Outcomes of trimodality bladder-sparing therapy for muscle-invasive bladder cancer

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Abstract

Introduction: Although radical cystectomy is considered the standard of care for muscle-invasive bladder cancer (MIBC), recent data has suggested comparable survival outcomes for bladder-sparing trimodality therapy (TMT). We conducted a retrospective, single-institution analysis of MIBC patients to evaluate the efficacy of TMT as an alternative, curative approach to surgical intervention.
Methods: We conducted a retrospective analysis of MIBC patients assessed by a multidisciplinary team at the Juravinski Cancer Centre from 2010–2016. Patients underwent transurethral resection of bladder tumor (TURBT) followed by radiotherapy with or without concurrent chemotherapy. Patients could receive neoadjuvant treatment. Clinical data and response rates were summarized, and overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method.
Results: Our analytic cohort included 115 patients, of whom 53 underwent TMT and 62 underwent radiotherapy alone following TURBT. Median age at diagnosis was 79 years and median followup was 21 months. Complete response rates in those receiving TMT and radiation without chemotherapy were 84.4% and 66.7%, respectively. For TMT patients, three-year OS and DFS were 68.5% and 49.6%, respectively. Patients who received TMT had reduction in risk of mortality (hazard ratio [HR] 0.49; p=0.026) and disease recurrence (HR 0.55; p=0.017) compared to those who had radiation without chemotherapy. Overall, four patients had grade 3 or higher late toxicity.
Conclusions: In this single-institution analysis, TMT appears to be a safe and effective approach in the short-term management of MIBC in appropriately selected patients. Extended followup and analysis are necessary to validate these results.

Introduction

The management of muscle-invasive bladder cancer (MIBC) continues to be a challenge, with clinicians balancing eradication of local disease and micrometastases with maintenance of an optimal quality of life. Given the mean age of diagnosis of 70 and significant association with smoking, MIBC patients often present with multiple comorbidities, which can compound the risks or even limit potential curative treatment options.[1]

In North America, radical cystectomy (RC) is regarded as the gold standard local management for organ-confined MIBC. Although RC is meant to be curative, approximately 40–50% of patients will develop recurrences after surgery, the majority of these occurring within three years.[2] Complications associated with RC have reported rates of postoperative morbidity of up to 64%, and 90-day mortality of up to 3%.[3-5] Sophisticated techniques for urinary reconstruction and diversion have been developed, but even the most advanced urinary drainage system may be a marginal substitute for a native bladder. Alternatively, bladder-sparing treatment involving concurrent chemotherapy and radiotherapy is emerging as a viable alternative to primary RC in selected cases. This treatment strategy provides patients with the opportunity to preserve their own bladder while still receiving radical therapy.

Historically, outcomes with bladder-sparing approaches have been felt to be inferior to surgery. In more recent years, good clinical results have been reported using trimodality therapy (TMT), which involves transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiotherapy, with the option of salvage cystectomy for invasive local recurrence. Five-year survival rates of 50–60% have been reported, with 80–90% of patients maintaining their native bladders post-treatment.[6,7] However, with prospective, comparative, level 1 evidence lacking, there is yet to be widespread acceptance of this approach.

In 2010, a multidisciplinary bladder cancer clinic was established at the Juravinski Cancer Centre (JCC) in association with McMaster University, where patients with bladder cancer are assessed by a joint team of uro-oncologists, medical oncologists, and radiation oncologists. This clinical setting allows for the provision of highly specialized, cohe-

sive care and provides a fertile ground for data collection of various curative approaches in the MIBC context. We conducted a retrospective analysis to describe the outcomes of patients with MIBC seen in a tertiary multidisciplinary clinic treated with bladder-sparing therapy.

Methods

A retrospective review was completed of adult patients (age ≥18 years) assessed in a multidisciplinary bladder clinic at the JCC between January 1, 2010 and December 31, 2016. The JCC is a tertiary care center in Hamilton, Ontario, Canada covering a local health integration network with a catchment of approximately 1.4 million people.[8] Patients included were diagnosed with MIBC on TURBT and received bladder-sparing treatment involving radiotherapy with or without chemotherapy, inclusive of neoadjuvant treatment. Patients with regional lymph node metastases were also included, but those with distant metastases were excluded. Patients were excluded if they had prior radiotherapy to the pelvis, small-cell histology, and palliative or low-dose radiation (<5000 cGy total dose). Institutional research ethics board approval was obtained on July 6, 2017.

