Urological Science

Journal homepage:www.e-urol-sci.com

Original Article

Comparison of Trimodal Therapy versus Radical Cystectomy for Each Stage of Muscle-invasive Bladder Cancer

Wen-Hsin Tseng[1], Steven K. Huang[1,2]*, Chien-Liang Liu[1], Jinn-Rung Kuo[3], Shun-Hsing Hun[4], Chun-Hao Chen[1], Chia-Cheng Su[1], Jhih-Cheng Wang[1], Kau-Han Lee[1], Kun-Lin Hsieh[1], Allen W. Chiu[5,6]

[1]Division of Urology, Department of Surgery, Chi Mei Medical Center, [2]Chia Nan University of Pharmacy and Science, [3]Division of Neurosurgery, Department of Surgery, Chi Mei Medical Center, [4]Division of Urology, Department of Surgery, Chi Mei Hospital, Tainan, [5]Department of Urology, Mackay Memorial Hospital, [6]School of Medicine, National Yang-Ming University, Taipei, Taiwan

Abstract

Purpose: Radical cystectomy (RC) has long been the standard of care for the management of muscle-invasive bladder cancer (MIBC). However, an increasing trend of bladder-sparing trimodal therapy (TMT) using maximal transurethral resection of bladder tumor, followed by radiation therapy (RT) with concomitant radiosensitizing chemotherapy, has been advocated. We compared the differences regarding long-term oncological outcomes between patients who accepted RC or TMT for MIBC. **Materials and Methods:** Between January 2012 and December 2018, 207 patients were diagnosed with MIBC at our center. We excluded patients with metastasis disease, received other treatments, and lost to follow-up. The patients were categorized into Group 1 (TMT) and Group 2 (RC). Both the groups with each tumor stage were compared for disease-free survival (DFS) and overall survival (OS) rates, and the risk factors for recurrence and survival were assessed. **Results:** In total, 58 (48.7%) patients in Group 1 underwent TMT and 61 (51.3%) patients in Group 2 underwent RC. The mean follow-up was 39.8 months. The 3-year DFS rates were 44.1% and 69.7% for Groups 1 and 2, respectively ($P = 0.003$). The 3-year OS rates were 61.7% and 72.5% for Groups 1 and 2, respectively ($P = 0.226$). We also analyzed the DFS with each stage, and the results showed a lower DFS rate for T2 and N0 stages. **Conclusion:** There was no significant survival benefit for MIBC with either RC or TMT. However, RC is associated with better outcome of DFS rate, especially for patients with early stages of MIBC in stages T2 and N0.

Keywords: Muscle-invasive bladder cancer, radical cystectomy, trimodal therapy

Introduction

In 2019, 80,470 patients were newly diagnosed with bladder cancer in the United States; this type of cancer ranks sixth among all cancers.[1] Muscle-invasive bladder cancer (MIBC) accounts for approximately 25% of newly diagnosed bladder cancers.[2] For patients with MIBC, radical cystectomy (RC) is widely accepted as the gold standard treatment, but several bladder-preservation treatments, including partial cystectomy, radiation therapy (RT) alone, and transurethral resection of bladder tumor (TURBT) with intravesical *Bacillus* Calmette–Guérin, were also proposed.[3] However,

Submitted: 06-Jan-2021 **Revised:** 02-Feb-2021 **Accepted:** 03-Feb-2021
Published: 14-Dec-2021

Access this article online

Quick Response Code:

Website: www.e-urol-sci.com

DOI: 10.4103/UROS.UROS_8_21

***Address for correspondence:** Dr. Steven K. Huang, Division of Urology, Department of Surgery, Chi Mei Medical Center, No. 901, Zhonghua Road, Yongkang, Tainan 710, Taiwan.
E-mail: b101096108@tmu.edu.tw

How to cite this article: Tseng WH, Huang SK, Liu CL, Kuo JR, Hun SH, Chen CH, *et al*. Comparison of trimodal therapy versus radical cystectomy for each stage of muscle-invasive bladder cancer. Urol Sci 2021;32:164-70.

a trimodal therapy (TMT) approach, including maximal transurethral resection followed by concurrent radiosensitizing chemotherapy and RT, is the most effective bladder-sparing strategy in selective patients.[2,3]

Randomized studies are the best approach for the comparison of RC and TMT; however, such research is almost impossible to achieve.[4] A limited number of retrospective studies compared the therapeutic benefits of various treatments on MIBC,[5-8] and most of them used databases to assess the overall survival (OS) rate. Notably, these studies encountered difficulties in developing uniform standard treatments, such as chemotherapy drugs or radiation dosages, and following up patient conditions or complications.

