


# The Effect of Tri-Modality Therapy with Bladder Preservation for Selective Muscle-Invasive Bladder Cancer

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## Abstract

**Objectives:** To compare the efficacy of complete transurethral resection of bladder tumor combined with postoperative chemoradiotherapy and radical cystectomy (RC) in the treatment of muscle-invasive bladder cancer (MIBC). **Methods:** This is a single-center, retrospective study. Clinical data of 125 patients with MIBC admitted to the First Affiliated Hospital of Soochow University from December 2012 to December 2015 were retrospectively analyzed, in which 79 patients (tri-modality therapy [TMT] group) received TMT bladder-sparing treatment, and 41 patients (RC group) received RC. The differences of probabilities for 1-year, 2-year, 5-year, and comprehensive overall survival (OS), progress-free survival (PFS) between 2 groups were calculated using Kaplan–Meier product limited estimates. Univariate and multivariate analyses were performed to detect potential risk factors for OS and PFS. **Results:** There was no statistical difference between the TMT group and RC group in the 1-year, 2-year, 5-year, comprehensive OS rate, and PFS rate. And survival analysis found no significant difference in OS and PFS between the 2 groups. Univariate analysis showed that age, TNM staging, and prognostic nutritional index (PNI) were associated with OS, while PNI was connected to tumor recurrence. Multiple linear regression analysis indicated that TNM staging and PNI were independent risk factors for OS. **Conclusions:** TMT can be used as an alternative to RC for MIBC patients under the premise of strict control of indications, rigorous postoperative follow-up, and timely salvage cystectomy. PNI was negatively correlated with OS and PFS, while TNM staging was positively correlated with OS.

## Keywords

MIBC, tri-modality therapy, bladder-sparing, PNI

## Abbreviations

AUC, area under curve; BMI, body mass index; CT, computed tomography; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; HBP, high blood pressure; MIBC, muscle-invasive bladder cancer; MRI, magnetic resonance imaging; OS, overall survival; PFS, progress-free survival; PNI, prognostic nutritional index; RC, radical cystectomy; ROC, receiver operating characteristic; RT, radiotherapy; TMT, tri-modality therapy; TURBT, transurethral resection of bladder tumor; cTURBT, complete TURBT.

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## Introduction

It is reported that bladder cancer is the second most common malignant cancer in the genitourinary system.<sup>1</sup> Radical cystectomy (RC) is known as the standard treatment for muscle-invasive bladder cancer (MIBC).<sup>2</sup> However, this procedure is highly invasive and risky, and has a significant impact on the quality of life of the patients.<sup>3</sup> A combined modality therapy that maximizes the preservation of bladder function without compromising oncotherapy is an alternative that may be considered.

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The Massachusetts General Hospital (MGH) experience<sup>4</sup> introduced a tri-modality therapy (TMT) with bladder preservation for selective MIBC patients, which shares a similar OS to RC patients. And a large number of studies reported that the bladder-sparing methods may produce favorable results in carefully selected patients from western society.<sup>5-7</sup> However, there is still a lack of data to verify whether this treatment is suitable for patients from China. Our study summarized the clinical data of 125 patients with MIBC admitted to the First Affiliated Hospital of Soochow University between December 2012 and December 2015, 79 of whom received TMT and 46 of whom received RC, and they were followed up for more than 5 years to compare the effects of 2 kinds of treatments on overall survival (OS) and progress-free survival (PFS).

## Materials and Methods

### Clinical Data

This is a single-center, retrospective study. From December 2012 to December 2015, patients diagnosed with MIBC were enrolled at the First Affiliated Hospital of Soochow University. Inclusion criteria included pathologically confirmed MIBC and clinical stage T2-T4aN0M0. Exclusion criteria included a history of autoimmune disease or infectious disease. A total of 125 patients were candidates for this study, including 114 males and 11 females, with 79 cases receiving TMT and 46 cases receiving RC. The mean tumor diameter was  $(33.90 \pm 2.61)$  mm and the average age was  $(69.66 \pm 1.92)$  years. According to TNM staging of the Union Internationale Contre le Cancer in 2017, there were 91 cases defined as T2, 22 cases defined as T3, and 12 cases defined as T4a. The follow-up time ranged from 5 to 97 months, with an average of  $51.36 \pm 4.12$  months. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our research was approved by the ethics committee of the First Affiliated Hospital of Soochow University (approved ID: No. 119[2020]) and all the patients signed consent forms before the study.

