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Journal of Cancer Science and Therapeutics

# Bladder-sparing trimodal therapy versus radical cystectomy for muscle-invasive bladder cancer: A systematic review and meta-analysis of comparative studies

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## Abstract

***Objective:*** *To compare oncologic outcomes between patients with muscle-invasive bladder cancer who were treated with radical cystectomy (RC) or trimodal therapy (TMT).*

***Materials and Methods:*** *The primary sources were the PubMed, Embase, and Cochrane Library electronic databases. Studies published between June 1990 and July 2017 that evaluated combination bladder-sparing surgery for a bladder tumour with radiotherapy (RT) and chemotherapy compared with RC surgery alone for MIBC were included. Published data were extracted and used to calculate the 5-year overall survival rates. The secondary efficacy endpoints were disease-free survival and local and distant recurrence.*

***Results:*** *Nine studies incorporating 15,160 cases were included in the final analysis. Pooled data from 8 studies that assessed overall survival rates for 15,089 patients showed no significant differences in this metric between the TMT and RC groups (HR: 1.27; 95% CI, 0.98-1.63; P=0.066). No significant differences were found between TMT and RC in the subgroup analyses according to the lymph node stage (Nx), age and physiclal status (PS) stage, but differences were found for patients with node-negative disease (HR: 1.36; 95% CI, 1.02-1.81; P=0.036). Disease-free survival and local and distant recurrence did not differ significantly between the techniques.*

***Conclusion:*** *RC seems to be suitable for node-negative disease patients. TMT yielded survival outcomes similar to those of patients who underwent RC. Given the inherent limitations of the included studies, future well-designed RCTs are needed to confirm and update the findings of this analysis.*

***Keywords:*** *trimodal therapy, radical cystectomy, survival, muscle-invasive, meta-analysis*

## Introduction

Radical cystectomy (RC) is the gold standard treatment option for muscle-invasive bladder cancer (MIBC) [1,2]. However, due to a combination of factors, including quality of life, performance status, quality of care, overall health and age, many patients with multiple comorbidities are unfit for RC and need a safe and effective treatment as an alternative [3-5].

Recently, several multimodal bladder-sparing protocols have been tested to challenge the well-established dogma of RC. The most studied conservative approach is trimodal therapy (TMT), which combines bladder-sparing surgery for a bladder tumour with radiotherapy (RT). Additionally, chemotherapy has been increasingly considered as an alternative therapy for MIBC [5-7].

Unfortunately, clinicopathologic stage discordance and inclusion biases limit the validity of comparisons between TMT and RC. The inverse probability of treatment-adjusted analyses or propensity score matching analyses have been used in some studies to directly compare the results of radical cystectomy and TMT [8-10]. However, no completed RCTs have compared the outcomes of multimodality treatment (MMT) with those of the gold standard, RC. A randomized comparison of TMT and RC was attempted but failed in part due to the patients' reluctance to be randomized for surgery when a bladder-preserving option was available [11].

Therefore, we deemed a meta-analysis of these published institutional studies justified. This study aimed to compare oncologic outcomes between patients with MIBC who were treated with RC or TMT and to assess the most effective strategy to help guide the most rational design of treatment for the disease.

## Methods

### Patient and public involvement

The patients and the public were not involved in setting the research question or the outcome measures, and no patients were involved in developing plans for the design or implementation of the study. We are unable to disseminate the results to study participants because of the nature of a meta-analysis.

### Literature search strategy

A literature search was performed from 1990 to July 2017 without restrictions on region, publication type, or language. The primary sources were the PubMed, Embase, and Cochrane Library electronic databases. The following MeSH terms and their combinations were searched in [Title/Abstract]: bladder cancer, bladder preservation, trimodality treatment, radiotherapy, chemotherapy, chemoradiation, chemoradiotherapy, organ-sparing, bladder-sparing, and salvage cystectomy.