In this study, we attempted to analyze data from a single institution to compare each stage of MIBC in patients who received RC or TMT to determine which treatment yielded better oncological outcomes for MIBC. We also used subsequent complications to compare the therapeutic benefits of RC and TMT.

Patients and Methods

A total of 667 patients pathologically diagnosed with urothelial carcinoma at Chi Mei Medical Center who underwent TURBT between January 2012 and December 2018 were enrolled in this retrospective study. The study was approved by the Institutional Review Board (IRB) Committee (Chimei Hospital IRB number 10903-005) and Chimei Hospital IRB that gave the waiver for informed consent. The patient composition, case number, and inclusion and exclusion criteria are listed in Figure 1. Tumor staging was performed in accordance with the American Joint Committee on Cancer tumor–node–metastasis classification;[2] 207 patients had muscle-invasive urothelial bladder carcinoma.

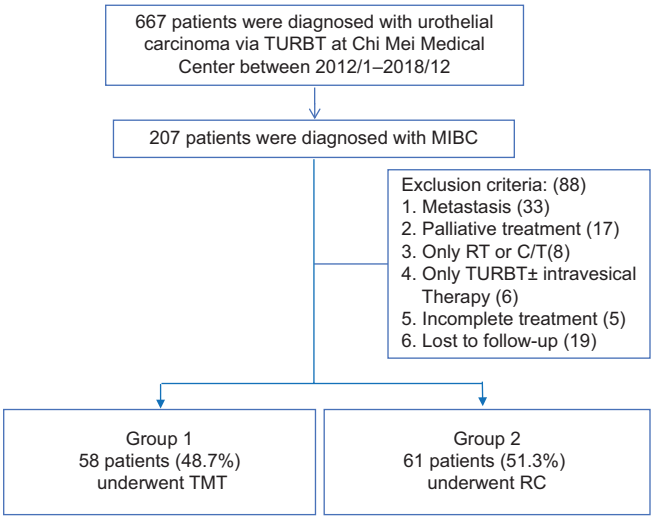

Figure 1: Flowchart of patients who underwent trimodal therapy and radical cystectomy. TURBT: Transurethral resection of bladder tumor, MIBC: Muscle-invasive bladder cancer, (): Number of patients, RT: Radiotherapy, C/T: Chemotherapy, TMT: Trimodal therapy, RC: Radical cystectomy

The decision to pursue RC, TMT, or other treatments was based on the patients' choice after a multidisciplinary discussion of treatment options by an experienced physician. We excluded patients had metastasis, only choose RT, chemotherapy, or TURBT with intravesical therapy or incomplete treatment, and who were selected for palliative treatment or lost to follow-up. In total, 58 patients (48.7%) in Group 1 underwent TMT and 61 patients (51.3%) in Group 2 underwent RC [Table 1].

Trimodal therapy group

In this group, the patients accepted maximal TURBT followed by radiosensitizing chemotherapy and RT. RT was given as intensity-modulated RT, aimed at delivering approximately 44–46 Gy to the urinary bladder and pelvic lymph nodes (internal iliac nodes, external iliac nodes, and obturator nodes) followed by a bladder boost to a total dose of approximately 66 Gy. Chemotherapy consisted of weekly administration of cisplatin-based chemotherapy. If renal function was impaired, cisplatin was replaced by weekly administration of gemcitabine or carboplatin.

Complications of therapy were graded in accordance with the Common Terminology Criteria for Adverse Events 5.0 for chemotherapy and the Radiation Therapy Oncology Group (RTOG) toxicity grading systems for radiation.[9,10]

Radical cystectomy group

RC was performed additionally with prostatectomy in men, whereas hysterectomy was conducted on the women and included standard (common iliac, external iliac, and obturator) pelvic lymph node dissection, followed by the formation of a urinary diversion. Postoperative complications were graded based on the Clavien and Dindo classification.[11]

These two group patients followed the protocols from the National Comprehensive Cancer Network guidelines;[2] computed tomography or magnetic resonance imaging scans for the chest, abdomen, and pelvis were performed at 6-month intervals until the 5th year and annually thereafter. Renal function/complete blood count/comprehensive metabolic panel/liver function tests were followed at 3-month intervals in the initial year. Then, the renal function tests were performed at 6-month intervals until the 5th year and annually thereafter. Cystoscopy and urine cytology were performed at 3-month intervals for the first 2 years, at 6-month intervals until the 5th year, and annually thereafter.

