Review

Current status and advances in bladder-sparing treatment for non-metastatic muscle-invasive bladder cancer

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Abstract

Background: Muscle-invasive bladder cancer (MIBC) is a highly aggressive malignancy for which radical cystectomy (RC) remains the standard treatment. While RC provides effective oncologic control, it significantly impairs patients' quality of life. As a result, there is growing interest in bladder-sparing strategies. Among these, trimodal therapy (TMT) remains the most established approach, and evolving regimens incorporating novel immune checkpoint inhibitors have expanded therapeutic possibilities. However, a standardized treatment protocol has yet to be defined. **Objective:** This review outlines the current status and recent advances in bladder-sparing treatments for MIBC, with a focus on treatment principles, established modalities such as TMT, and emerging immunotherapy-based strategies. **Conclusion:** TMT offers a well-tolerated and potentially curative alternative to RC for select patients with localized MIBC. Its success relies on appropriate patient selection and multidisciplinary collaboration. Immunotherapy-based bladder preservation approaches have shown promising outcomes but require further validation in large-scale randomized clinical trials.

Keywords: Bladder preservation, Bladder-sparing treatment, Immunotherapy, Multimodal therapy, Muscle-invasive bladder cancer, Trimodal therapy

1. Introduction

Muscle-invasive bladder cancer (MIBC) is a potentially lethal form of bladder cancer, characterized by the invasion of cancer cells into the bladder's muscular layer. MIBC requires aggressive treatment to achieve local control, prevent metastasis, and prolong survival. Radical cystectomy (RC) is the cornerstone of treatment for localized MIBC and remains the gold standard for patients who are medically fit for major surgery.[1] It involves the complete removal of the bladder, pelvic lymph nodes, and, in some cases, adjacent organs, such as the prostate and seminal vesicles in men or the uterus and part of the anterior vaginal wall in women. This extensive surgical approach aims to achieve optimal oncologic control through eliminating the primary tumor and potential sites of regional spread.[2] Studies have demonstrated that RC provides excellent local tumor control, with 5-year overall survival (OS) rates ranging from 50% to 70% for patients with non-metastatic disease.[3] Despite its efficacy, the procedure is often accompanied by high complication rates, which significantly impact patients and are closely linked to their pre-operative health condition, associated with significant morbidity and a substantial impact on the quality of life, particularly due to the need for urinary diversion. As a result, many patients are either unsuitable for RC or choose to decline it. Consequently, bladder-sparing treatment approaches have become preferred alternatives for these patients. This review summarizes the current literature on trimodal therapy (TMT) and immunotherapy for bladder preservation.

2. TMT

2.1. The role and efficacy of TMT

Bladder-sparing therapies, particularly TMT—which integrates transurethral resection of bladder tumor (TURBT), chemotherapy, and radiotherapy—have gained prominence as viable alternatives for patients who are either medically ineligible for or decline RC.[4,5] The standard radiotherapy

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protocol typically involves external-beam radiation targeting the bladder and selected pelvic lymph nodes, beginning with a dose of approximately 40 Gy. This is followed by a whole-bladder boost to 54 Gy, with an additional localized boost to the tumor area to reach a cumulative dose of 64–65 Gy. A Phase III trial's results support the concurrent use of radiosensitizing chemotherapy regimens, particularly cisplatin or a combination of mitomycin C and 5-fluorouracil.[6,7] Cystoscopic evaluation, including systematic rebiopsy, should be conducted either at the end of the TMT or shortly after induction therapy to identify nonresponders promptly, allowing timely salvage RC.

