survival curve in Fig. 1C shows similar rates at three years in both groups (74% in group 1 and 70% in group 2) (p=0.84). At three years, 14.7% (n=8) of patients in the NAC-TMT group died vs. 13.4% (n=9) in the TMT group (p=0.55). The OS Kaplan-Meier curve (Fig. 1D) demonstrates similar OS in the NAC-TMT and TMT groups at 83% and 80%, respectively (p=0.59).

Table 2 depicts univariable and multivariable analyses assessing bRFS as the main outcome measure. On both univariable and multivariable analysis, only presence of CIS was a statistically significant predictor of local bladder recurrence, with a calculated hazard ratio of 2.13 (95% confidence interval [CI] 1.06–4.27) and p=0.0045. The bRFS

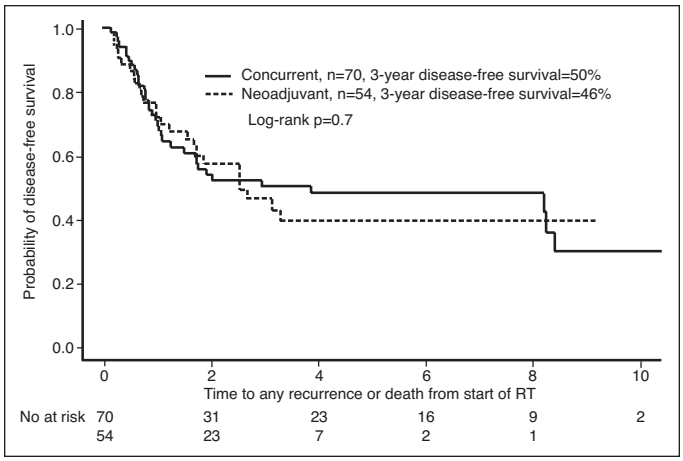

Fig. 1B. Disease-free survival according to receipt of neoadjuvant chemotherapy. RT: radiation therapy.

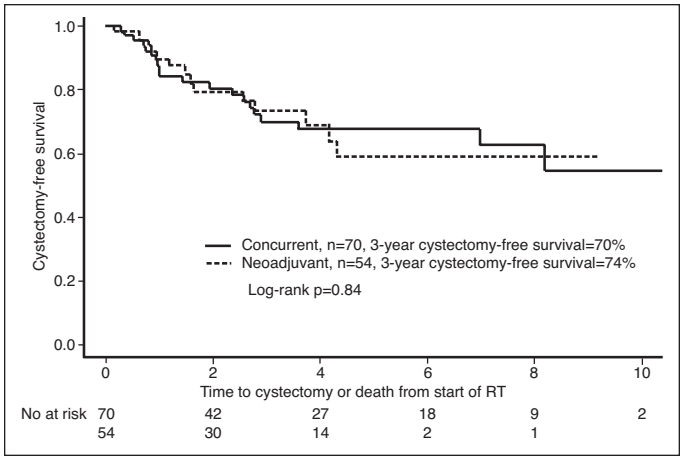

Fig. 1C. Cystectomy-free survival. RT: radiation therapy.

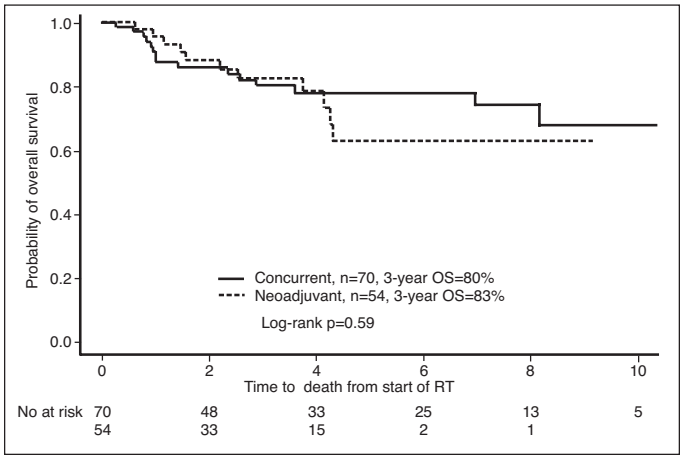

Fig. 1D. Overall survival (OS). RT: radiation therapy.

in patients without concomitant CIS was 76% compared to 29% in patients with CIS. A subgroup analysis of patients with CIS is illustrated in Fig. 2. The bRFS rates were similar between patients who received NAC (31%) and patients who did not (27%) (p=0.49). We noted that the disease-free survival was higher in patients with CIS who had NAC (26% in NAC-TMT vs. 19% in TMT) (p=0.19) (Fig. 2B). Moreover, the OS in patients with CIS who had NAC plus TMT was higher than that of patients who had TMT only (82% vs 68%, p=0.57) (Fig. 2C). However, it should be mentioned that these results were not statistically significant.

