

## Research Letter

# Trimodality Treatment for Muscle-Invasive Bladder Cancer: An Institutional Experience



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## Abstract

**Purpose:** As an alternative to radical cystectomy, tri-modality treatment (TMT) is an effective treatment approach for selected patients with muscle-invasive bladder cancer (MIBC). The purpose of this report is to contribute to the literature by summarizing institutional outcomes of a bladder-preserving TMT approach for patients with MIBC.

**Methods and Materials:** Patients treated with TMT for MIBC from 1998 to 2019 were identified. Patient, disease, and treatment factors were recorded. Overall survival (OS), disease-free survival (DFS), and bladder-preserved DFS were estimated with the Kaplan-Meier method. Prognostic factors were evaluated with Cox proportional hazards regression.

**Results:** Thirty-two patients treated with TMT to a median dose of 64.8 Gy for T2 (78%), T3 (19%), and T4 (3%) disease were followed for a median of 19 months (mean, 36; range, 6-213); 31% had associated carcinoma in situ; 25% had associated hydronephrosis. Cisplatin was the most commonly used chemotherapeutic agent. OS rates were 84% at 1 year and 61% at 5 years. DFS rates were 84% and 61% and bladder-preserved DFS rates were 84% and 60% at 1 year and 5 years, respectively. Salvage cystectomy rates at 1 year and 5 years were 4% and 9%, respectively. Four patients had locally invasive recurrences at 8, 11, 34, and 37 months after initial MIBC diagnosis, 2 of whom underwent salvage radical cystectomy. Ten (31%) patients developed distant disease at a median of 13 months after diagnosis. Unlike local recurrence, distant recurrences were associated with worse OS and hazard ratios of 3.4 ( $P = 0.039$ ).

**Conclusions:** OS and DFS were comparable to those of published data. Our outcomes support TMT as an effective option for carefully selected patients with MIBC.

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## Introduction

Bladder cancer was the sixth most common cancer site in the United States in 2019.<sup>1</sup> Muscle-invasive bladder

cancer (MIBC) is disease invasive to at least the muscularis layers of the bladder (stage T2, American Joint Committee on Cancer Eighth Edition) and may extend to perivesical tissue or beyond (stage T3 or T4).<sup>2</sup> MIBC represents approximately 25% of all localized bladder cases and (compared with other lower stages) portends a worse prognosis with higher rates of metastasis and cancer mortality at 6 months if untreated.<sup>3</sup> Treatment options include radical cystectomy (RC) or organ-preserving tri-modality treatment (TMT) consisting of maximal transurethral resection of bladder tumor (TURBT), radiation therapy

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(RT), and chemotherapy. With a median presenting age above 70 years, MIBC treatment should ideally seek balance between adequate curative therapy and consideration of patient comorbidities, performance status, and quality of life. No randomized data exist adequately comparing RC to TMT to guide management decisions. We present a retrospective analysis of the TMT experience at a large academic medical center with the goal of enhancing the bladder preservation literature.

## Methods and Materials

### Patient identification and selection

We identified patients with a histologically confirmed diagnosis of MIBC (staged T2 or greater) who received curative intent bladder preserving therapy at our institution from 1998 to 2019. Information on patient, disease, and treatment characteristics was collected after approval by the institutional review board.

**Table 1** Patient, tumor, and treatment characteristics

Characteristic	No. (%) / Median & IQR
Age at diagnosis (y)	Median, 73.5; IQR, 64.5-80
Sex	
Male	25 (78.1)
Female	7 (21.9)
Clinical stage	
T2	25 (78.1)
T3+	7 (21.9)
Tumor size (cm)	Median, 3.5; IQR, 2-5
Tumor histology	
Urothelial	26 (81.3)
Other	6 (18.7)
Tumor-associated CIS	
Present	10 (31.3)
Absent	18 (56.3)
Unknown	4 (12.5)
Hydronephrosis	
Present	8 (25.0)
Absent	23 (71.9)
Unknown	1 (3.1)
Neoadjuvant chemo	
Yes	12 (37.5)
No	19 (59.4)
Unknown	1 (3.1)
TURBT	
Visibly complete	17 (53.1)
Incomplete	9 (28.1)
Unknown	6 (18.8)
RT dose (Gy)	Median, 64.8; IQR, 61.2-64.8

*Abbreviations:* CIS = carcinoma in situ; IQR = interquartile range; RT = radiation therapy; TURBT = transurethral resection of bladder tumor.