Two large-scale studies by Rodel *et al*.[8] and Efstathiou *et al*.[9] evaluated selective bladder preservation through combined-modality therapy (CMT) as a potential alternative to RC for MIBC. These studies highlighted that CMT, which involves TURBT followed by concurrent chemotherapy and radiotherapy, could achieve long-term survival outcomes comparable to RC in carefully selected patients. Rodel *et al*.[8] reported that 72% of patients experienced a complete response (CR) after CMT, with 64% maintaining local control over 10 years. Disease-specific survival (DSS) at 10 years was 42%, and more than 80% of long-term survivors retained their bladders. They emphasized that early-stage tumors and complete tumor resections were key predictors of success. Similarly, Efstathiou *et al*.[9] observed a CR rate of 72% among patients, with a 10-year DSS of 59% and OS of 35%. Approximately 70% of patients preserved their bladders, and salvage cystectomy was effective in cases of recurrence. Importantly, achieving CR and complete TURBT were associated with improved survival outcomes. Both studies suggest that CMT is a viable alternative to RC for appropriately selected MIBC patients, offering substantial bladder preservation without compromising survival. However, they underscore the need for rigorous patient selection, close surveillance, and further comparative trials to validate these findings.

The SPARE trial aimed to evaluate the feasibility of a prospective randomized trial in MIBC, comparing outcomes between RC and selective bladder preservation after neoadjuvant chemotherapy (NAC).[10] The trial involved patients with T2–3N0M0 MIBC who were randomized to RC or selective bladder preservation before undergoing a cystoscopy following three chemotherapy cycles. While accrual and compliance with assigned treatment strategies were primary endpoints, challenges in recruitment and adherence limited the trial's feasibility. Of 45 patients enrolled over 30 months, 24% in the RC group received radiotherapy instead. Long-term bladder preservation was achieved in 73% of patients treated with radiotherapy per protocol, with no significant difference in OS across groups. The study highlighted the impact of clinician and patient treatment preferences on randomization and the difficulty of drawing firm conclusions due to the limited sample size.[11] Despite the trial failing, Softness *et al*.[12] emulated the SPARE trial to compare OS between RC and TMT for cT2–3cN0cM0 MIBC using data from the National Cancer Database. Among 2048 patients (1812 RC and 236 TMT), propensity score-adjusted analyses showed no significant difference in OS between the two treatments. However, RC appeared to provide improved OS for cT3 disease.

Although direct head-to-head randomized comparisons between TMT and RC are lacking, recent multi-institutional retrospective studies provide valuable insights into the comparative effectiveness of these approaches. A multi-institutional analysis of 722 patients (440 underwent RC and 282 received TMT) who were propensity score-matched (PSM) in a 3:1 ratio, with 837 receiving RC and 282 undergoing TMT. Five-year metastasis-free survival was comparable between the two groups: 74% for RC versus 75% for TMT in inverse probability of treatment-weighting (IPTW) analyses and 74% versus 74% in PSM analyses. Similarly, 5-year cancer-specific survival rates were closely matched: 81% for RC and 84% for TMT in IPTW analysis, and 83% versus 85% in PSM analysis. Disease-free survival also showed no significant differences, with 73–76% for RC and 74–76% for TMT across methodologies. However, OS slightly favored TMT, with IPTW analysis revealing a 5-year OS of 73% for TMT compared to 66% for RC. Furthermore, PSM analysis supported this finding, with OS rates of 77% for TMT versus 72% for RC. Pathological staging of RC patients revealed pT2 in 28%, pT3–4 in 44%, and nodal involvement in 26%, with a perioperative mortality rate of 2.5% and soft tissue positive margin rate of 1%. For TMT patients, salvage cystectomy was required in 13% of cases.[13]

The Radiation Therapy Oncology Group (RTOG)/NRG has long advocated for the use of radiation therapy in bladder preservation. Prospective data have shown that, especially with modern treatment approaches, long-term clinical outcomes are comparable to those observed in cystectomy series.[14] A pooled analysis of the RTOG trials evaluating chemoradiotherapy (CRT) with a concurrent cisplatin regimen,[15-20] encompassing 468 patients, reported a clinical CR rate of 69%. The OS rates were 57% at 5 years and 36% at 10 years, while DSS rates were 71% at 5 years and 65% at 10 years. Five-year cancer specific survival rates range from 50% to 82%, with OS rates between 36% and 74%. Non-muscle-invasive recurrences following CRT were more frequent, with a 5-year incidence of 31%, compared to a 5-year incidence of 13% for muscle-invasive recurrences.[21,22] Approximately 25–30% of patients undergoing TMT required salvage cystectomy. There is no conclusive evidence supporting the use of neoadjuvant or adjuvant chemotherapy in this context.[23]