### Inclusion and exclusion criteria

The inclusion criteria were published full articles, clinical trials, and retrospective series written in English. All available retrospective comparative studies (cohort or case–control studies) that compared TMT with RC and had at least one of the quantitative outcomes mentioned in the next section of this article were included. Articles reporting bladder preservation only in non-MIBC (NMIBC) patients and that only included patients who underwent RC or TMT alone as a group was excluded. Non-symmetrical comparative studies (patients who received adjuvant chemo-radiotherapy after maximum resection of their tumours) were excluded. Patients who showed no evidence of bladder tumours completed the TMT, whereas those with recurrent invasive tumours did not receive additional CRT and were assigned to undergo a salvage cystectomy during the evaluation were excluded from this study. To avoid overlapping patient data from duplicate publications, registry analyses were cross-checked with institutional studies and compared with other registry studies, and the larger or more complete publication was included.

### Data extraction

Two authors (Zaishang Li and Xueying Li) independently extracted and summarized information using predefined data abstraction forms. Any disagreement was resolved by the adjudicating senior authors (Fangjian Zhou and Hui Han). The following details were extracted: first author, year of publication, study period, institution and country of the study, study design, inclusion and exclusion criteria, matching criteria, numbers of patients enrolled in each type of group, disease duration in years, condition of the patients, disease stage (T stage, N stage and G stage) and the reported outcome. Details on the therapeutic interventions included the surgical procedure, chemotherapy regimen, radiation dosage, and treatment schedule.

The primary outcome was the 5-year overall survival rate. If sufficient data were available, prespecified subgroup analyses were conducted for studies that included the year, node-positive status or conditions of the patients. The secondary outcomes were disease-free survival and local and distant recurrence. When survival was not reported in the text, this outcome was independently calculated from the survival curves by two reviewers (Zaishang Li and Xueying Li). Missing data from studies deemed potentially eligible were sought from the authors via e-mail request.

### Patient and public involvement

The methodological quality of the retrospective studies was assessed using the modified Newcastle-Ottawa scale, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcomes [12]. A score of 0-9 (allocated as stars) was allocated to each study except RCTs. RCTs and observational studies that achieved six or more stars were considered high quality.

The relative frequency of survival at 5 years between RC and TMT was expressed as an odds ratio (OR) and its 95% CI using Stata version 12 (Stata Corp, College Station, TX, USA). Statistical heterogeneity between studies was assessed using the Chi-square test with significance set at $P<0.10$, and heterogeneity was quantified using the $I^2$ statistic. The random-effects model was used if heterogeneity was found between studies; otherwise, the fixed-effects model was used. Sensitivity analyses were performed for high-quality studies. Funnel plots were used to screen for potential publication bias.

## Results

### Studies

Nine studies incorporating 15,160 cases (1886 TMT cases and 13,274 RC cases) met the initial search criteria and were included in the analysis (Figure 1) [9,10,13-19]. Among the studies, only one randomized trial [18] and one propensity score matching analysi [9] failed to achieve the target (stop/go) accrual rates. Two publications were registry analyses (the Surveillance Epidemiology and End Results database and the National Cancer Database) [10,13], and 6 were institutional series [9,14-18]. Eight articles [9,10,13,16-19] were related to overall survival rates, and 4 studies [9,13,14,18] referred to disease specific survival (DSS) and 4 studies [15-17,19] referred to local and distant recurrence rates . Generally, the quality of the included studies was low. The characteristics of the included studies are shown in Table 1.

### Overall survival rates

Pooled data from the 8 studies [9,10,13,16-19] that assessed overall survival rates for 15,089 patients showed no significant difference in this metric between the TMT and RC groups (HR: 1.27; 95% CI, 0.98–1.63; P=0.066; Figure 2).