Table 2. Univariable and multivariable Cox proportional hazards analysis for bladder recurrence

Covariate	HR (95%CI)	p	MVA	p
Chemo type		0.27		
Concurrent	Reference			
Neoadjuvant plus concurrent	1.43 (0.76–2.69)			
Surgical candidate		0.058		
Yes	Reference			
No	2.35 (0.97–5.66)			
Presence of CIS		0.0045		0.033
None	Reference		Reference	
Yes	2.61 (1.35–5.05)		2.13 (1.06–4.27)	
cT stage		0.15		
cT2	Reference			
cT3	1.96 (0.94–4.08)	0.072		
cT4a, cT4b	1.86 (0.56–6.18)	0.31		
cN stage				
cN0	Reference			
cN1	1.26 (0.49–3.26)	0.63		
cN2/cN3	0.67 (0.16–2.79)	0.58		
cNx	0.75 (0.18–3.16)	0.7		
ECOG				
0	Reference		Reference	
1	2.11 (1.03–4.3)	0.04	1.81 (0.85–3.84)	0.12
2/3	2.61 (1.0–6.84)	0.051	2.18 (0.81–5.81)	0.12
Age				
	1.03 (1.0 – 1.06)	0.072		

CI: confidence interval; CIS: carcinoma in situ; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MVA: multivariable analysis.

Discussion

MIBC is a lethal disease that requires definitive treatment. RC is the mainstay of treatment for localized, non-metastatic MIBC.[3-5] However, RC is associated with increased morbidity and quality of life impairment.[13] For this reason, other treatment modalities that aim for bladder preservation have been studied.

TMT consisting of maximal TURBT followed by concurrent chemotherapy and radiotherapy is an alternative for patients who refuse cystectomy or are not eligible for surgery.[3] We have previously published a propensity score-matched analysis demonstrating that, in the setting of a multidisciplinary bladder cancer clinic, TMT yields survival outcomes similar

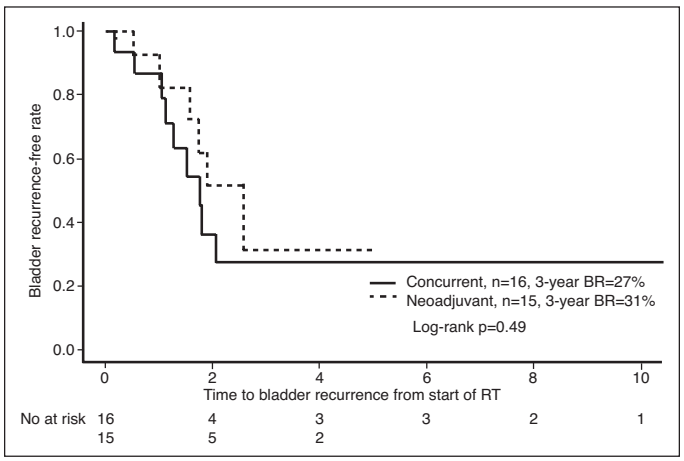

Fig. 2A. Bladder recurrence-free (BR) in patients with concomitant carcinoma in situ. RT: radiation therapy.

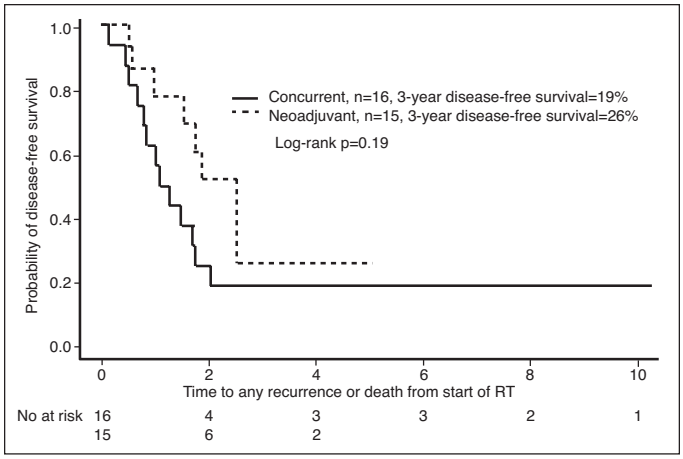

Fig. 2B. Disease-free survival in patients with carcinoma in situ according receipt of neoadjuvant chemotherapy. RT: radiation therapy.