Data were abstracted from patient charts by a primary reviewer (EN). Quality assurance was performed by a second reviewer (HY) who verified the data set, collecting 98 discrepancies out of a total of 2917 data points and these were settled by a third investigator (HL). Patient demographics, resection status, pathology, treatment data, tumor response, and survival characteristics were recorded. Treatment data included radiation dose and fractionation, and chemotherapy regimens were recorded for both neoadjuvant and concurrent modalities. Resection status was evaluated from visible disease seen during TURBT. Late toxicity was evaluated as per the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Complete response was defined as no evidence of disease on first followup cystoscopy and radiographic imaging if available, following completion of the treatment course. In the absence of cystoscopy or imaging findings, biopsy is not routine practice to assess for response at the JCC.

Descriptive statistics were used to summarize patient characteristics and outcomes. The Kaplan-Meier method was used to estimate time-to-event outcomes, including the primary outcome of overall survival (OS, defined as the date from diagnosis to death due to any cause), and the secondary outcome of disease-free survival (DFS, defined as the date of diagnosis to relapse or death due to any cause). Patients without an event were censored at last followup. Cox proportional hazards regression was performed to investigate factors potentially prognostic of outcomes. Forward stepwise selection was conducted to construct a multivariable model. Cumulative incidence methods were used to account for the competing risk of non-cancer-related deaths. All tests were two-sided and a $p<0.05$ was considered statistically significant.

Results

Our analytic cohort included 115 patients diagnosed with MIBC between 2010 and 2016 who were treated with TMT (n=53) or radiotherapy without concurrent chemotherapy (n=63). The median age at diagnosis was 79 years, with a median followup of 21 months from the date of diagnosis or initial TURBT. Baseline patient demographics and tumor data are summarized in Table 1.

Treatment characteristics

In total, 53 patients underwent concurrent chemoradiotherapy, 11 of whom received neoadjuvant chemotherapy. Radiotherapy without chemotherapy was given to 57 patients. Additionally, five patients received neoadjuvant chemotherapy followed by radiation alone due to toxicities or patient choice, and these patients were included in the radiotherapy without chemotherapy cohort.

Table 1. Patient and tumor data

Characteristic	n (%)
Age at diagnosis	Median 79; range 47–95
Sex	
Male	87 (75.7)
Female	28 (24.3)
Smoking history	93 (82.3)
Tumor size, cm	Median 3.1; range 0.9–10
Resection status	
Complete	84 (73.0)
Incomplete	31 (27.0)
Pathology	
Urothelial cell	111 (96.5)
Squamous cell	4 (3.5)
T stage	
T2	95 (82.6)
T3	15 (13.0)
T4	5 (4.4)
N stage	
N0	107 (93.0)
N1	3 (2.6)
N2	5 (4.3)
Grade	
High	111 (96.5)
Low	4 (3.5)
Hydronephrosis	37 (32.2)
Tumor-associated carcinoma in situ	11 (13.8)
Lymphovascular invasion	17 (14.8)
Response to treatment	
Complete	68 (59.1)
Incomplete	22 (19.1)
No cystoscopy	25 (21.7)

The most common radiation fractionation schedule was 4500 cGy in 25 fractions to the pelvis, with an additional 1498 cGy in eight fractions to the bladder (45 patients; 39.1%). The next most common fractionation was 6000 cGy in 30 fractions to the bladder alone (33 patients; 28.7%). Neoadjuvant chemotherapy consisted of four cycles of either gemcitabine and cisplatin (12 patients; 75%) or methotrexate, vinblastine, doxorubicin, and cisplatin (four patients; 25%). In terms of concurrent chemotherapy regimen, 42 patients (79.2%) received weekly cisplatin, five patients (9.4%) received weekly carboplatin, five patients (9.4%) received concurrent 5-fluorouracil and mitomycin C, and one patient (1.9%) received weekly gemcitabine.