When the primary outcomes were divided into subgroups according to the lymph node stage, age and PS stage, no significant differences were found between TMT and RC for the Nx group (HR: 1.20; 95% CI, 0.76–1.90; P=0.430, Figure 3A), matched age(HR: 1.15; 95% CI, 0.87–1.51; P=0.319; Figure 3B), any age-matched PS (HR: 1.86; 95% CI, 0.89–3.91; P=0.101; Figure 3B), PS matched (HR: 1.17; 95% CI, 0.77–1.78; P=0.471; Figure 3C) and any PS group (HR: 1.34; 95% CI, 0.95–1.90; P=0.094; Figure 3C). However, the pooled data confirmed a significant benefit for RC in patients with node-negative disease (HR: 1.36; 95% CI, 1.02 to 1.81; P=0.036; Figure 3A).

### Secondary efficacy endpoints

Four studies [9,13,14,18] including 14,700 cases (1426 TMT cases and 13,274 RC case) reported disease specific survival (DSS), which was not significantly longer in the TMT group than in the RC group (HR: 0.95; 95% CI, 0.60–1.49; P=0.819; Figure 4).

Additionally, these four studies [15-17,19] assessed local and distant recurrence for 199 patients. Pooled data confirmed a nonsignificant benefit for RC (n=115) in both local recurrence (HR: 0.67; 95% CI, 0.18–2.50; P=0.550; Figure 5A) and distant recurrence (HR: 1.16; 95% CI, 0.31–4.41; P=0.826; Figure 5B).

## Discussion

This meta-analysis included 9 studies involving 15,160 patients that compared the efficacy of TMT and CR for the management of bladder cancer. This analysis showed a nonsignificant benefit for RC in unselected patients. However, RC therapy seemed beneficial in the subgroups with node-negative disease.

The present study is unique because we used a meta-analysis to compare TMT and RC. MMT combining bladder-sparing surgery with subsequent chemotherapy and radiotherapy (RT) is the most-studied bladder-sparing strategy to achieve a possible reduction of side effects and a high quality of life. This strategy is increasingly requested by patients [1,2]. One non-completed RCT compared

| Study | Year | Country | Type | Patient | | Clinical T stage | Node positive | Surgery for TNM | Chemotherapy | Radiotherapy | Follow-up | Matching criteria | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | TNM | PC | | | | | | | | |
| Bekelman et al. [13] | 1995-2005 | SEER | R | 417 | 1426 | T2-4 | N0 | TURBT | NA | NA | 40.8/44.4 | 1;2;4;5;7 | 7 |
| Fumitaka Koga et al.[14] | 1997-2006 | Japan | R | 39 | 58 | T2-4a | No | TURBT or PR | Cisplatin | 40 | 43 | NA | 4 |
| Gofrit et al. [18] | 1998-2008 | Israel | R | 33 | 33 | T2-4a | N0 | TURBT | Cisplatin or carboplatin | 66 | 35/36 | 1;2;4 | 6 |
| Haresh et al.[16] | 2002-2004 | India | Cohort study | 13 | 30 | T2-4 | N0 | NA | CMV | 60 | 24 | 4 | 5 |
| Huddart et al. [19] | 2007-2010 | SPARE | RCT | 20 | 25 | T2-T3 | N0 | NA | NAC | 55-60 | 58 | 4;6.7 | RCT |
| Kulkarni et al. [9] | 2008-2012 | MDB-CC | R | 56 | 56 | NA | Both | TURBT | Cisplatin-based | 66 | 4.51 | 1;2;3;4;6;7 | 7 |
| Martin et al. [24] | 1988-1991 | France | R | 18 | 22 | T2-4 | Both | TURBT | 5-FU/cisplatin | 44 | 27 ±12 | 1;6;7 | 6 |
| Thomas S et al. [10] | 2004-2011 | NCDB | R | 1257 | 11;586 | T2-4 | NA | NA | NA | NA | 44 | 1;2;3 | 6 |
| Yadav et al. [17] | 2001-2004 | India | R | 33 | 38 | T2-4a | Both | TURBT | Cisplatin | 60 | 32 | NA | 4 |