### Treatment Protocols

**RC Group.** All the patients underwent transurethral resection of bladder tumor (TURBT) first and the pathology was confirmed as MIBC. Meanwhile, preoperative chest, abdomen, and pelvic enhanced computed tomography (CT) or magnetic resonance imaging (MRI) confirmed no distant metastasis. At the same time, the Eastern Cooperative Oncology Group (ECOG) score was 0 to 2 points. Finally, RC and urinary diversion were performed after informed consent was signed with the family members.

**TMT Group.** All the patients first received TURBT and the pathology was proved as MIBC. No distant metastasis was confirmed by preoperative chest, abdomen, and pelvic enhanced CT or MRI. And the ECOG score was 0 to 2, with no

contraindication found for radiotherapy (RT) or chemotherapy. After the informed consent was signed, the patients underwent complete TURBT (cTURBT), in which all the visible bladder tumors should be resected with random bladder biopsy and surgical wound base biopsy negative. Intravenous chemotherapy including gemcitabine  $1000 \text{ mg/m}^2$  (day 1 and day 8), cisplatin  $70 \text{ mg/m}^2$  (day 2) was performed within 2 to 4 weeks after the surgery, with a cycle of 3 weeks, a total of 3 cycles. Carboplatin was used to replace cisplatin when the creatinine clearance rate was 40 to 60 mL/min. RT of 24 to 25 Gy was received after chemotherapy.

### Follow-up

All patients were reexamined every 3 months within 2 years, every 6 months within 2 to 5 years, and once a year after 5 years. The reexamination included a chest x-ray and abdominal and pelvis CT or MRI. For patients who received TMT, cystoscopy, and urine cytology should be taken every 3 months for 2 years, every 6 months for 5 years, and annually for at least 10 years.

### Statistical Analysis

The quantitative data were expressed as mean  $\pm$  standard deviation, and comparisons between 2 groups were determined using the Mann-Whitney *U*-test. The comparisons of cumulative data between the 2 groups were examined by  $\chi^2$  test. Statistical analyses were performed using SPSS 22.0. GraphPad Prism 8.0 was used to draw survival curves. Kaplan-Meier and log-rank tests were used for survival analysis. Multiple linear regression analysis was used to find independent risk factors. And a *p*-value was considered statistically significant if *p* < .05. The sample size calculation was calculated by R software (version 4.1.0) and the number in our study to show significance was 103.<sup>8</sup> All the data was checked by 2 different senior statisticians.

## Results

### Baseline Levels Comparison Between 2 Groups

There was no significant difference found between the RC group and TMT group in age, gender, body mass index (BMI), high blood pressure (HBP), diabetes mellitus (DM), TNM staging, tumor diameter, preoperative creatinine levels, and prognostic nutritional index (PNI) (Table 1).

### OS and PFS in 2 Groups

The TMT group was followed up for 9 to 97 months, with an average of  $47.84 \pm 5.18$  months, and the RC group was followed up for 5 to 90 months, with an average of  $57.41 \pm 6.69$  months. There was no significant difference between the 2 groups in follow-up time (*t* = 2.253, *p* = .051). The 1-year, 2-year, 5-year, and comprehensive OS rate (94.94% vs

**Table 1.** Comparisons of patients' characteristics between the TMT group and the RC group.

Factors	TMT group	RC group	$t/\chi^2$ value	<i>p</i> -value
Age (years)	69.79 ± 2.51	69.44 ± 3.06	0.173	.863
Gender			0.623	.533
Male (n)	73	41		
Female (n)	6	5		
BMI (kg/m <sup>2</sup> )	23.11 ± 0.88	23.58 ± 1.11	0.659	.511
HBP			0.988	.323
Yes (n)	22	24		
No (n)	45	34		
DM			1.454	.146
Yes (n)	30	16		
No (n)	61	18		
TNM staging			2.182	.336
T2N0M0 (n)	61	30		
T3N0M0 (n)	12	10		
T4aN0M0 (n)	6	6		
Tumor diameter (mm)	31.96 ± 2.79	32.22 ± 5.24	1.943	.054
Creatinine level (μmol/L)	96.00 ± 16.74	100.96 ± 25.33	0.340	.735
PNI (%)	45.97 ± 1.78	43.22 ± 2.79	1.74	.084

Abbreviations: TMT, tri-modality therapy; RC, radical cystectomy; BMI, body mass index; HBP, high blood pressure; DM, diabetes mellitus; PNI, prognostic nutritional index.