Response to treatment

Of 53 patients receiving concurrent chemoradiotherapy, 38 (71.7%) had a complete response. In contrast, of 62 patients who received radiation without concurrent chemotherapy, 30 (48.4%) had a complete response. Overall, nine (7.8%) had only non-muscle-invasive recurrence, 16 (13.9%) had muscle-invasive recurrence alone, 20 (17.4%) had distant recurrence, and eight (7.0%) had both invasive and distant recurrence (Table 2). Two patients were found to have upper tract disease of urothelial origin. Among the 68 patients who initially had complete response to treatment, 10 (14.7%) had bladder recurrence (eight invasive, two non-invasive), one (1.5%) had local nodal recurrence, and seven (10.3%) had distant recurrence. At last known followup, 32 (47.1%) complete responders to either treatment were alive without evidence of disease, four (5.9%) patients died from bladder cancer, 11 (16.2%) died from other causes, and 12 (17.6%) were lost to followup. In total, four patients (3.5%) had salvage cystectomy, all of whom did not have complete response to their primary treatment. Of note, 25 patients did not have a post-treatment cystoscopy due to disease progression or distant metastases (13), loss to followup (two), death from another cause (two), patient preference (three), or unlikelihood of pursuing salvage treatment in the event of a recurrence (five).

Treatment toxicities

A total of four patients (3.5%) had grade 3 or greater late toxicity, two of whom had concurrent chemoradiotherapy and two received radiation alone following TURBT. These cases included severe urinary incontinence, nocturia, and proctitis causing bleeding. One patient had an aortoenteric fistula in the fourth part of the duodenum. However, being at the level of L3, this would not have been directly in the field of the patient's radiation and, after review, it was not felt to be toxicity from his treatment but rather chronic inflammation and ulceration. There were no incidences of cystectomy for treatment-related bladder toxicity. Of the four patients who had salvage cystectomy, toxicities included a postoperative small bowel obstruction in one patient and acute kidney injury in two patients, one of whom required a percutaneous nephrostomy tube.

Survival

The three-year OS and DFS rates for all 115 patients were 68.9% (95% confidence interval [CI] 58.5, 77.1) and 39.5% (95% CI 29.6, 49.2), respectively. In the 53 patients who had

Table 2. Outcome and recurrence data

	No. of patients (%)	3-year OS	3-year DFS	3-year cumulative incidence of recurrence	Non- muscle-invasive recurrence only (%)	Muscle-invasive recurrence only (%)	Metastatic disease only (%)	Muscle-invasive + metastatic disease (%)	Salvage cystectomy (%)
Concurrent chemoradiotherapy	53 (46.1)	68.5	49.6	20.7	3 (5.7)	7 (13.2)	11 (20.8)	3 (5.7)	1 (1.9)
Neoadjuvant chemotherapy + chemoradiotherapy*	11 (9.6)	26.0	53.7	39.0	1 (9.1)	0 (0.0)	3 (27.3)	0 (0.0)	0 (0.0)
Radiotherapy without concurrent chemotherapy†	62 (53.9)	50.1	30.7	27.8	6 (9.7)	9 (14.5)	9 (14.5)	5 (8.1)	3 (4.8)
All patients	115	58.9	39.5	24.4	9 (7.8)	16 (13.9)	20 (17.4)	8 (7.0)	4 (3.5)
Concurrent chemoradiotherapy (surveillance cystoscopy)	46 (40.0)	80.8	58.0	13.5	3 (6.5)	7 (15.2)	6 (13.0)	2 (4.4)	1 (2.2)
Radiotherapy without concurrent chemotherapy (surveillance cystoscopy)	46 (40.0)	54.7	31.0	18.2	6 (13.0)	9 (19.6)	4 (8.7)	5 (10.9)	3 (6.5)
No surveillance cystoscopy	23 (20.0)	20.9	18.5	62.6	0 (0.0)	0 (0.0)	10 (43.5)	1 (4.4)	0 (0.0)

*Patients are included in the concurrent chemoradiotherapy cohort. †Five patients received neoadjuvant chemotherapy. DFS: disease-free survival; OS: overall survival.

concurrent chemoradiotherapy, three-year OS and DFS rates were 68.5% (95% CI 51.1, 80.8) and 49.6% (95% CI 33.6, 63.7), respectively. When excluding those patients who did not have followup cystoscopy, the 46 concurrent chemoradiotherapy patients had three-year OS and DFS rates of 80.8% (95% CI 63.7, 90.4) and 58.0% (95% CI 39.9, 72.4). Complete survival data is presented in Table 2.

Survival data of patients who received concurrent chemoradiotherapy were compared to those who had radiation alone following TURBT (Fig. 1). Risk of mortality (hazard ratio [HR] 0.49; p=0.026) and disease recurrence (HR 0.55; p=0.017) were both reduced with the addition of concurrent chemotherapy. Furthermore, the chemoradiotherapy cohort was divided into those with and without neoadjuvant chemotherapy (Fig. 2). There were no significant differences in mortality (HR 2.02; p=0.25) or disease recurrence (HR 0.80; p=0.69) in these groups. Survival data of all patients were plotted based on the extent of resection on initial TURBT (Fig. 3).