**Table 1.** Characteristics of the included trials. Atching criteria1: age; 2: gender; 3: T stage; 4=N stage; 5: grade; 6: status; 7: comorbidity score; and 8: time.

the outcomes of MMT with RC but failed to meet the original recruitment targets [20]. Very few retrospective studies have compared TMT and RC, and these studies present their own sets of limitations [9,10,13-19]. Given the retrospective nature of these studies, selection bias hinders the ability to definitively address the differences observed in the baseline characteristics between the TMT and RC groups [21].

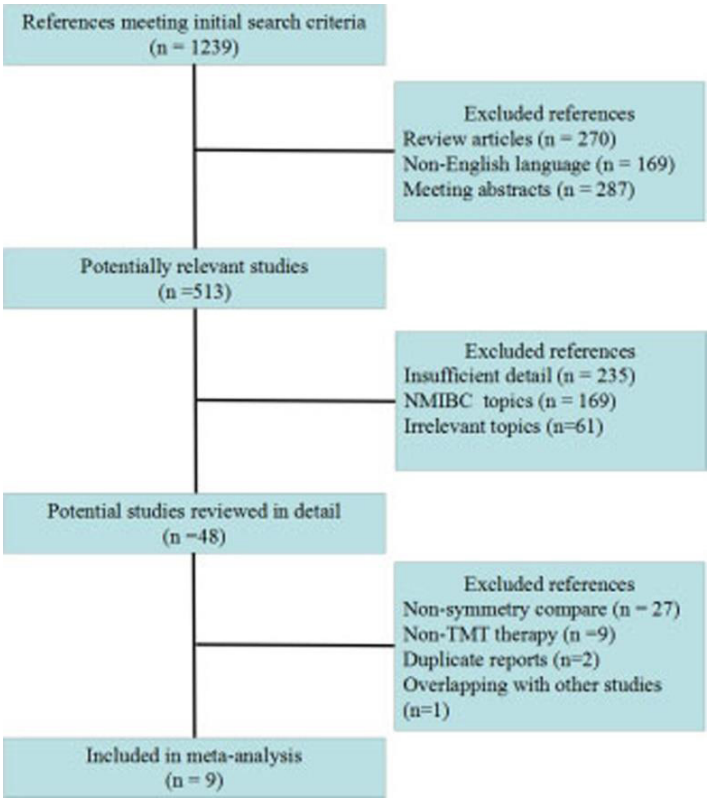


**Figure 1.** Flowchart of study selection procedure. NMIBC: Non-Muscle-Invasive Bladder Cancer; TMT: Trimodal Therapy.

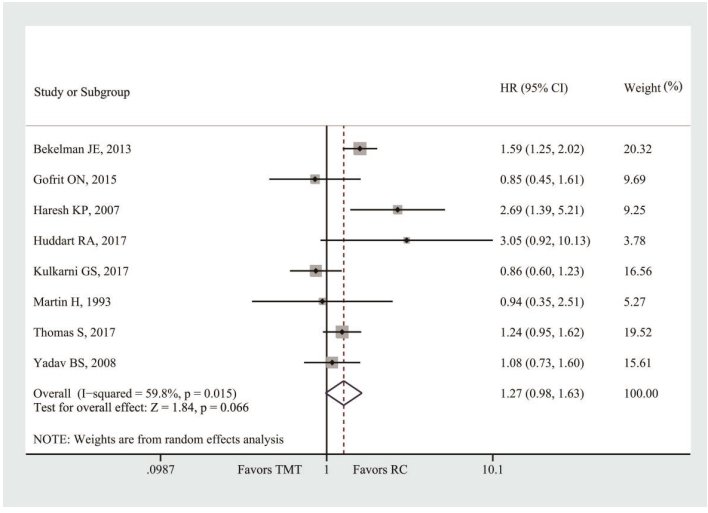


**Figure 2.** Forest plot and meta-analysis of overall survival rates.

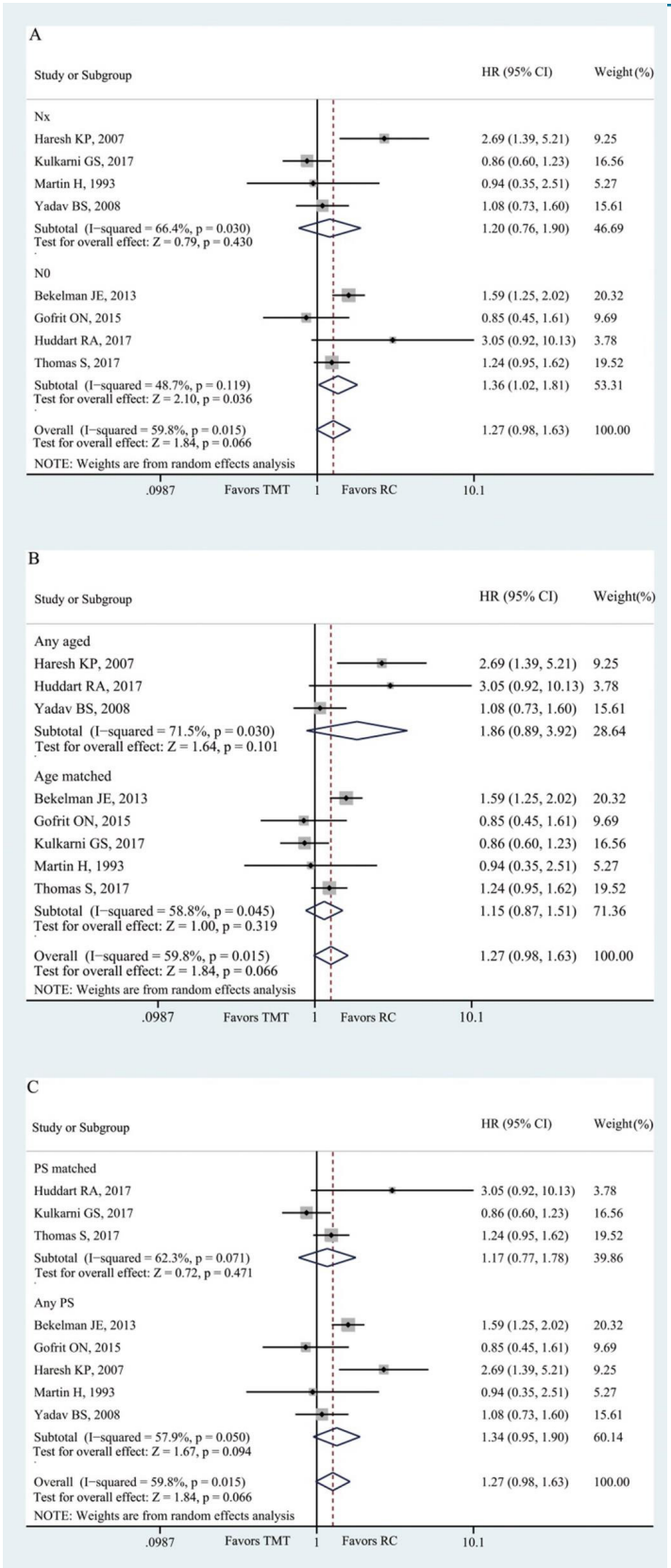


**Figure 3.** Forest plot and meta-analysis of overall survival rates measured by lymph node stage(A), age(B) and PS stage(C) .