**Table 2.** Comparisons of OS and PFS between 2 groups.

	TMT group	RC group	$\chi^2$ value	<i>p</i> -value
1-year OS			0.342	.732
Censored	75	43		
Death	4	3		
1-year PFS			1.025	.305
Censored	59	38		
Recurrence	20	8		
2-year OS			1.353	.176
Censored	63	41		
Death	16	5		
2-year PFS			1.584	.113
Censored	40	30		
Recurrence	39	16		
5-year OS			1.887	.059
Censored	26	23		
Death	53	23		
5-year PFS			1.255	.209
Censored	9	9		
Recurrence	70	37		
Comprehensive OS			.886	.376
Censored	21	9		
Death	58	37		
Comprehensive PFS			1.172	.241
Censored	8	8		
Recurrence	71	38		

Abbreviations: TMT, tri-modality therapy; RC, radical cystectomy; OS, overall survival; PFS, progress-free survival.

93.48%, 79.75% vs 89.13%, 32.91% vs 50.00%, 26.58% vs 19.57%, respectively) and PFS rate (74.68% vs 82.61%, 50.63% vs 65.22%, 33.75% vs 48.89%, 10.13% vs 17.39%, respectively) in TMT group and RC group showed no statistical significance (Table 2). And the survival analysis proved that patients who received TMT or RC shared a similar time of OS and PFS (Figure 1).

### Influencing Factors of OS and PFS

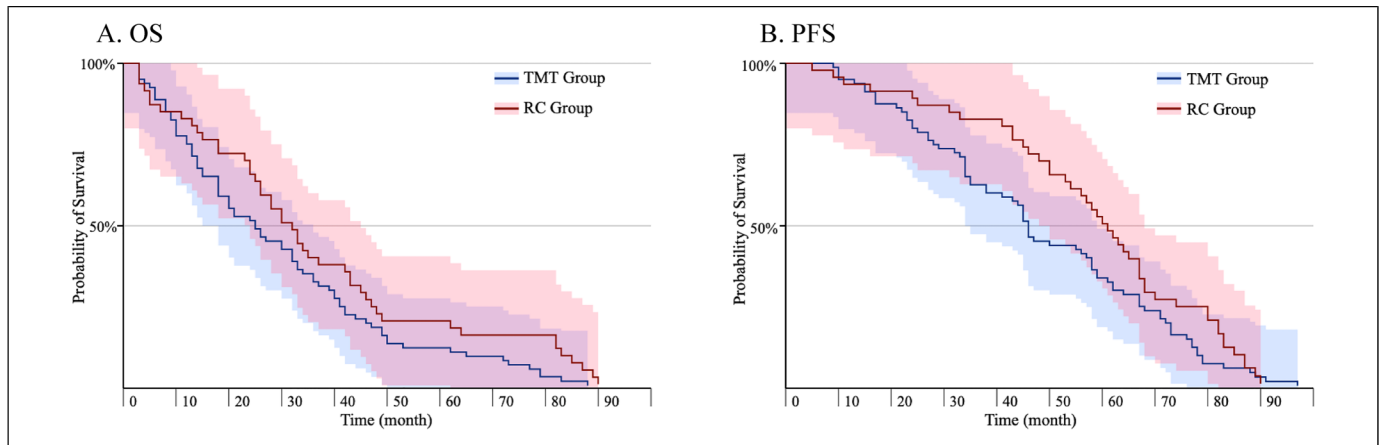
Univariate analysis demonstrated that age, TNM staging, and PNI were negatively associated with OS, while PNI was negatively connected to PFS (Table 3). Further multiple linear regression analysis found that TNM staging and PNI were independent risk factors for OS (Table 4). A receiver operating characteristic (ROC) curve was drawn and the area under curve (AUC) was 0.7675 (Figure 2).

### Discussion

Bladder cancer is 1 of the most common malignancies in urology.<sup>1</sup> Among the first diagnosed patients with bladder cancer, approximately 25% to 30% are MIBC.<sup>9</sup> The standard mode of treatment for MIBC is RC, which includes radical cystectomy, urinary diversion, and bilateral pelvic lymph node dissection.<sup>4</sup> For men, the prostate and seminal vesicle glands should be removed simultaneously, and for women, the uterus, bilateral adnexa, and part of the anterior wall of the vagina should be removed at the same time. It is reported that the 5-year PFS rate was 58% to 68%, and the 5-year OS rate was 66%.<sup>10</sup> However, due to the wide range of surgical resection, long operation time, and high incidence of complications, the quality of life of patients after surgery is greatly affected, young patients will lose fertility function, and most patients will lose sexual function,<sup>3</sup> many patients will finally give up the surgery.