Prognostic factors for survival

Univariate and multivariate analyses for predictors of OS and DFS are listed in Tables 3 and 4. In the multivariate analyses for all patients, the use of concurrent chemotherapy and age were significant predictors of DFS (Table 4). TURBT resection status and presence of hydronephrosis were significant predictors of both OS and DFS in all patients. In the multivariate analyses for the 53 patients who received concurrent chemoradiotherapy, age and complete TURBT resection were again significantly associated with both OS and DFS. Presence of hydronephrosis was predictive of OS, but not of DFS.

Discussion

In this single-institution, retrospective analysis, we show preliminary results in MIBC patients treated with TMT, with three-year OS and DFS of 68.5% and 49.6%, respectively, when receiving chemoradiotherapy after TURBT. These findings are in keeping with other reported series for bladder-sparing outcomes.[6,7,9] Our data builds upon emerging evidence that TMT is well-tolerated, with a grade 3 or greater late toxicity rate of 3.5%, and adds to the growing data supporting the use of bladder-sparing treatment with curative intent.

The use of non-surgical approaches to MIBC has been proportionally decreasing over time in some jurisdictions.[10] Certain ideas, such as the belief that TMT has worse patient survival and greater morbidity compared to RC, may contribute to the reluctance in offering bladder-sparing approaches in eligible patients.[11,12] Furthermore, structural barriers, such as the absence of multidisciplinary clinics and logistical difficulties, play a role in the reduced implementation.[11,12] One academic institution found that only 10% of RC patients saw a radiation oncologist prior to surgery.[13] Another study reported that between 2005 and 2012, only 29% of MIBC patients received consultation regarding the use of systemic therapy at a major American institution.[14]

