Review Article

Bladder-sparing approaches for muscle invasive bladder cancer: a narrative review of current evidence and future perspectives

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Background and Objective: In recent years, the application of less-invasive "bladder-sparing" trimodal therapy (TMT) in selected muscle-invasive bladder cancer (MIBC) patients unfit for or who declined radical cystectomy (RC) has been increasing. This review aims to summarize the current evidence and future perspectives of bladder-sparing therapy for MIBC.

Methods: A non-systematic Medline/PubMed literature search was conducted on July 2022 with the following keywords 'MIBC', 'bladder-sparing', 'chemotherapy', 'radiotherapy', 'trimodal', 'multimodal', and 'immunotherapy'.

Key Content and Findings: All monotherapies are inferior to RC or combination therapy and should not be routinely used for curative intent. Radiotherapy (RT) alone has been shown to have poorer outcomes when compared to chemoradiotherapy. The ideal selection criteria for TMT include good bladder function and capacity, clinical stage within cT2, complete transurethral resection of bladder tumor (TURBT), no prior history of pelvic RT, no extensive carcinoma in situ (CIS), and absence of hydronephrosis. The emergence of immunotherapy may further increase the effect of bladder-sparing therapy. Novel predictive biomarkers are awaited for more precise patient selection and better oncological outcomes.

Conclusions: TMT is a well-tolerated and offers a curative alternative approach to RC for selected patients with localized MIBC. Appropriate patient selection and a multi-disciplinary approach is crucial in achieving good oncologic control with bladder-sparing therapy.

Keywords: Muscle invasive bladder cancer (MIBC); bladder preservation therapy; bladder-sparing; chemoradiation; trimodal therapy (TMT)

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Introduction

Bladder cancer is the 7th most common cancer in males, and it ranks the 10th when both genders are included (1). An estimate of 573,278 new bladder cancer patients and 212,536 new bladder cancer-associated deaths occurred in 2020 worldwide according to the recent report of the global cancer burden (2).

The gold standard treatment for muscle invasive bladder cancer (MIBC) is radical cystectomy (RC). However, the 5-year overall survival (OS) after RC is only about 50% (3-6). As RC is associated with nonnegligible morbidity and mortality, clinicians have sought alternative treatments for patients unfit for or refusing RC. Organ-sparing

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Table 1 The search strategy summary

Items	Specification
Date of search	20 July 2022
Databases and other sources searched	Medline/PubMed
Search terms used	'MIBC', 'bladder-sparing', 'chemotherapy', 'radiotherapy', 'trimodal', 'multimodal', and 'immunotherapy'
Timeframe	January 1987 to July 2022
Inclusion and exclusion criteria	Study type: original studies of RCTs, cohort studies, case-control studies, and case series. Language restriction: English
Selection process	Selection process was conducted independently by two of the authors (Fan and He). When there was a disagreement, consensus was obtained by the adjudicating of the senior author (Huang)

MeSH, medical subject heading; RCT, randomized controlled trial; MIBC, muscle invasive bladder cancer.

multimodality approaches have been widely used as first-line therapies in multiple malignancies, such as breast cancer (7), cervical cancer (8), and anal cancer (9). Organ preservation could ideally maintain satisfactory function of the native organ following treatment. In recent years, the application of less-invasive "bladder-sparing" trimodal therapy (TMT) has been increasing, which involves maximal transurethral resection of bladder tumor (TURBT), followed by concurrent chemotherapy and RT (10). TMT is a well-tolerated and offers a curative alternative approach to RC for selected localized MIBC patients (11). Several organizations, including the European Association of Urology (EAU) and the American Urological Association (AUA), have updated the guidelines to support the application of chemotherapy combined with RT in selected MIBC patients unfit for or who declined RC (1,12,13). This review aims to summarize the current evidence and future perspectives of bladder-sparing therapy for MIBC. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-124/rc).

Methods

We performed a non-systematic Medline/PubMed literature search on 20 July 2022 with the following keywords 'MIBC', 'bladder-sparing', 'chemotherapy', 'radiotherapy', 'trimodal', 'multimodal', and 'immunotherapy'. The search strategy is summarized in *Table 1*.

TURBT

A TURBT is usually the first and crucial treatment for bladder cancer. The EAU, AUA, and National Comprehensive Cancer Network (NCCN) guidelines recommend thoracic, abdominal and pelvic CT scan to evaluate the clinical stage MIBC (1,12,13).

However, it is worth noting that all monotherapies are inferior to RC or combination therapy and should not be routinely used for curative purposes (1,12-14). As a therapeutic option, TURBT is only possible when the tumor is confined to the superficial muscle layer and second biopsy reveals a free of residual (invasive) tumor (1,15). It is worth noting that about 20% of MIBC have nodal involvement at final pathology. Therefore, the staging ability and the potential therapeutic effect of an extended pelvic lymph node dissection (ePLND) is missed in a TURBT-only approach. Thus, as a solo modality, TURBT should not be recommended as the standard of care in patients with MIBC.