A population-based study utilizing the Surveillance, Epidemiology, and End Results database (2004–2020) evaluated 4471 patients with cT2–T4aN0M0 urothelial carcinoma of the bladder, including 3391 (76%) treated with TMT and 1080 (24%) with external beam radiation therapy. The 5-year cancer-specific mortality (CSM) rate was 43.6% for TMT and 52.7% for external beam radiation therapy overall, with rates of 42.0% versus 51.9% in organ-confined cases. TMT was identified as an independent predictor of lower CSM. However, no survival benefit was observed for TMT in non-organ-confined patients. TMT usage increased over time, particularly in organ-confined cases, underscoring its role in improving outcomes for organ-confined patients.[24]

Patients with urothelial carcinoma exhibiting divergent differentiation, such as squamous differentiation or sarcomatoid features, who underwent TMT demonstrated outcomes similar to those with pure urothelial carcinoma (PUC). A retrospective study of 303 patients treated with TMT found that 66 (22%) had variant urothelial carcinoma (VUC). Of these, 50 (76%) exhibited squamous and/or glandular differentiation, while 16 (24%) presented with other variant forms. The CR rates following induction TMT were similar between patients with PUC (83%) and those with VUC (82%). The 5-year and 10-year DSS rates were 75% and 67%, respectively, for PUC compared to 64% for both time points in VUC. OS rates at 5 and 10 years were 61% and 42%, respectively, for PUC versus 52% and 42% for VUC. In addition, salvage cystectomy rates were comparable between the two groups. It is important to note that the study's retrospective design and focus on specific variants of urothelial carcinoma limit the generalizability of these findings.[25]

2.2. Maximal TURBT and repeat TURBT

While maximal TURBT is recommended as part of TMT, its necessity and benefits remain debated due to risks such as bladder perforation and delayed systemic treatment.[26,27]

Current guidelines (American Urological Association, European Association of Urology, and National Comprehensive Cancer Network) recommend maximal TURBT in TMT to achieve local tumor control and enhance treatment efficacy.[1] Complete resection of all visible tumors is associated with higher CR rates, improved bladder-intact DSS, and superior OS. Key studies, including those by Mak *et al*.,[22] Efstathiou *et al*.,[9] Rodel *et al*.,[8] and Pak *et al*.,[28] consistently highlight that complete TURBT before therapies such as NAC and TMT significantly improves prognosis compared to incomplete resection. On the other hand, Zamboni *et al*.[29] found that despite complete TURBT before RC, 53% of patients still had muscle-invasive disease at the time of RC, and no clear correlation between complete resection and oncologic outcomes was established.

A thorough cystoscopic evaluation, including systematic rebiopsy, should be performed either at the completion of TMT or shortly after the induction phase. This approach ensures that patients who do not respond to the treatment are identified early. Early detection of nonresponse is crucial as it allows clinicians to promptly transition these patients to salvage RC before the cancer progresses further. Timely intervention can improve patient outcomes by preventing delay in the treatment of residual or recurrent disease, thus optimizing the chances for better survival and quality of life.[7,30]

However, several studies have explored the role of re-TURBT in bladder preservation for MIBC and showed that re-TURBT did not significantly influence pathological responses, with one study reporting a 32% rate of false downstaging following NAC.[31] In addition, re-TURBT before NAC did not show an association with improved survival outcomes. While the absence of disease on re-TURBT specimens was linked to better prognosis, complete resection did not correlate with achieving pT0 disease at cystectomy.[32] Notably, a study of 153 patients found no significant survival difference between those with complete or incomplete TURBT, although incomplete resection was associated with a higher hazard of death.[33] These findings suggest that while re-TURBT may help in disease staging, it is not essential for achieving complete resection or improved survival outcomes in MIBC, highlighting the challenges of achieving pT0 even with advanced techniques, such as blue-light TURBT.