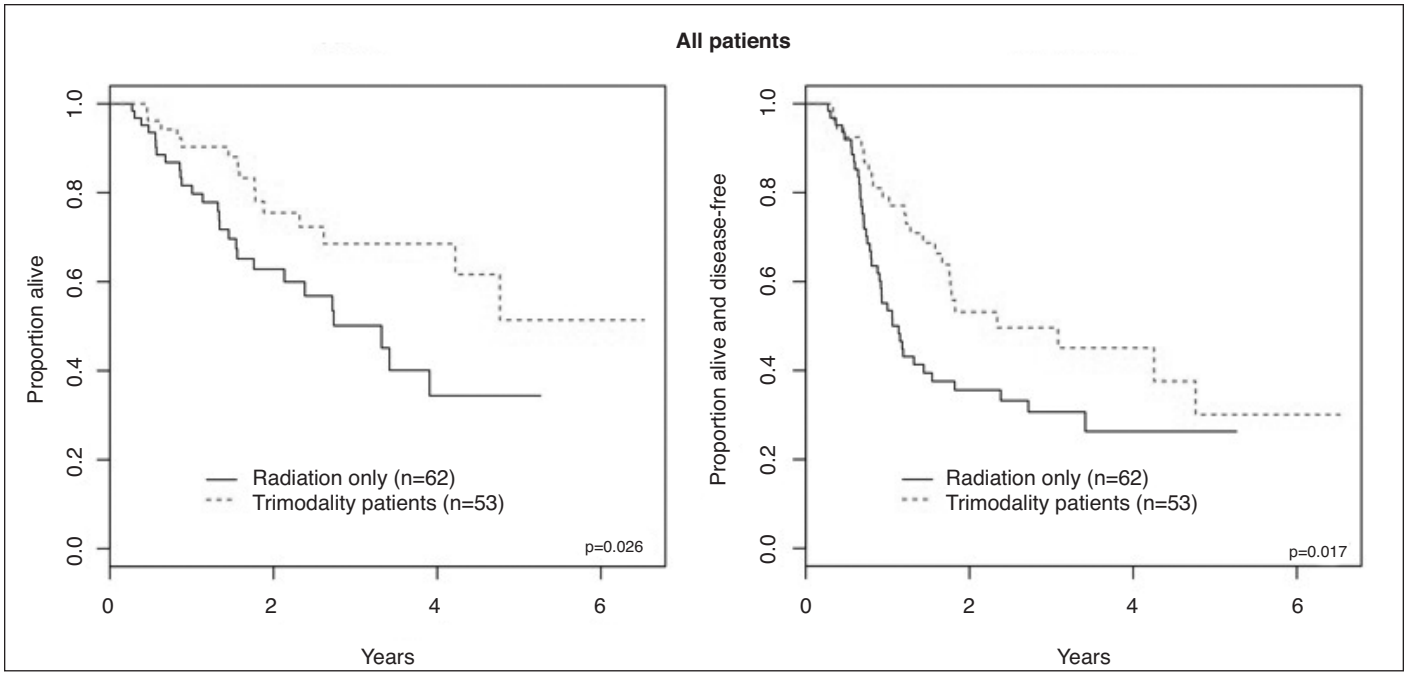

Fig. 1. Survival of patients receiving chemoradiotherapy vs. radiation without concurrent chemotherapy.

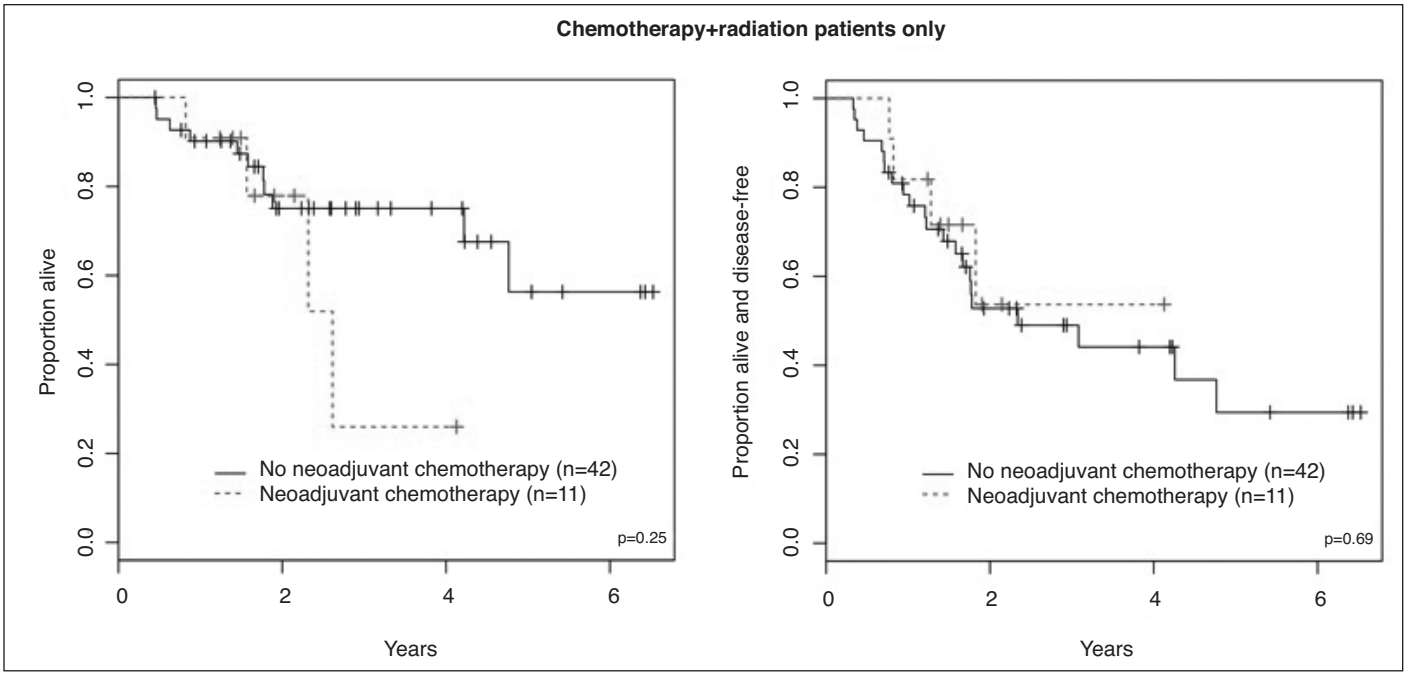

Fig. 2. Survival of concurrent chemoradiotherapy patients with and without neoadjuvant chemotherapy.