### Follow-up and disease status evaluation

Follow-up evaluation after completion of treatment most recently has involved urine cytology and regular cystoscopy with TURBT (as needed) at 3-month intervals for the first year with less frequent follow-up afterward. At the time of this analysis, 5 patients were lost to follow-up, with no record of continued oncologic/palliative care or death.

### Statistical analysis

All survival periods, including overall survival (OS), were defined from date of histologic confirmation of MIBC. Disease-free survival (DFS) was defined by date of invasive local recurrence or distant metastasis. Bladder-preserved DFS (bpDFS) was defined as DFS in the setting of preserved native bladder.

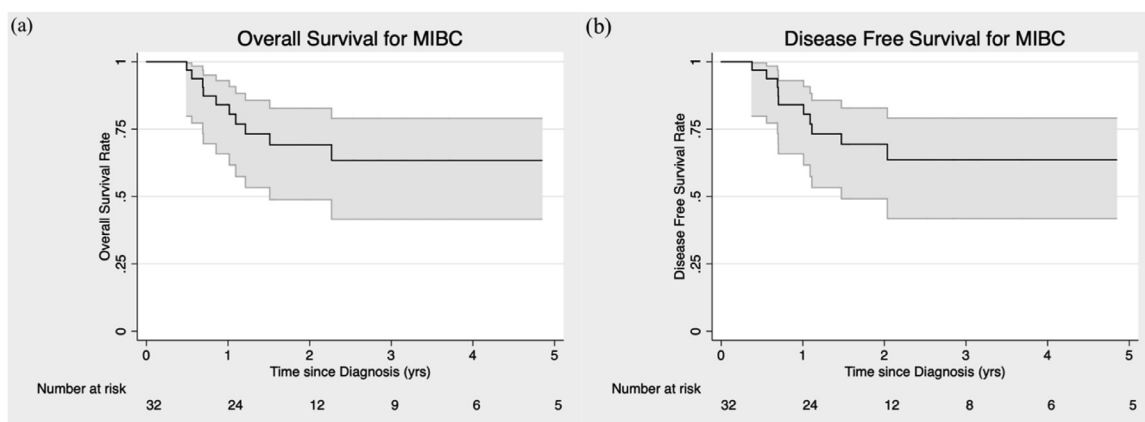
Kaplan-Meier survival analysis was used to calculate OS, DFS, and bpDFS rates; statistical comparisons between groups were done with log-rank analysis. Univariate regression was done using Cox proportional hazard regression. A *P* value of < .05 was considered statistically significant. All analyses were performed in STATA software version 14.2 (StataCorp LLC, College Station, TX).

## Results

### Patient, tumor, and treatment characteristics

Thirty-two patients with a median age of 74 treated with TMT for MIBC were identified at our institution from 1998 to 2019 (Table 1). Median follow-up was 19 months (mean, 36; range, 6-213) for all patients. For the 15 surviving patients with current oncologic care, median follow-up was 30 months (mean, 50; range, 17-213).