Statistical analysis

The end points were used to assess long-term outcomes after performing TMT or RC for MIBC. Disease-free survival (DFS) and OS rates between the groups were assessed using the Kaplan–Meier curves for each stage of MIBC. With the use of Cox proportional hazards model, multivariate analysis of the risk factors for recurrence and survival was performed. $P < 0.05$ was considered to be statistically significant.

Results

Table 1 presents the clinical and pathological characteristics of 58 (48.7%) patients in Group 1 (TMT) and 61 (51.3%) patients in Group 2 (RC). The analysis between the two groups showed no significant difference in sex, body mass index, living habit (smoke, alcohol, and betel nuts), survival rate, or length of follow-up. However, patients who received RC in Group 1 were significantly younger (mean: 70.5 and 65.4 years between Groups 1 and 2, respectively; $P = 0.01$), had a lower score in Charlson Comorbidity Index (CCI) (mean: 4.7 (Group 1) and 3.9 (Group 2); $P = 0.03$), and lower overall recurrence rate within a mean follow-up of 3 years (62.1% for Group 1 and 36.1% Group 2; $P = 0.005$).

The DFS rates were 70.7%, 44.1%, and 29.1% in Group 1 at 1, 3, and 5 years of follow-up, respectively, and 85.2%, 69.7%, and 57.6% in Group 2 [Table 2]. Figure 2 shows the Kaplan–Meier curves of the DFS rates for both the groups. The results showed a lower DFS rate in Group 2 compared with Group 1 (log-rank test = 0.003), but the OS rates revealed no significant difference. However, Group 1 (TMT) included fewer patients with stage T3 (10 pts vs. 23 pts) and more patients with stage T4 cancer than Group 2 (RC) (12 pts vs. 5 pts) [Table 1, $P = 0.018$]. We separated each stage of MIBC to compare the DFS and OS rates of Groups 1 (TMT) and 2 (RC) as shown in Figure 3, respectively. Only stages T2 and N0 were associated with a significantly low DFS rate in Group 2 (log-rank test: $P < 0.001$ and $P = 0.001$). The DFS rates exhibited no significant difference in stages T3 and T4, whereas N1 and OS rates showed no significant difference in any stage.

As indicated by the multivariate analysis results in Table 3, patients with high CCI score were at a high risk for recurrence and low risk for survival ($P = 0.016$ and 0.001, respectively). Patients who underwent RC were also at a high risk for recurrence ($P = 0.01$).

Appendix Table 1 presents the side effects of the treatments. Chemoradiation was well tolerated by most patients and showed less toxicity than those at stage 2. Most side effects

Table 1: Characteristics of patients in the two studied groups

	Group 1 (TMT)	Group 2 (RC)	Total	*P*
Number of patients, *n* (%)	58 (48.7)	61 (51.3)	119	
Mean age (years, ±SD)	70.5 (±10.9)	65.4 (±10.4)		0.01
Sex (male: female)	45:13	43:18	88:31	0.378
BMI (±SD)	23.5 (±3.9)	24.4 (±3.5)		0.215
CCI	4.7 (±2.2)	3.9 (±1.9)		0.038
Stage T (T2:T3:T4)	36:10:12	33:23:5	69:33:17	0.018
Stage N (N0:N1)	52:6	49:12	18:101	0.156
Smoke (yes: no)	21:37	20:41	41:78	0.695
Alcohol (yes: no)	16:42	12:49	28:91	0.309
Betel nuts (yes: no)	7:51	8:53	15:104	0.864
Recurrence (yes: no)	36 (62.1%):22	22 (36.1%):39	58 (48.7%):61	0.005
Survival (yes: no)	25 (43.1%):33	20 (32.8%):41	45 (37.8%):74	0.246
Mean follow-up (months, ±SD)	38.9 (±25.9)	40.6 (±21.9)	39.8	0.701