James et al.<sup>11</sup> first reported that TURBT combined with postoperative chemotherapy, nearly one-third of patients benefitted from the degradation of TNM staging. Büchser et al.<sup>2</sup> conclude that the bladder preservation rate could reach up to 79% and the 5-year OS and PFS were 52% and 64% within 10 years under the strategy of TMT, which was made up of cTURBT and chemoradiotherapy. A prospective study also found that the complete response rate after TMT was 69% and the 5-year OS and PFS were 57% and 71%, and the outcomes were similar to that of RC.<sup>4</sup> Recently, more and more relevant studies have found that TURBT combined with postoperative chemoradiotherapy is another option for the treatment of MIBC.<sup>3,12-14</sup> However, there are few reports on the effect of TMT strategy on the Chinese population.

Our study was aimed to compare the efficacy of TMT treatment with RC treatment in some Chinese populations. Despite the 1-year OS (94.94% vs 93.48%), TMT group had a lower rate than RC group in 2-year and 5-year OS (79.75% vs 89.13%, 32.91% vs 50.00%). But no statistical significance was found between the 2 groups. And although the 1-year,



**Figure 1.** Survival curve of OS and PFS for TMT group and RC group. (A) Survival curve of OS showed that there was no significant difference between the TMT group and the RC group ( $t = 1.690, p = .091$ ). (B) Survival curve of PFS also showed that there was no significant difference between the TMT group and the RC group ( $t = 1.867, p = .062$ ).

Abbreviations: OS, overall survival; PFS, progress-free survival; TMT, tri-modality therapy; RC, radical cystectomy;

2-year, and 5-year PFS rates of the TMT group were lower than that of the RC group (74.68% vs 82.61%, 50.63% vs 65.22%, 33.75% vs 48.89%, 10.13% vs 17.39%), there was still no significant difference between 2 groups. The survival curve of OS and PFS of the TMT group and RC group further verified that the 2 treatments were statistically equally effective for patients with MIBC of T2-T4aN0M0. Our research also found that PNI was negatively associated with OS and PFS in MIBC, which was consistent with the results of Peng et al.<sup>15</sup>

We summarized the experience of our hospital in TMT strategy as follows: (1) cTURBT emphasizes the resection of all visible bladder tumors, and the resection depth should

be appropriate to see the fat layer outside the bladder. And pathology of the basal tissue must be negative. (2) Platinum-based chemotherapeutic regimens are recognized as effective therapeutic measures for MIBC. If renal function is poor, it is recommended to change cisplatin to less nephrotoxic carboplatin. The main adverse reactions during chemotherapy included nausea and vomiting, alopecia, bone marrow suppression, and abnormal liver function, and no serious complications occurred in our study. The response rate of MIBC to RT is low, but Gemcitabine has a radiosensitization effect for patients who received low-dose external irradiation, which included bladder and pelvic lymph nodes. There were 4