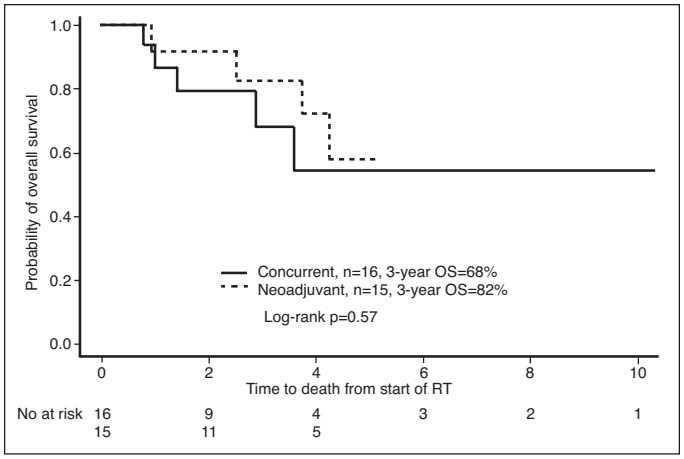

Fig. 2C. Overall survival (OS) in patients with carcinoma in situ according receipt of neoadjuvant chemotherapy. RT: radiation therapy.

to those of matched patients undergoing RC.[13] Additionally, using the National Cancer Database (NCDB), Zhong et al recently published another propensity-score matched comparison of MIBC patients treated with curative intent with bladder preservation vs. RC. They reported no significant difference in survival between bladder preservation and RC (39.1% vs. 42.6%, respectively).[14] Conflicting data on equivalence of outcome of TMT compared to RC do exist, however. For example, using the Surveillance, Epidemiology, and End Results Medicare-linked database (SEER), Williams et al reported a decreased overall and cancer-specific survival in patients who underwent TMT compared to RC (HR 1.49 and 1.55, respectively).[15]

It is well-known that the addition of NAC increases the rate of pathological downstaging.[11] Rosenblatt et al reported that chemo-induced downstaging might act as a marker of OS in patients with MIBC undergoing RC.[11] In a bladder preservation setting, NAC may also promote long-term oncological bladder control by controlling the potential field defects that lead to downstream bladder cancer recurrences. Despite this hypothesis, we found that the bRFS and RFS rates were similar between both groups. In the NAC-TMT group, the bladder tumor recurrence rates were higher than those reported in Tunio et al (44% vs. 10%).[16]

Although associated with an improved quality of life,[9] unlike RC patients, TMT patients remain at risk for intravesical recurrence. Huddart et al concluded that the loco-regional recurrence rate at two years was lower in patients who underwent RC (15.3%) compared to patients who had TMT (68.9%), as the bladder remains at risk for intravesical recurrences.[17] In a retrospective series of 348 patients undergoing TMT with or without neoadjuvant or adjuvant chemotherapy, it was shown that the 10-year risk of non-invasive, invasive, pelvic, and distant recurrences were 29%, 16%, 11%, and 32%, respectively.[18] The combined local recurrence rate of 45% is similar to our findings, suggesting that maintaining local control requires vigilant monitoring in the TMT setting. Nevertheless, despite clinically significant intravesical recurrence rates, our OS and disease-specific survival rates were similar to those published in the literature, suggesting that intravesical bladder recurrences can be readily salvaged by either established non-MIBC treatment regimens or by RC. Trying to obviate this risk of local recurrence, other neoadjuvant therapies were suggested.

Cisplatin-based NAC is the standard of care for patients with localized non-metastatic MIBC before RC.[3] According to Rosenblatt et al, the rate of complete pathological downstaging after chemotherapy can reach up to 22.7%. The authors concluded that the survival benefits of NAC are due to the downstaging of the primary tumor.[7,11] The addition of NAC to the regimens given to patients undergoing bladder preservation is being implemented in several centers. Sternberg et al posited that bladder-sparing can be selected in patients based on their response to NAC.[19] Jiang et al reported a two-year OS of 74% in patients who had NAC, then TMT. They concluded that NAC followed by TMT can have encouraging oncological outcomes.[20] On the other hand, Mirza et al stated that the benefit of NAC with concurrent chemoradiotherapy is not clearly defined yet.[21] Our study has failed to show a positive impact of NAC in TMT patients, although that was not the main hypothesis we were testing. The role of NAC will remain unclear until additional evidence is published, such as a prospective, randomized trial that could provide clarity to the question.[21]