2.3. Patient selection for TMT

Patient selection remains crucial for optimal outcomes. The criteria for selecting suitable patients for TMT primarily focus on ensuring a high likelihood of response and the ability to tolerate the therapy safely. In addition, factors associated with higher rates of distant metastases are critical indicators for predicting OS following TMT.[34] Ideal candidates for TMT meet the following criteria: they have a solitary cT2 tumor without extensive carcinoma *in situ*, a tumor size less than 5 cm, and a macroscopically complete TURBT. In addition, they should have no evidence of hydronephrosis, no history of prior pelvic radiotherapy, and the ability to comply with routine surveillance, including regular cystoscopy and imaging.[7,9,35-37] Notably, a study compared the effectiveness of TMT and RC by matching MIBC patients based on their calculated other-cause mortality risk. After matching, RC was associated with significantly improved CSM in cT2 MIBC patients. However, no difference in CSM was observed between TMT and RC for cT3–4 MIBC patients, suggesting that RC offers an oncologic advantage for cT2 MIBC, but both treatments have similar outcomes for cT3–4 MIBC.[38]

Patients with poor baseline bladder function are generally not considered suitable for TMT, as bladder function is

unlikely to improve post-treatment. A subset of patients who undergo bladder preservation with TMT may develop symptoms such as urgency and control problems.[39] As such, baseline dysfunction in these areas should be taken into account when evaluating a patient's eligibility for TMT. Furthermore, long-term surveillance is crucial after TMT to allow for timely intervention, such as salvage therapy, if necessary. Therefore, patients who cannot adhere to regular follow-ups or cystoscopic evaluations are typically not deemed appropriate for this approach.[40]

Careful patient selection is also necessary for those with involvement of the trigone or bladder neck, as these features are associated with higher rates of nodal involvement and worse survival outcomes.[41] Limited and conflicting data exist regarding the effectiveness of TMT for patients with variant histologies, particularly pure non-urothelial variants.[42] Further research is required to determine whether these patients are better managed with RC or TMT.

2.4. Biomarkers of TMT response

The development and validation of predictive biomarkers are crucial for personalizing treatment decisions and enhancing patient outcomes.[43] Discoveries related to genomic alterations in bladder cancer have identified several potentially targetable mutations, which could significantly influence therapeutic decisions.[44] For example, mutations in DNA repair genes, including *ERCC2*, *FANCC*, *ATM*, and *RB1*, have been associated with responses to neoadjuvant platinum-based chemotherapy, potentially guiding the use of targeted therapies based on specific mutation profiles.[45-48] In addition, the rise of pan-cancer clinical trials, often referred to as basket or umbrella trials, is allowing patients to be enrolled based on molecular and genetic predictors, offering a more individualized approach to treatment. These trials are expected to enhance our understanding of personalized medicine's role in bladder cancer and other cancers.

The article by Miyamoto *et al*.[49] reviews the potential role of molecular biomarkers, highlighting the potential of molecular alterations and genomic signatures as prognostic and predictive biomarkers. These biomarkers, if validated in future prospective trials, could help identify patients more likely to benefit from bladder preservation therapy. Moreover, they could guide the integration of other treatment modalities, such as immunotherapy, to enhance the efficacy of radiotherapy, offering a more personalized approach to MIBC management.

Efstathiou *et al*.[50] investigated the prognostic significance of immune and stromal signatures in MIBC treated with TMT. The researchers performed transcriptome-wide gene expression profiling of primary tumors from 136 MIBC patients treated with TMT and compared their findings with a cohort of 223 MIBC patients who received NAC followed by RC. The analysis identified four distinct molecular subtypes in the TMT group: luminal, luminal-infiltrated, basal, and claudin-low. Key findings included the association of T-cell activation and interferon gamma signaling with improved DSS in the TMT cohort, but not in the NAC and RC cohorts. In contrast, a stromal signature was linked to worse DSS in the NAC and RC cohorts, though it did not affect the TMT cohort. These results suggest that higher immune infiltration may predict better outcomes in patients undergoing TMT, while higher stromal infiltration could indicate poorer outcomes after NAC and RC.