A prospective study by Solsona *et al.* reported complete TURBT in 133 highly-selected MIBC patients with no residual tumor in post-treatment biopsy. Recurrent non(N)-MIBC occurred in 30% of patients, whereas disease progression occurred in another 30% of patients. After 5, 10, and 15 years, the results showed that OS was 73.7%, 39.8%, and 24.8%, respectively, and cancer-specific survival (CSS) was 81.9%, 79.5%, and 76.7%, respectively (16). A study by Herr demonstrated similar results with a 76% 10-year CSS in 99 MIBC patients who underwent TURBT alone (17).

The goal of a "maximal TURBT" is to reset all visible tumors without compromising surgical safety. Several studies have investigated the association of a visibly complete TURBT between complete response (CR) rate, OS, and long-term bladder preservation rate after TMT (18,19).

According to Efstathiou *et al.*, although a visibly complete TURBT is preferred, CR was achieved in 57% patients with a visibly incomplete TURBT following the combination therapy of chemoradiation (18). Fluorescence-based cystoscopy may show multifocal lesions which may have otherwise been missed, such as carcinoma in situ (CIS) or smaller Ta/T1 tumors, when focusing on a T2 tumor, thereby reducing recurrence rates (20-23).

Chemotherapy

Chemotherapy alone rarely produces durable complete disease remissions for MIBC. Chemotherapy can be used preoperatively (neoadjuvant chemotherapy, NAC) or postoperatively (adjuvant chemotherapy, AC) prior to RC. In patients who undergo bladder-sparing treatments for MIBC, chemotherapy plays a crucial role by increasing the radio-sensitivity of the bladder tumor. Chemotherapy agents used as radiosensitizers for TMT include gemcitabine, mitomycin C, fluorouracil/cisplatin, etc. Survival outcomes are improved with radio-sensitizing chemotherapy prior to RT when compared to RT alone (24). Compared with RT monotherapy, synchronous chemotherapy with mitomycin C and fluorouracil combined with RT has been shown to significantly improve locoregional tumor control, with no significant increase of adverse events (25). The 2 years' locoregional disease-free survival (DFS) was 67% in the chemoradiation group and 54% in the RT alone group. The chemoradiation combination therapy was well-tolerated, 80% of patients completed chemotherapy and 95% of patients completed RT (25).

Several studies have reported encouraging results of NAC prior to TMT (26,27). Jiang *et al.* assessed 57 consecutive MIBC who underwent NAC prior to TMT, and the result showed that 2-year OS, disease-specific survival, and bladder-intact DFS were 74%, 88%, and 64%, respectively (26). Hafeez *et al.* reported that response to NAC is a favorable prognostic factor which can be applied to choose patients for RT, resulting in bladder preservation in more than 80% of selected patients (27). Other studies have investigated adjuvant chemotherapy after TMT, but shown worse completion rates and tolerability compared with NAC, with grade 3–4 toxicity rate as high as 75% (28-30). Therefore, NAC is preferred in TMT.

RT

RT has been used as a treatment for bladder cancer since 1926, but RT alone has been shown to have poorer outcomes when compared to chemoradiotherapy (25). A conventional course of RT usually includes external beam radiotherapy (EBRT) to the bladder and limited pelvic lymph nodes (LNs) with an initial dose of 40–45 Gy, followed by another boost to the whole bladder of 50-54 Gy, and a further tumor boost to a total dose of 60–66 Gy (1). There are 2 RT regimens most commonly used during RT for MIBC: a split course regimen with interval cystoscopy is typically used in the US (18), whereas European centers generally use the continuous course regimen which is now more commonly used (25). If an incomplete response is observed during the split course regimen, patients undergo immediate salvage RC (12).

Controversy exists on the optimal radiation fields, especially on whether treatment should entail partial bladder radiation (tumor) or whole bladder radiation. Partial bladder radiation spares normal tissue with less toxicity, but may miss any occult tumor that has not been diagnosed by cystoscopy or imaging (14). Another controversial topic of RT is the optimal radiation volume to regional LNs. Radiation Therapy Oncology Group (RTOG) protocols in the US include whole pelvic radiation and an additional boost volume to the bladder and gross tumor. Considering the high LNs metastases rate (20–30%) seen in pT2-T3 disease, it seems rational to give radiation to regional LNs (31). Meanwhile, in the BC2001 trial protocol in Europe, radiation was administered to the bladder only, and the results showed that pelvic relapse rate with RT only to the bladder were merely 5.8%, indicating that not all patients need RT to the pelvic LNs (32). Nonetheless, a limitation of this study should be considered as it included a high proportion of low-risk MIBC diseases (84% were T2N0M0) with a low LN metastases rate. Therefore, selective treatment of LNs (when nodes are negative) is optional, and should consider the patient's comorbidities and the risk of toxicity to adjacent critical structures.

Patient selection

Appropriate patient selection is crucial in achieving good oncologic control with bladder-sparing therapy. The ideal selection criteria for TMT include good bladder function and capacity, clinical stage within cT2, complete TURBT, no prior history of pelvic RT, no extensive CIS, and absence of hydronephrosis (14).