Of the 32 patients, 25 (78%) had T2 disease, 6 (19%) had T3 disease, and 1 (3%) had T4 disease. Twenty-six (81%) patients had urothelial histology, 4 (13%) had neuroendocrine/small cell, 1 (3%) had adenocarcinoma, and 1 (3%) had sarcomatoid histology. Cisplatin was the most commonly used neoadjuvant (in 83% of the 12 patients receiving neoadjuvant chemotherapy [NAC]; 42% received combination methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC]) and concurrent chemotherapeutic agent (33%). Other agents included gemcitabine in 9 (30%) patients and 5-fluorouracil in 6 (20%) patients. Two patients did not receive chemotherapy. Radiation therapy was to a mean dose of 64.8 Gy using intensity modulated radiation therapy (including with volumetric modulated arc therapy) in 47% of cases.



**Figure 1** Survival rates for muscle-invasive bladder cancer (MIBC).

### Failure and salvage cystectomy

Four patients had local, invasive recurrences at 8, 11, 34, and 37 months after initial MIBC diagnosis. Two patients, both with invasive local recurrence, underwent salvage radical cystectomy at 8 and 15 months after diagnosis; 1 patient was managed nonoperatively and 1 patient developed evidence of distant disease 4 months beyond local recurrence. Initial distant recurrences were more common, with 10 (31%) patients developing distant disease at a median of 13 months after diagnosis. Rates of salvage cystectomy at 1 year and 5 years were 4% and 9%, respectively. There were no cystectomies or prolonged intervention for late high-grade (ie, 3 or 4) radiation-induced toxicity or bleeding; unfortunately, graded toxicity was not uniformly recorded across the timespan covered in this study period.

### Cancer-related outcomes

OS rates were 84% and 61% at 1 year and 5 years, respectively. DFS rates were 84% and 61% at 1 year and 5 years, respectively (Fig 1). bpDFS rates were 84% and 60% at 1 year and 5 years, respectively (Table 2). Any recurrence (local or distant) was non-significantly associated with poorer OS, with a hazard

ratio of 2.7 (95% confidence interval [CI], 0.8-9;  $P = .098$ ). In comparison to local recurrence, distant recurrences were significantly associated with OS, with a hazard ratio of 3.4 (95% CI, 1.1-11;  $P = .039$ ) (Fig. 2). Figure 3 shows numerically superior outcomes with complete TURBT and T2 stage (compared with T3/T4); however, this was not statistically significant ( $P = .16, .34$  respectively). No other patient, tumor, or treatment variables were statistically significant predictors of cancer-related outcomes.

### Discussion

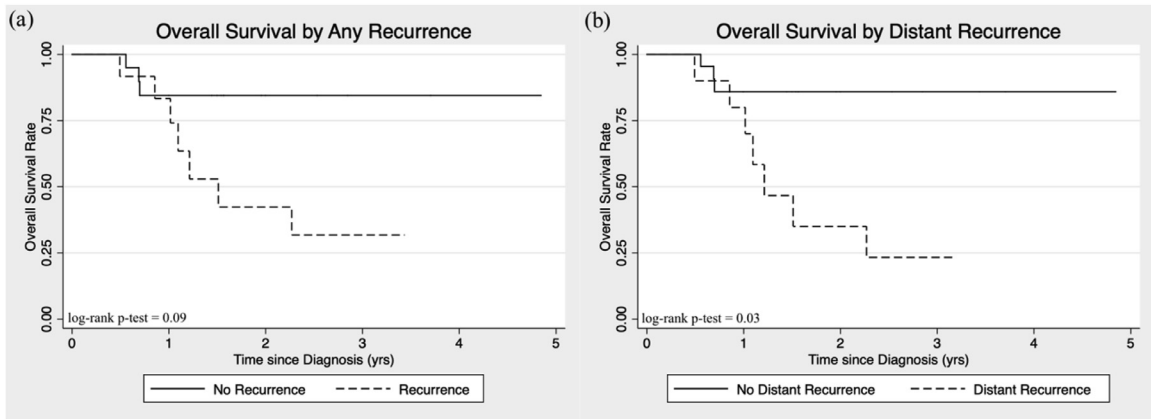
In this retrospective series, we aimed to summarize the TMT experiences at our institution and contribute to the literature regarding the selection and management of patients in a bladder-preserving treatment approach.