Multidisciplinary clinics have been a vital resource in improving collaboration among physicians involved in MIBC treatment and allow for optimization of treatment decisions in complex scenarios. There is evidence that referral rates between urology, medical oncology, and radiation oncology significantly improve after a multidisciplinary approach is diligently applied.[15] One institution found that after initiating multidisciplinary care for MIBC, the proportion of patients receiving neoadjuvant chemotherapy increased from 7% to 42%.[16] In addition, two systematic reviews reported a positive association between multidisciplinary care and improved patient survival and satisfaction.[17,18] This model can empower individuals to tailor their treatment to better serve their own health goals,

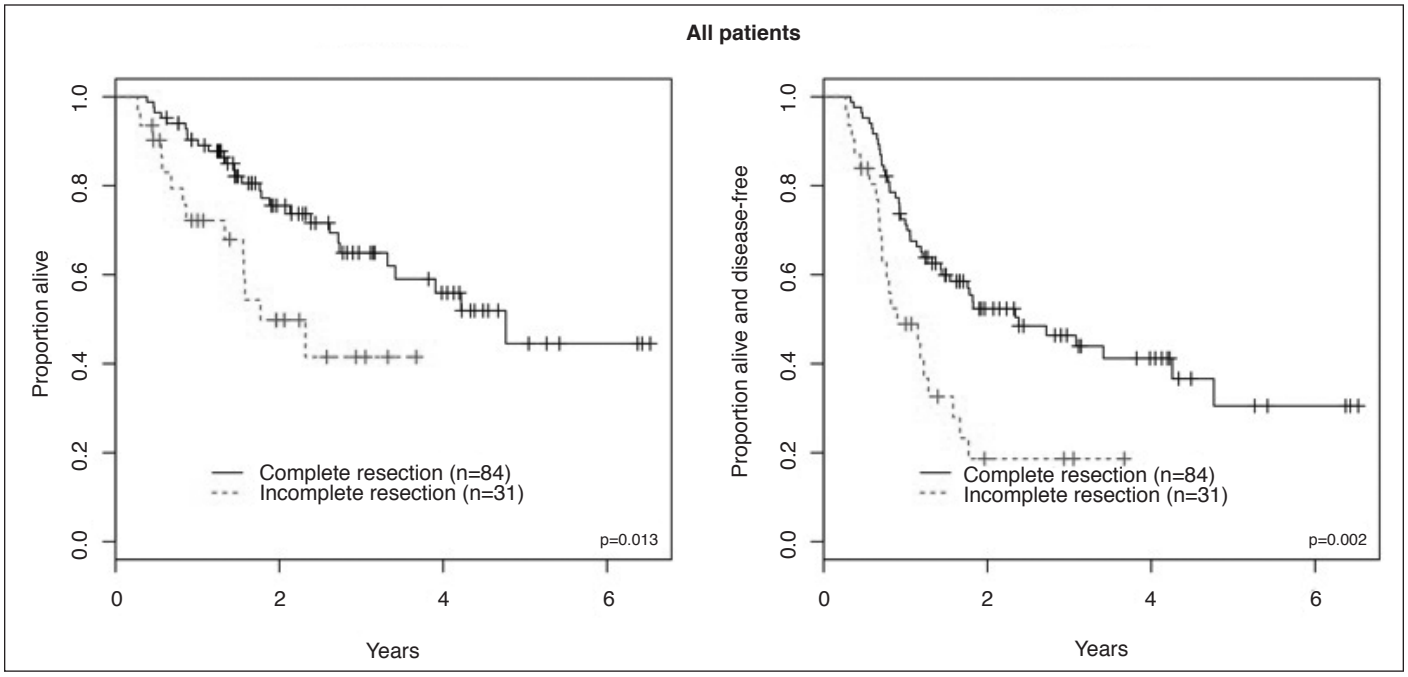

Fig. 3. Survival of patients receiving complete vs. incomplete resection on initial transurethral resection of bladder tumor.

Table 3. Univariate analysis for predictors of overall survival and disease-free survival