The high-risk factors associated with poor prognosis after

TMT include incomplete or inability to achieve maximal TURBT, hydronephrosis, diffuse multifocal tumors, extensive CIS, and cT3-cT4a disease (14). Higher tumor stages appear less responsive to chemotherapy and RT. According to an observational study including 415 MIBC patients treated with bladder-sparing therapy, the response rate decreased as the tumor stage increased (metastases-free survival at 5 years T2, 85%; T3, 63%; and T4, 34%) (19). Multifocal lesions were associated with a greater risk of local recurrence following CR to bladder-sparing treatment. MIBC patients with tumor-related hydronephrosis show reduced CR rates to bladder-sparing therapy and therefore should not be routinely offered (19). Although the above high-risk factors are not absolute contraindications to TMT, the chance of cure is significantly diminished (14).

Oncological outcomes

No prospective randomized trial has successfully compared the oncological outcomes between TMT and RC. A prospective randomized phase III trial to compare TMT versus RC was ultimately closed due to poor recruitment (33).

Several observational studies have compared the oncological outcomes between TMT and RC, with 5-year OS and CSS rates varying between 36% and 74% and 50% and 84%, respectively, and the salvage cystectomy rates have varied between 10% and 30% (25,28,34-36). A meta-analysis of the combined data of 6 RTOG bladder-sparing studies demonstrated 5-year OS and CSS of 57% and 71%, respectively, with salvage cystectomy rates of 21% (37). However, due to the risk of selection bias, misidentification, and misclassification, the clinical significance of these data must be interpreted with caution (11). Clinicopathologic stage discordance and inclusion biases have also limited the validity of direct comparison between TMT and RC (34). Patients treated with TMT were generally older than those who underwent RC, and had more co-morbidities, thus they may have poorer prognosis.

Future perspectives

In recent years, the emergence of immunotherapy has led to a great innovation in the treatment of malignant tumors (38,39). Immune checkpoint inhibition (ICI) provides enduring response in patients with advanced or metastatic bladder cancer (40,41). Preclinical studies have shown that RT can enhance the effect of ICI by enhancing the systemic antitumor immune response by enhancing the cross-presentation of tumor antigens and the upregulation of PD-L1 expression (42). Several comparative randomized phase II trials evaluating the effect of combining ICI with chemoradiotherapy (iCRT) are still ongoing (43-47). The ICI regimens used include anti-programmed death-1 (PD-1; pembrolizumab or nivolumab) or anti-programmed cell death ligand-1 (PD-L1; atezolizumab or durvalumab) monotherapy, or a combination of anti-PD-1 and anti-CTLA-4 (ipilimumab and nivolumab). Almost all these trials are still in the recruiting phase, with early results showing complete remission in 90% of patients, 1-year DFS, metastasis-free survival (MFS), and OS between 77% and 100%, and immune-mediated toxicity seen in about 10% of patients (43-48). The final results of these trials may reveal the real effect of the immunotherapy combined with radiotherapy (iCRT) treatment modality, and the following limitations should be considered (48). Firstly, several TMT schemes are being combined with ICI, but the best scheme for MIBC remains undetermined. Secondly, a standardized response evaluation after iCRT still needs to be defined. Thirdly, there was a selection bias in the above phase I–II trials in which most included patients had a relatively high performance status. However, in clinical practice, most patients who receive bladder-preservation therapy are usually older, less physically fit, and have more comorbidities. Moreover, the ideal biomarkers of treatment response and immune evasion in patients undergoing iCRT therapy remain to be further developed. Finally, the difficulty in comparing outcomes among studies should be considered. Despite preliminary findings are encouraging, harmonization of terminology and definition of clinical endpoints among trials will be mandatory to correctly assess the potential role of CRT and immunotherapy combination as bladder-sparing solution in routine clinical practice (49).

The current selection criteria for TMT are mainly based on patient's clinical and pathological factors, but novel biomarkers that can predict response after TMT are receiving increasing attention. Several studies have demonstrated that DNA damage response markers, including MRE11 and ERCC1/2, serve as predictors of CSS in 2 independent TMT cohorts (50,51). In patients with low MRE11 expression, RC was associated with significantly longer CSS compared with RT (51).

In ERCC1 immunohistochemistry, 6 out of 8 positive cases had no complete response to chemoradiotherapy, whereas 12 out of 14 negative cases had complete remission, suggesting ERCC1 expression level may predict the efficacy

of chemoradiation therapy for MIBC (50). T-cell activation and interferon-γ signaling signatures appear to be associated with improved CSS after TMT, whereas higher stromal infiltration is associated with poorer outcomes after NAC and RC (52). Although the above biomarkers are promising in predicting response after TMT, further validation is still required in prospective trials.

Conclusions

TMT is a well-tolerated and offers a curative alternative approach to RC for selected patients with localized MIBC. Appropriate patient selection and a multi-disciplinary approach is crucial in achieving good oncologic control with bladder-sparing therapy. Novel predictive biomarkers are anticipated for more precise patient selection and better oncological outcomes.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-124/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-124/coif). The authors have no conflicts of interest to declare.

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.

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