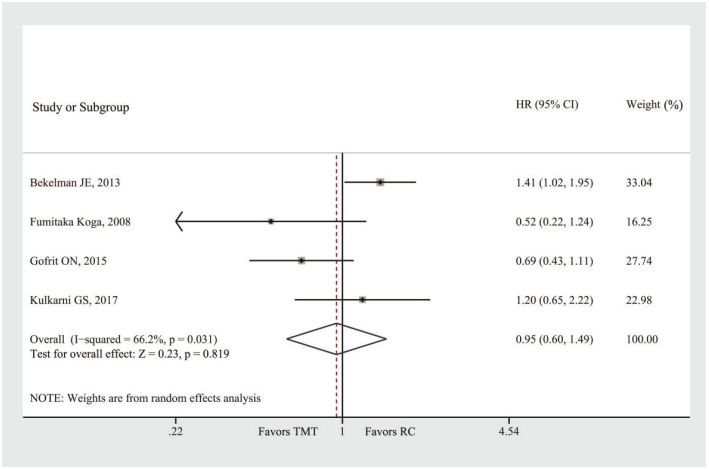


**Figure 4.** Forest plot and meta-analysis of disease specific survival rates

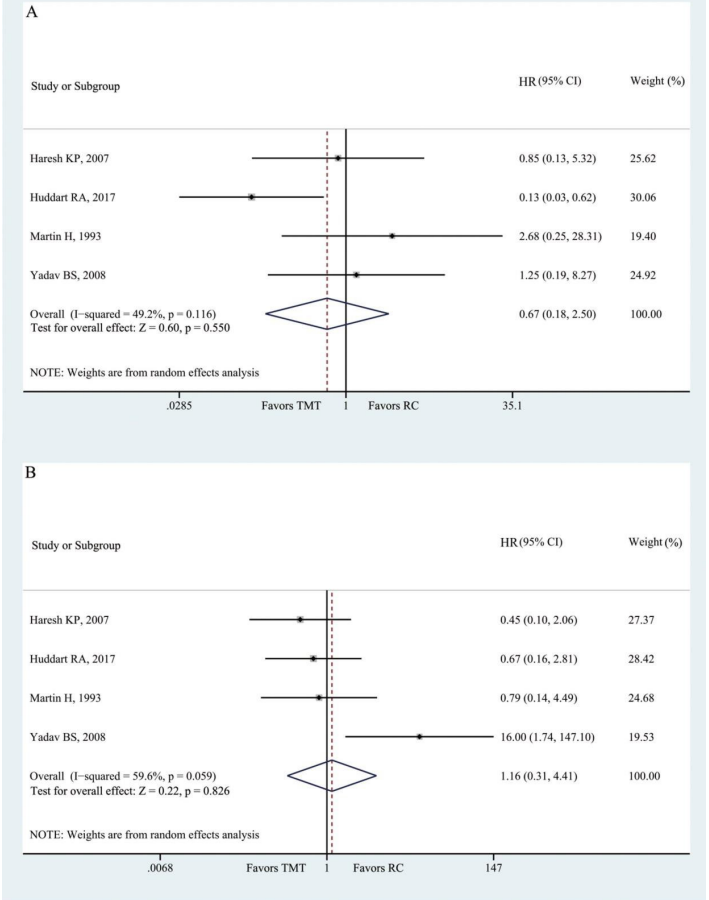


**Figure 5.** Forest plot and meta-analysis of overall survival rates measured by local recurrence(A), distant recurrence(B).

We suggest that bladder preservation with TMT leads to acceptable outcomes. In a retrospective series of patients undergoing chemoradiation after surgery, the 5-year OS rates were 36-74%, which were similar to the survival outcomes of patients who underwent RC [2,22]. In 2013, Smit AB et al. used the National Cancer Database (NCCDB) to assess the comparative effectiveness of TMT and RC and found that chemoradiation resulted in a similar OS as radical cystectomy(8). However, another study found that trimodal therapy generally was associated with worse long-term overall survival based on the NCCDB [10]. To account for selection bias, Yeon Joo Kim et al. compared the clinical outcomes between RC and TMT using propensity score matching with 50 patients in the RC arm and 29 patients in the TMT arm with similar overall survival (56% vs. 57%) [23]. Similarly, Kulkarni et al. found that TMT yielded survival outcomes similar to those of the matched patients who underwent RC in the setting of a MDBCC [9]. According to our analysis, data from 8 studies that assessed overall survival rates in 15,089 patients also showed no significant differences between TMT and RC; therefore, these strategies may be considered reasonable treatment options in well-selected patients.