Characteristic	Statistic	Overall survival		Disease-free survival	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
All patients					
Hydronephrosis	Presence vs. absence	2.54 (1.38, 4.66)	0.003	1.95 (1.19, 3.18)	0.008
Resection status	Complete vs. incomplete	0.43 (0.22, 0.84)	0.013	0.43 (0.26, 0.73)	0.002
Age	Continuous	0.99 (0.96, 1.02)	0.51	0.97 (0.95, 1.00)	0.021
Gender	Female vs. male	1.05 (0.53, 2.09)	0.89	0.81 (0.46, 1.44)	0.48
Smoking history	No vs. yes	1.40 (0.67, 2.93)	0.38	1.24 (0.68, 2.28)	0.49
Tumor size	Log-transformed	2.15 (0.88, 5.26)	0.092	3.99 (1.95, 8.18)	<0.001
T stage	3–4 vs. 2	1.12 (0.50, 2.52)	0.79	1.35 (0.74, 2.47)	0.34
Lymphovascular invasion	No vs. yes	0.91 (0.38, 2.17)	0.83	0.79 (0.41, 1.51)	0.47
Chemotherapy	Yes vs. no	0.49 (0.26, 0.92)	0.026	0.55 (0.33, 0.90)	0.017
Neoadjuvant chemotherapy	Yes vs. no	0.94 (0.26, 0.92)	0.89	0.91 (0.48, 1.97)	0.93
Concurrent chemoradiotherapy					
Hydronephrosis	Presence vs. absence	3.87 (1.21, 12.33)	0.022	2.03 (0.69, 5.98)	0.20
Resection status	Complete vs. incomplete	0.28 (0.09, 0.82)	0.021	0.25 (0.11, 0.59)	0.002
Age	Continuous	0.96 (0.92, 0.99)	0.021	0.96 (0.92, 0.99)	0.021
Gender	Female vs. male	1.68 (0.53, 5.31)	0.38	1.53 (0.64, 3.65)	0.34
Smoking history	No vs. yes	0.65 (0.09, 4.98)	0.68	0.76 (0.18, 3.24)	0.71
Tumor size	Log-transformed	2.43 (0.58, 10.25)	0.23	6.27 (2.07, 19.01)	0.001
T stage	3–4 vs. 2	0.72 (0.16, 3.20)	0.67	1.78 (0.74, 4.24)	0.20
Lymphovascular invasion	No vs. yes	1.11 (0.25, 5.03)	0.89	0.81 (0.30, 2.16)	0.67
Neoadjuvant chemotherapy	Yes vs. no	2.02 (0.62, 6.62)	0.25	0.80 (0.27, 2.36)	0.69

CI: confidence interval.

while stratifying patients according to the best current practice guidelines.

Recent data on the use of bladder-preserving therapy for MIBC has shown promising results as an alternative to RC. Kulkarini et al conducted a propensity score matched-cohort analysis with patients undergoing TMT and RC, and showed five-year disease-specific survival (DSS) of 76.6% and 73.2%, respectively, which is in keeping with modern MIBC cystectomy series.[6] In addition, Giacalone et al conducted an analysis of successive prospective protocols for 475 patients treated with bladder-sparing treatment and found long-term DSS rates comparable to those reported in RC data.[7]

With respect to contemporary RC outcomes, Dalbagni et al followed 300 patients post-cystectomy and found a three-year OS of 70%, with a five-year OS of 57%.[19] Furthermore, a multicenter review by Sonpavde et al analyzed 2724 patients with T2–T4 disease treated with RC and found a two-year DFS of 63% and three-year DFS of 57%.[20] In comparison, the TMT patients in our study had somewhat poorer outcomes. There is an inherent selection bias in comorbidities and performance status when comparing all-comers receiving bladder-preserving treatments to surgical candidates. These differences can be appreciated in our patient population's mean age, which was 11.2 years greater than the RC patients

Table 4. Multivariate analysis for predictors of overall survival and disease-free survival

Characteristic	Statistic	Overall survival		Disease-free survival	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
All patients					
Hydronephrosis	Presence vs. absence	3.09 (1.59, 6.03)	<0.001	2.03 (1.13, 3.63)	0.017
Resection status	Complete vs. incomplete	0.38 (0.19, 0.76)	0.006	0.34 (0.20, 0.59)	<0.001
Age	Continuous	0.96 (0.93, 1.00)	0.051	0.94 (0.91, 0.96)	<0.001
Chemotherapy	Yes vs. no	—	—	0.38 (0.21, 0.70)	0.002
Lymphovascular invasion	Yes vs. no	—	—	2.08 (1.04, 4.15)	0.038
Concurrent chemoradiotherapy					
Hydronephrosis	Presence vs. absence	5.59 (1.52, 20.61)	0.010	—	—
Resection status	Complete vs. incomplete	0.20 (0.06, 0.67)	0.009	0.17 (0.07, 0.44)	<0.001
Age	Continuous	0.93 (0.88, 0.99)	0.015	0.94 (0.91, 0.98)	0.002

CI: confidence interval.

in the aforementioned review.[20] Similarly, when comparing our data to other TMT series, there can be a degree of selection bias with study protocols excluding those with advanced age, hydronephrosis, and comorbidities that preclude them from ideal treatment options.