TMT: Trimodal therapy, RC: Radical cystectomy, SD: Standard deviation, BMI: Body mass index, CCI: Charlson Comorbidity Index

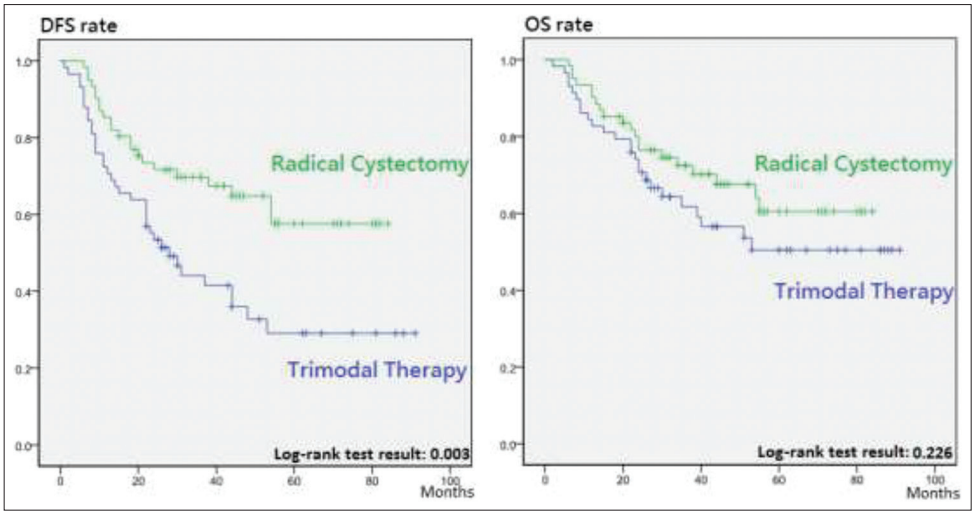

Figure 2: Kaplan–Meier curve of the disease-free survival and overall survival rates for the two groups