Studying individual factors impacting response to TMT, it has been reported that CIS, along with age, sex, tumor size >3 cm, grade, and number of tumors are predictive factors for progression after bladder preservation.[22] Additionally, patients with large multifocal tumors or tumor-related hydronephrosis have higher rates of recurrence with bladder preservation.[8] Consequently, these patients are often counselled towards RC at our institution. Using multivariable analysis,

we observed that the primary factor associated with bladder tumor recurrence was the presence of concomitant CIS. Mirza et al discussed the factors used to identify patients suitable for bladder preservation. They concluded that the presence of CIS is a strong predictor of recurrence; however, it has little impact on survival so it should not be an absolute contraindication for bladder preservation treatment modalities.[21] Even in RC patients, these findings are substantiated by Thomas et al and Parker et al, who both concluded that although the presence of CIS is associated with decreased complete pathological response to NAC, OS is not impacted.[23,24] In our CIS cohort sub analysis, the OS and disease-free survival were higher in patients who had NAC-TMT compared to patients who had TMT only.

Although not statistically significant, these data are hypothesis-generating, and may suggest that patients with CIS should be directed towards NAC compared to patients without CIS in the TMT setting. Ultimately, care should be taken when counselling patients with CIS for bladder preservation. For example, patients with CIS who opt for TMT may require more frequent cystoscopic assessments or adjuvant intravesical therapies to modify the risk of recurrence in the preserved bladder. Additional research is required to determine the optimal management of patients with CIS who undergo TMT.

Despite its merits, our study has certain limitations that need to be mentioned. First, results were obtained from a retrospective analysis of a multidisciplinary clinic database that includes several urologists, medical, and radiation oncologists. The data are also from a single institution. The presence of unmeasured confounders or those that could not be controlled for with adjustment methods remain a real possibility. Second, the median followup was limited to 3.6 years, but the short life expectancy of patients who undergo TMT likely influences this value. Third, the number of the patients undergoing TMT in the study was only 124 over a long period during which practices changed. However, we anticipate this number will surely increase in the coming years because of the increasing number of patients undergoing TMT for MIBC internationally and at our institution.

Conclusions

Bladder preservation presents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to collaborate in a multidisciplinary team environment. The result is a treatment strategy that maximizes quality of life and can ensure adequate oncological outcomes. This non-randomized study demonstrated that intravesical recurrence after TMT is common and is not influenced by upstream receipt of NAC. Our results have shown that care should be given to patients with CIS because of the increased risk of recurrence, knowing that receipt of NAC does not obviate this risk.

Competing interests: Dr. Sridhar has been an advisory board member for Astellas, Janssen, Pfizer, Roche, and Sanofi; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bayer, Janssen, and Roche. Dr. Fleshner has been a consultant or advisory board member for AbbVie, Amgen, Astellas, Bayer, Ferring, Hybridyne Health, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bavarian Nordic, Bayer, Ferring, Janssen, Medivalion, Nucleix, Progenics Pharmaceutical, Sanofi, and Spectracure AB. Dr. Zlotta has been an advisory board member for Janssen, Rho Inc., and Sanofi. Dr. Catton has been an advisory board member for and received honoraria from AbbVie, Bayer, Janssen, and Sanofi; has received institutional grant support for fellowship programs from AbbVie; and has participated in several clinical trials with OCOG, CCTG, and NRG. Dr. Berlin was a member of the board of directors of Vaccinex Inc. until May 2020; and has received honoraria for research grants and advisory board participation from AbbVie, Astellas, Bayer, Ferring, Janssen, and TerSera. Dr. Chung has received honoraria from Sanofi; and has participated in clinical trials supported by AbbVie. Dr. Kulkarni has been an advisory board member for Ferring, Janssen, Merck, and Theralase; has received honoraria from AbbVie, Amgen, Astellas, Biosyent, Ferring, Janssen, Merck, Roche, and TerSera; and has participated in clinical trials supported by AbbVie, Bristol Myers Squibb, Eleven Biotherapeutics, Merck, and Theralase. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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Correspondence: Dr. Girish S. Kulkarni, Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; girish.kulkarni@uhn.ca