The benefit of adding concurrent chemotherapy to radiotherapy as a sensitizing agent has been well-established in bladder cancer. Notably, a multicenter, phase 3 trial by James et al showed that chemoradiotherapy had benefits in DFS, with a relative reduction of 33% in risk of locoregional recurrence and 50% in invasive recurrence compared to radiation without chemotherapy.[9] Conversely, there is less of a consensus regarding the potential benefit of neoadjuvant chemotherapy when used in conjunction with bladder-sparing approaches. An international phase 3 trial (BA06 30894) looked at patients receiving neoadjuvant chemotherapy prior to radiotherapy or cystectomy and performed a subgroup analysis of the 403 patients undergoing radiotherapy alone.[21] They found a 20% reduction in risk of death and 9% reduction in locoregional recurrence with the addition of neoadjuvant treatment. Conversely, RTOG 8903 found no difference in complete response or OS with or without neoadjuvant chemotherapy;however, the study was underpowered, as one-third of the patients stopped treatment early due to severe toxicities.[22]

Our data showed that TMT is generally well-tolerated with few complications, and there were low rates of grade 3 or greater late toxicity in our patient cohort. This aligns with published data that suggests TMT patients have similar long-term urinary, bowel, and sexual function in comparison to RC patients.[23,24] In particular, Zietman et al reported on a series of MIBC patients following TMT and found 75% of them had normally functioning bladders by urodynamic studies.[24] These patients were favored to have a high quality of life based on global health parameters, as well as an improved perception of body image post-treatment compared to RC.[22,24] In addition, data from Giacalone et al found that receiving TMT prior to salvage cystectomy did not significantly affect perioperative mortality or postoperative complications.[7]

Our study was limited by its retrospective design, heterogeneous population, and short median followup time restricting the application of long-term survival outcomes in this cohort. This was also a single-center report at a tertiary care clinic, and results may not be generalizable to other centers with varying multidisciplinary structures. It is important to highlight the fact that 25 patients did not have a followup cystoscopy to assess response following treatment. It was felt that these patients should be included to represent a more accurate portrayal of the patient population being considered for TMT. Furthermore, our study had only 16 patients in total receiving neoadjuvant chemotherapy, five of whom were in the radiotherapy without concurrent chemotherapy cohort. As a result, the ability to make inferences about survival outcomes for patients who received neoadjuvant therapy followed by bladder-sparing treatment is limited by sample size and heterogeneous treatment allocation. Finally, in addition to the selection bias between our cohort and RC patients in the literature, those receiving TMT vs. radiotherapy without chemotherapy in our study may also differ in performance status and disease burden, favoring those who are able to tolerate a full course of concurrent chemoradiotherapy.

Conclusions

Our study supports the concept of curative bladder-sparing treatment of TMT in MIBC but given the median followup of 21 months, these findings warrant continued surveillance to obtain longer-term data. Currently, RC remains a standard option for patients with MIBC, and in the absence of randomized, control trials, care should be taken with direct comparisons between RC and TMT modalities. However, for appropriately selected patients, TMT is a safe and effective alternative while retaining one's native bladder. Patients with MIBC should be assessed jointly by uro-oncologists, radiation oncologists, and medical oncologists in the setting of a multidisciplinary bladder clinic to review all treatment options prior to embarking on potentially curative therapy.

Competing interests: Dr. Pond has received honoraria from Takeda. Dr. Pinthus has been an advisory board member and speakers' bureau member for and received honoraria from Ferring. Dr. Kapoor has been an advisory board member for BMS, Eisai, Ipsen, Novartis, Pfizer, and Roche; and a speakers' bureau member for Novartis. Dr. Mukherjee has been a speakers' bureau member for AstraZeneca; has received honoraria from Amgen, AstraZeneca, Merck, Novartis, and Roche; and has participated in clinical trials supported by AstraZeneca and Roche. Dr. Lalani has received honoraria for ad hoc consultation or advisory board meetings from BMS, Eisai, Ipsen, Merck, Pfizer, Rocher and TerSera; and has participated in clinical trials (unrelated to this work) supported by Merck. Dr. Dayes has been an advisory board member for Abbvie and Astellas; and has participated in clinical trials supported by Bayer. Dr. Lukka has been a speakers' bureau member for and received honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Sanofi, and TerSera; has investments in Vertex Pharma; and has participated in clinical trials supported by Sanofi. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed

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