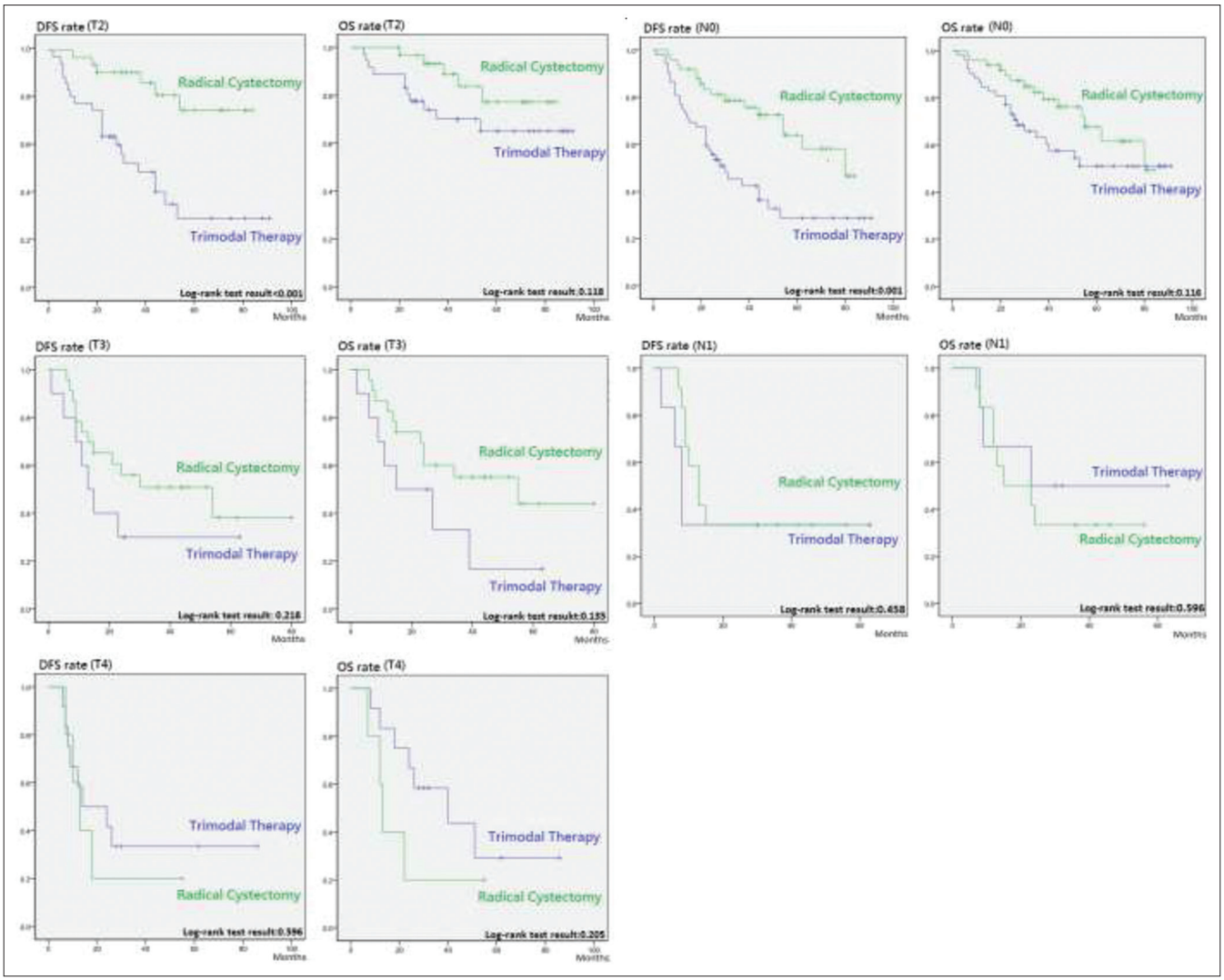

Figure 3: Kaplan–Meier curve of the disease-free survival and overall survival rates for each T and N stage

Table 2: Comparison of the two patient groups based on recurrence and progression

Years	DFS rate (%)		OS rate (%)	
	TMT	RC	TMT	RC
1	70.7	85.2	82.8	90.2
3	44.1	69.7	61.7	72.5
5	29.1	57.6	50.4	60.5

TMT: Trimodal therapy, RC: Radical cystectomy, DFS: Disease-free survival, OS: Overall survival

of genitourinary chemoradiation were radiation cystitis, recurrent hematuria, and the need for operation to check bleeding (7 patients; 12.1%). The most common side effects of chemoradiation gastrointestinal included nausea and vomiting. Four patients (6.9%) needed endoscopy for hemostasis. Most of the patients in Group 1 (TMT) showed no chemoradiation cardiac disorders, but one patient suffered from cardiac respiratory failure after chemoradiation therapy. In Group 2 (RC), the most common postoperative complications were urinary tract infection (18%) and blood transfusion (27.9%). Severe complications were rare, and no postoperative mortality was observed.

Discussion

In the past decade, the increasing trend of utilizing organ-preserving therapies in the management of multiple cancers has been observed. For MIBC, a multidisciplinary approach has led to the development of bladder-sparing approaches using TMT, which includes maximal TURBT followed by RT with concomitant radiosensitizing chemotherapy.[2] Although several studies reported that TMT can yield favorable results in well-selected patients,[12] no randomized nor retrospective studies determined which patients are suitable for TMT or RC. Several retrospective studies compared the therapeutic benefits of MIBC,[5-8] and most of them used nonuniform databases, including Surveillance, Epidemiology, and End Results Program-Medicare,[5] or National Cancer Database,[6,7] to assess the survival outcomes.

Table 3: Multivariate analysis based on recurrence and survival

	Recurrence		Survival	
	HR	*P*	HR	*P*
Age	0.991 (0.958-1.026)	0.613	1.006 (0.968-1.046)	0.742
Sex (male: female)	0.794 (0.377-1.675)	0.545	0.787 (0.332-1.865)	0.587
Smoke (yes: no)	1.218 (0.461-3.218)	0.691	1.215 (0.391-3.771)	0.736
Alcohol (yes: no)	0.975 (0.336-2.825)	0.962	0.970 (0.282-3.335)	0.961
Betel nuts (yes: no)	0.225 (0.047-1.076)	0.062	0.162 (0.019-1.368)	0.094
BMI	0.951 (0.880-1.028)	0.210	0.968 (0.887-1.056)	0.458
Cisplatin	1.140 (0.477-2.723)	0.768	0.324 (0.070-1.509)	0.151
CCI	1.211 (1.036-1.416)	0.016	1.388 (1.150-1.676)	0.001
TMT and RC	0.435 (0.231-0.821)	0.010	0.798 (0.360-1.645)	0.499