Our results are critical for recommending treatment options, especially for node-negative patients. Clinicopathologic stage discordance and inclusion biases limit the validity of comparisons between the two procedures [7,24]. RC series are limited to selected patients, such as those with smaller, unifocal tumours without CIS or hydronephrosis. Furthermore, contemporary TMT series involve more highly selected populations, such as the elderly or those more comorbidities and/or larger disease extents. Although some meta-analyses and systematic reviews assume the oncologic equivalence of bladder preservation modality treatments compared with RC [7,21,24,25], drawing a conclusion on which treatment option is reasonable for well-selected patients is difficult. This meta-analysis used subgroups according to the lymph node stage (Nx), age and PS stage and found no significant differences between TMT and RC. However, our exploratory analysis showed little benefit for RC compared with TMT in patients with node-negative disease (HR: 1.36; 95% CI, 1.02 to 1.81; P=0.036; Figure 3A).

To assess any impact on survival, we also performed an analysis including DSS and the local and distant recurrence rates. Several large studies have offered long-term follow-up and addressed the DSS and local recurrence and distant recurrence rates [7,21,25]. Our results were similar to those analyses. However, these results should be validated by more studies. Our analysis supports the concept that TMT leads to acceptable outcomes and therefore may be considered as a reasonable treatment option for well-selected patients, especially those who are not willing to undergo surgery [21].

This analysis has some limitations that must be considered. First, as is the case for any meta-analysis, data were combined from different studies, each of which was retrospective except for one RCT with a small sample size. However, all of these studies were retrospective in nature and presented the associated selection biases, including comparing TMT with RC. To overcome this bias, subgroup analyses were applied to create comparable TMT and RC cohorts. Second, the multifarious adjuvant therapies (chemotherapeutic agents and radiation protocols) and surgical techniques may have affected the results. The different experience levels of the doctors with the two different approaches could have influenced the outcomes. Inherent bias exists in retrospective studies. Therefore, only data that evaluated the same end points were available. The bladder-preserving multimodality strategy is still controversial. However, the discordance of the patients' clinicopathologic stages limits the validity of comparisons between the two procedures, especially in a RCT. Therefore, a meta-analysis is needed. Third, our study did not analyse complications and tolerance. Heterogeneity could exist within these studies, although none of them addressed this issue. Moreover, a systematic assessment of acute and late toxicity and their effects on quality of life is lacking at present [7]. Finally, the difference between the two procedures was not significant, possibly because the studies were retrospective and presented remedial model selection bias. Therefore, all analyses may be considered exploratory rather than hypothesis-tested in our study. However, we believe that the present analysis will be important for future systematic reviews or RCTs.

## Conclusion

In summary, our analysis provides reasonable support for the use of organ-sparing TMT and suggests that appropriately selected patients with MIBC should be offered the opportunity to discuss various treatment options. Due to a striking lack of randomized data, international collaboration for the development and support of prospective studies must be prioritized. The results of this meta-analysis should contribute to the rational design of these prospective studies.


## Acknowledgements

We are grateful to authors and the enrolled patients, their families, and the referring physicians. We also gratefully acknowledge the contribution of all colleagues in this study. Additionally, we thank our families for their support.


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Rec: Jan 10, 2020; Acc: Jan 24, 2020; Pub: Jan 27, 2020

J Cancer Sci Therap. 2020;3(1):15
DOI: gsl.cancer.2020.00015