The most common curative treatment for MIBC has historically been RC, with 5-year recurrence-free and OS rates of 68% and 66%, respectively.<sup>4</sup> These results are in line with and comparable to findings from a large, multi-trial pooled analysis of 6 Radiation Therapy Oncology Group studies with 5-year DFS and OS of 71% and 57%.<sup>5</sup> Our institutional experience with bladder preservation yields similar oncologic control rates with 5-year DFS and OS of 61% (95% CI, 37%-77%) and 61% (95% CI, 38%-77%), respectively. Further, in our cohort, 22% of patients had T3 or greater disease and only 53% had confirmed visibly complete TURBT. Other single-institutional data reveal that TMT may yield DFS rates approaching 85% at 5 years when examining a more carefully selected cohort (with complete TURBT, etc).<sup>6</sup> Although distant recurrence was associated with poorer OS, local recurrence was not; 4 patients have had locally recurrent disease, none of whom died. This highlights the importance of close clinical (incorporating cystoscopy and urine cytology) and radiographic follow-up after

**Table 2** Survival and bladder preservation rates

Characteristic	1 year	5 year
Overall survival	84%	61%
DFS	84%	61%
Bladder preserved DFS	84%	60%
Cumulative salvage RC	4%	9%

Abbreviations: DFS = disease free survival; RC = radical cystectomy.



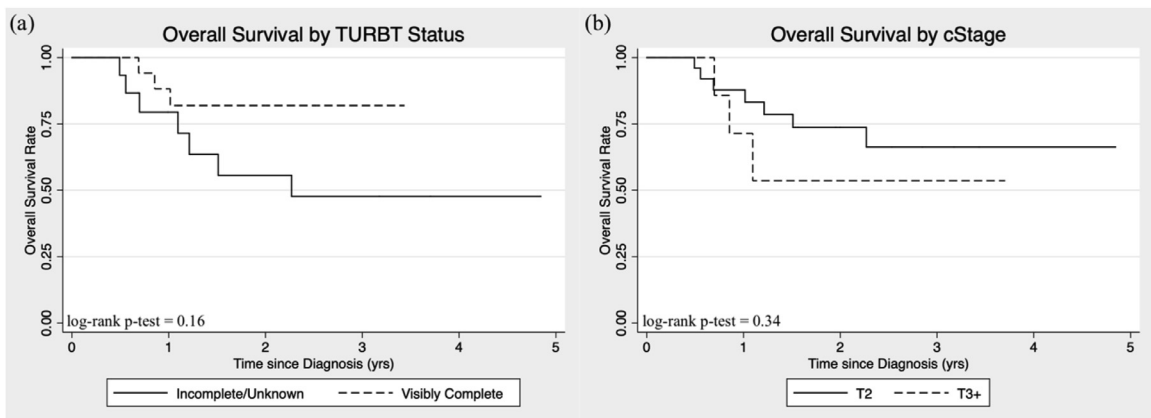
**Figure 2** Disease recurrence and survival.

TMT. These patients may undergo successful surgical salvage.

Our institutional approach (especially in recent years) is to use intensity modulation radiation therapy with inclusion of the draining lymphatics; patients are simulated and treated using an empty bladder geometry that is confirmed with daily image guidance with cone beam computed tomography. Almost 40% of patients in our series received NAC before chemoradiation. Of those undergoing NAC, more than 80% received cisplatin-based chemotherapy regimen with 42% getting MVAC. These factors were not statistically significant predictors of survival in our analysis. Randomized trial data show that NAC improves survival rates before RC, but these findings have not been replicated with TMT.<sup>7</sup> An older study, Radiation Therapy Oncology Group 8903, found no benefit with the addition of 2 cycles of MVAC before TMT with 64.8 Gy.<sup>8</sup> However, such a strategy has been undergoing further examination more recently – a large series of patients receiving NAC followed by chemoradiation demonstrated that 2 to 4 cycles of gemcitabine and cisplatin were well tolerated and resulted in 2-year OS of 74%.<sup>9</sup>