TMT: Trimodal therapy, RC: Radical cystectomy, BMI: Body mass index, CCI: Charlson Comorbidity Index, HR: Hazard ratio

Database studies recognized that the heterogeneity of patient population, large variations in the combined treatments, unbalanced prognostic factors, and nonstandardized reporting of results among the trials may introduce biases, especially in subgroup analyses. Therefore, we compared the oncological outcomes with complications of RC or TMT in each stage of MIBC.

In our study, 58 (48.7%) and 61 (51.3%) patients with MIBC underwent TMT and RC, respectively. The patients who received TMT were significantly older (mean age: 70.5 and 65.4 years for TMT and RC, respectively; $P = 0.01$) and yielded higher CCI (mean: 4.7 for TMT and 3.9 for RC; $P = 0.03$). This study was compatible with database research[5-7] that compared surgery with chemoradiation and which included younger and healthier patients. However, more stage T4 patients were selected for TMT than for RC (12 and 5 patients in TMT and RC, respectively; $P = 0.018$). This finding presents that in addition to age and health condition, tumor stage would also influence the urologists' option for treatment. As shown in Figure 3, we separated each stage of MIBC to compare the DFS and OS rates and observed that only tumor stages T2 and N0 showed a significantly lower DFS rate in patients accepting RC (log-rank test: $P < 0.001$ and $P = 0.001$). These results also mean that for late-stage tumors, such as T3, T4, or N1, when the patient was young and healthy, RC and TMT showed similar oncological outcomes in terms of DFS and OS rates.

In the comparison of the treatments with TMT and RC, side effects were important factors, but the database studies usually lacked related results. The most common complications of RC were blood transfusion (27.9%), infection (18%), and percutaneous nephrostomy (PCN; 11.5%). All complications were classified below Grade 3 Clavien–Dindo outcomes, and most of them can be controlled by conservative treatment. Five patients (8.2%) accepted operation within 90 days for enterolysis or cystorrhaphy, and seven patients (11.5%) received PCN for urinary diversion. All patients were discontinued from undergoing PCN and were discharged within 90 days (mean hospital, 20.9 days). Henningsohn *et al*.[13] observed that patients who had an orthotopic reconstruction had a better quality of life than those who had an ileal conduit; therefore, most patients in our institution accepted orthotopic reconstruction (62.3%). On the other hand, most of the complications of TMT were nausea/vomit (63.8%), radiation cystitis (37.9%), and infection (22.4%), and all of them were under RTOG grade 3 toxicity [Appendix Table 1]. About radiation cystitis, seven patients (12.1%) had recurrence hematuria and accepted transurethral hemostasis. The average operation period was around 19 months after complete treatment by RT.

In the multivariate analysis results in Table 3, patients with a high CCI score were at a high risk for recurrence and low risk for survival ($P = 0.016$ and 0.001, respectively). Patients who underwent RC had significantly low risk for recurrence ($P = 0.01$) but exhibited no different risk for survival that was corresponding to the Kaplan–Meier curves in Figures 2 and 3. Especially, the early-stage bladder tumors, such as T2 and N0, showed a significantly low DFS rate in the RC group (log-rank test: $P < 0.001$ and $P = 0.001$).

In accordance with Aua/Asco/Astro/Suo Guideline, in patients accepting bladder-preserving therapy, the clinician should perform regular surveillance with cystoscopy.[14] This condition means that patients who underwent TMT wound confront physical pain and psychological stress at every 3-month intervals for the first 2 years, at 6-month intervals until the 5th year, and annually thereafter. Messing[15] reported that by evaluation of large databases, review of publications, or examination of individual patient records, diagnosis of any cancer, particularly bladder cancer, induces considerable psychological stress. Vartolomei *et al*.[16] reported that treatment with RC resulted in reduced depression and anxiety at 1 year after surgery. Williams *et al*.[17] noted that compared with RC, TMT was associated with higher costs among patients with MIBC. The differences in costs were largely attributed to medication and radiology expenses associated with TMT.