**Table 3.** Univariate analysis of influencing factors of OS and PFS.

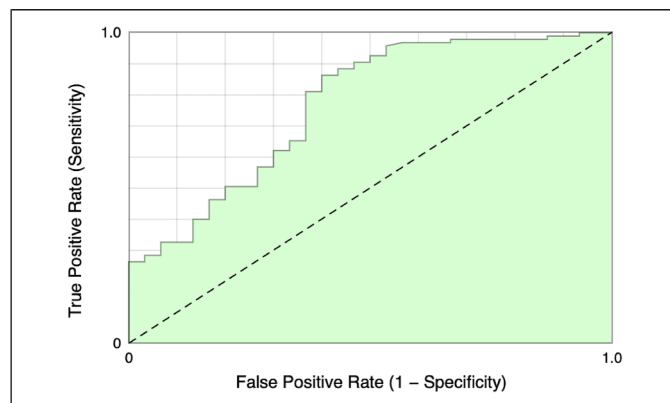
Factors	OS		$t/\chi^2$ value	$p$ -value	PFS		$t/\chi^2$ value	$p$ -value
	Censored	Death			Censored	Recurrence		
Age (years)	66.13 ± 3.69	70.77 ± 2.23	2.068	0.041	65.88 ± 6.09	70.21 ± 2.03	1.502	.136
Gender			0.266	0.790			0.386	.700
Male (n)	27	87			15	99		
Female (n)	3	8			1	10		
BMI (kg/m <sup>2</sup> )	24.34 ± 1.53	22.95 ± 0.76	1.733	0.086	25.02 ± 2.18	23.03 ± 0.71	1.955	.053
HBP			0.454	0.650			0.309	.757
Yes (n)	15	52			8	59		
No (n)	15	43			8	50		
DM			1.487	0.137			0.813	.416
Yes (n)	25	66			13	78		
No (n)	5	29			3	31		
TNM Staging			8.757	0.013			4.211	.122
T2N0M0 (n)	28	63			15	76		
T3N0M0 (n)	2	20			1	21		
T4aN0M0 (n)	0	12			0	12		
Tumor diameter (mm)	29.67 ± 4.88	35.23 ± 3.07	1.819	0.071	33.44 ± 7.83	33.96 ± 2.81	0.133	.895
Creatinine level (μmol/L)	79.80 ± 6.80	103.52 ± 18.09	1.449	0.150	86.88 ± 9.61	99.43 ± 15.89	0.596	.552
PNI (%)	39.31 ± 3.55	46.74 ± 1.52	4.437	<0.001	37.51 ± 4.47	46.05 ± 1.53	3.929	<.001

Abbreviations: BMI, body mass index; HBP, high blood pressure; DM, diabetes mellitus; PNI, prognostic nutritional index; OS, overall survival; PFS, progress-free survival.

**Table 4.** Multiple linear regression analysis for independent risk factors of OS.

Factors	Coefficient	Std. error	95% confidence Interval	t value	p-value
Age	0.004	(0.003)	(-0.003, 0.01)	1.188	.237
TNM staging					.007
T2N0M0	0	(0)	(0, 0)	0	-
T3N0M0	0.209	(0.081)	(0.049, 0.369)	2.592	.011
T4aN0M0	0.191	(0.072)	(0.049, 0.332)	2.663	.009
PNI	0.017	(0.004)	(0.008, 0.026)	3.763	< .001
constant	-0.312	(0.261)	(-0.829, 0.205)	-1.194	.235

Abbreviations: OS, overall survival; PNI, prognostic nutritional index.

**Figure 2.** ROC curve of the model for independent risk factors for OS with an AUC of 0.7675.

Abbreviations: ROC, receiver operating characteristic; OS, overall survival; AUC, area under curve.

patients who developed radiation cystitis, of which 2 patients disappeared after the end of RT after symptomatic treatment, and 1 patient developed urethral stricture requiring regular urethral dilation. (3) Bladder preservation requires close follow-up, and timely salvage cystectomy is recommended in the case of recurrent invasive tumor or recurrent nonmuscular invasive bladder cancer. There were 12 cases that underwent salvage RC after recurrence, which accounted for 15.19% of the TMT group. And among the 12 recurrent cases in the TMT group, 5 cases were diagnosed with pelvic metastasis.

There were some limitations reserved in this study. First, it is a retrospective study and conducted in a single-center, which may cause bias and misleading findings. Second, the limited number of patients may make the conclusions statistically underpowered. Third, the follow-up period is not very long compared to similar studies, which makes the results less convincing.

## Conclusions

Based on the experience of our center, TMT strategy for MIBC with the T2-T4aN0M0 stage can help improve the quality of life while preserving the bladder, and also achieve a similar long-term OS and PFS to RC. Therefore, under the premise of strict control of indications, full informed consent before surgery, rigorous follow-up after surgery, and timely salvage cystectomy, the TMT strategy can be used as an alternative to RC for MIBC patients.

## Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accord with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Affiliated Hospital of Soochow University (No. 119) and informed consent was taken from all individual participants.

## Author Contributions

(I) Conception and design: Zhang Zhiyu and Zhang Jianglei; (II) administrative support: Jun Ouyang and Zhang Jianglei; (III) provision of study materials or patients: Zhang Zhiyu and Zhou Qi; (IV) collection and assembly of data: Zhang Zhiyu, Zhou Qi, and Song Zhen; (V) data analysis and interpretation: Zhang Zhiyu and Zhou Qi; (VI) manuscript writing: all authors; (VII) final approval of manuscript: all authors.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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