The largest patient series, from Massachusetts General Hospital, reported 5-year local invasive recurrence rates and distant failure rates of 16% and 32%, respectively.<sup>6</sup> A current, ongoing study, SWOG/NRG-s1806, is slated to become the largest prospective trial of TMT ever conducted. Although the trial is testing the addition of immune checkpoint inhibitor atezolizumab to TMT, it will provide important prospective validation of TMT for a carefully selected patient population ideal for the therapy.

Our study is limited in that, as a retrospective analysis, no uniform selection criteria for TMT in patients was applied. TMT in this cohort was offered to patients who were not ideal candidates and had other factors such as T3+ disease, presence of hydronephrosis, carcinoma in situ, and lack of visibly complete TURBT, all of which have been shown as predictors of poorer disease control and OS.<sup>6</sup> Although these variables were associated with poorer outcomes in this cohort, the results were not statistically significant, due in part to the limited number of patients in this series. Despite the patient heterogeneity, this cohort’s outcomes are comparable to similar series. This means that for better-selected patients, TMT could



**Figure 3** Transurethral resection of bladder tumor (TURBT) status, clinical stage, and survival.

yield even better results and thus represent a very viable treatment modality for certain patients.

To date, although attempted, no randomized controlled trial has been able to adequately compare outcomes between RC and TMT.<sup>10,11</sup> Multiple challenges exist when attempting to randomize patients to these very different treatment modalities, including strong preferences expressed by patients and providers.<sup>12</sup> For these reasons, the decision to pursue either RC or TMT requires a multidisciplinary approach and elucidation of careful selection criteria for bladder preservation.

## References

1. Howlader N, Krapcho M, Miller D, et al., eds. SEER Cancer Statistics Review, 1975-2016. Bethesda, MD: National Cancer Institute; 2020. Available at: [http://seer.cancer.gov/csr/1975\\_2012/](http://seer.cancer.gov/csr/1975_2012/). Accessed June 22, 2020.
2. *AJCC Cancer Staging Manual*. 8th ed. Chicago, IL: American Joint Committee on Cancer, Springer; 2017.
3. Martini A, Sfakianos JP, Renstrom-Koskela L, et al. The natural history of untreated muscle invasive bladder cancer. *BJU Int*. 2020;125:270–275.
4. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. *J Clin Oncol*. 2001;19:666–675.
5. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol*. 2014;32:3801–3809.
6. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: An updated analysis of the Massachusetts General Hospital experience. *Eur Urol*. 2017;71:952–960.
7. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349:859–866.
8. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: Initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*. 1998;16:3576–3583.
9. Jiang DM, Jiang H, Chung PWM, et al. Neoadjuvant chemotherapy before bladder-sparing chemoradiotherapy in patients with nonmetastatic muscle-invasive bladder cancer. *Clin Genitourin Cancer*. 2019;17:38–45.
10. Ploussard G, Daneshmand S, Efstathiou JA, et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: A systematic review. *Eur Urol*. 2014;66:120–137.
11. Huddart RB, Lewis R, Bahl A, Falconer A, Maynard L, Hall E. Results of the SPARE feasibility study – selective bladder preservation against radical excision in muscle invasive T2/T3 transitional cell carcinoma of the bladder (CRUK/07/011). *Int J Radiat Oncol Biol Phys*. 2012;84:S119–S120.
12. Paramasivan S, Huddart R, Hall E, Lewis R, Birtle A, Donovan JL. Key issues in recruitment to randomised controlled trials with very different interventions: A qualitative investigation of recruitment to the SPARE trial (CRUK/07/011). *Trials*. 2011;12:78.