This study had several limitations. First, this research was a retrospective study with small sample size, and patients treated with TMT were old and had comorbidity that could have introduced bias. Therefore, randomized studies are needed to validate the outcomes, although such approach

presents difficulty in the study design. Second, Shariat *et al*.[18] reported that 42% of patients showed stage progression following cystectomy; thus, the TMT group must have been underestimated by cancer staging in our study.

Conclusion

To our knowledge, this work is the first study to compare the oncological outcomes with complications of RC or TMT in each stage of MIBC. In our study, RC and TMT showed no significant survival benefits for MIBC. However, RC was associated with desirable outcomes for DFS rates, especially for patients in early stages of MIBC, especially T2 and N0 stages.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). Bladder Cancer. 2020 Version 3. Available from: http://www.nccn.org. [Last accessed on 2020 Jan 17].
3. Ploussard G, Daneshmand S, Efstathiou JA, Herr HW, James ND, Rödel CM, *et al*. Critical analysis of bladder sparing with trimodal therapy in muscle-Invasive bladder cancer: A systematic review. Eur Urol 2014;66:120-37.
4. 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.
5. Bekelman JE, Handorf EA, Guzzo T, Evan Pollack C, Christodouleas J, Resnick MJ, *et al*. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: Examining confounding and misclassification biasin cancer observational comparative effectiveness research. Value Health 2013;16:610-8.
6. Smith AB, Deal AM, Woods ME, Wallen EM, Pruthi RS, Chen RC, *et al*. Muscle-invasive bladder cancer: Evaluating treatment and survival in the National Cancer Data Base. BJU Int 2014;114:719-26.
7. Seisen T, Sun M, Lipsitz SR, Abdollah F, Leow JJ, Menon M, *et al*. Comparative effectiveness of trimodal therapy versus radical cystectomy for localized muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2017;72:483-7.
8. Gofrit ON, Nof R, Meirovitz A, Pode D, Frank S, Katz R, *et al*. Radical cystectomy vs. chemoradiation in T2-4aN0M0 bladder cancer: A case-control study. Urol Oncol 2015;33:19.e1-5.
9. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. [Last accessed on 2020 Nov 27].
10. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-6.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
12. Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm M, Heney NM, *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;71:952-60.
13. Henningsohn L, Steven K, Kallestrup EB, Steineck G. Distressful symptoms and well-being after radical cystectomy and orthotopic bladder substitution compared with a matched control population. J Urol 2002;168:168-74.
14. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, *et al*. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. J Urol 2017;198:552-9.
15. Messing EM. Psychological stress and suicide in bladder cancer patients. Bladder Cancer 2018;4:245-6.
16. Vartolomei L, Ferro M, Mirone V, Shariat SF, Vartolomei MD. Systematic review: Depression and anxiety prevalence in bladder cancer patients. Bladder Cancer 2018;4:319-26.
17. Williams SB, Shan Y, Ray-Zack MD, Hudgins HK, Jazzar U, Tyler DS, *et al*. Comparison of costs of radical cystectomy vs trimodal therapy for patients with localized muscle-invasive bladder cancer. JAMA Surg 2019;154:e191629.
18. Shariat SF, Palapattu GS, Karakiewicz PI, Rogers CG, Vazina A, Bastian PJ, *et al*. Discrepancy between clinical and pathologic stage: Impact on prognosis after radical cystectomy. Eur Urol 2007;51:137-49.

Appendix Table 1: Side effects of chemoradiation (Common Terminology Criteria for Adverse Events and Radiation Therapy Oncology Group Toxicity Grading Systems) and surgery (Clavien-Dindo) on muscle-invasive bladder cancer

Grade	Chemoradiation genitourinary ($n=58$), n (%)	Chemoradiation gastrointestinal ($n=58$), n (%)	Chemoradiation cardiac disorders ($n=58$), n (%)	Radical cystectomy ($n=61$), n (%)
0	24 (41.4)	17 (29.3)	54 (93.1)	10 (16.4)
1	12 (20.7)	37 (63.8)	0	9 (14.8)
2	7 (12.1)	3 (5.2)	3 (5.2)	23 (37.7)
3	15 (25.9)	1 (1.7)	0	19 (31.1)
4	0	0	1 (1.7)	0
5	0	0	0	0