Mutations in *ATM*, *RB1*, *FANCC*, and *ERCC2* have been identified as predictive biomarkers for achieving cancer-free surgical specimens (pT0) following neoadjuvant cisplatin-based chemotherapy in bladder cancer.[46,51,52] For example, Kamran *et al*.[53] investigated genomic and transcriptomic markers of response to organ-sparing chemoradiation therapy. They analyzed tumor samples from 76 patients using whole-exome sequencing and transcriptomic profiling to correlate molecular features with long-term outcomes, including modified bladder-intact event-free survival (mBI-EFS). Their findings revealed that alterations in DNA damage response genes were associated with improved outcomes, with somatic *ERCC2* mutations standing out as a significant predictor of favorable long-term response. Patients with *ERCC2* mutations had significantly better mBI-EFS and bladder-intact survival, and *ERCC2* mutant cell lines exhibited greater sensitivity to cisplatin and radiation. A multicenter trial (S1314) validated this finding using the Caris 592 Gene Panel, analyzing 105 pre-NAC tumor specimens from patients treated with either gemcitabine and cisplatin or dose-dense methotrexate, vinblastine, adriamycin, and cisplatin. Tumors harboring any of these mutations demonstrated significantly higher odds of achieving pT0, with a high negative predictive value (86%) but moderate positive predictive value (48%).[54] These results support the integration of genetic profiling with clinical assessment to optimize patient selection for bladder preservation strategies following NAC.

Based on these findings, Geynisman *et al*.[55] hypothesized that combining biomarker selection with clinical staging could prospectively identify MIBC patients who might avoid cystectomy or chemoradiation while still preserving oncologic outcomes. Pre-NAC TURBT specimens were sequenced (Caris) for mutations in *ATM*, *ERCC2*, *FANCC*, or *RB1*. Patients with one or more mutations and no clinical evidence of disease, as confirmed by restaging TUR, urine cytology, and imaging after NAC, were enrolled in predefined active surveillance (AS). The remaining patients received bladder-directed therapy. With a median follow-up of 41 months, the

RETAIN trial showed that 66% of patients (47 out of 71) were metastasis-free, with a 2-year metastasis-free survival rate of 72% in the intent-to-treat population, which did not meet the predefined cutoff for non-inferiority. *Post hoc* analysis revealed a 2-year metastasis-free survival rate of 76.9% in the AS group, compared to 70.5% in the other patients, but this difference was not statistically significant. The 2-year OS was 84.3% in the intent-to-treat group and 88.5% in the AS group, with no difference between the AS and non-AS groups. Among AS patients, 69% experienced some recurrence of urothelial carcinoma, with 46% remaining metastasis-free and preserving their bladder. However, 38% of AS patients developed metastatic disease, most of whom had a local recurrence before metastasis, suggesting that early cystectomy could have prevented metastasis. Despite 50% of AS patients avoiding cystectomy without metastatic disease, the study did not meet the non-inferiority threshold, and further refinement of the risk-adapted approach is needed.

Magliocco *et al*.[56] explored the potential of meiotic recombination 11 (MRE11), a DNA repair protein, as a prognostic biomarker for MIBC patients undergoing TMT. The research, which pooled data from six prospective clinical trials, found that higher MRE11 expression, measured through the nuclear-to-cytoplasmic signal ratio, was associated with significantly lower disease-specific mortality. Specifically, patients with an MRE11 ratio above 1.49 had a 50% lower risk of bladder cancer-related death compared to those with lower expression. This suggests that MRE11 could serve as a valuable biomarker to identify MIBC patients at risk of poor outcomes, who might benefit from more intensive therapy.

2.5. Follow-up monitoring of TMT treatment

Patients undergoing bladder-sparing therapy require diligent and individualized follow-up. Approximately 82% of tumor recurrences following TMT occur within the first 5 years post-treatment, with nearly 30% of these representing predominantly local failures. The median time to recurrence is approximately 2 years.[57] As such, surveillance strategies should be carefully tailored to the specific therapeutic regimen and patient risk profile, both during and after treatment. These typically include routine cystoscopic evaluations, urine cytology, and imaging modalities, such as ultrasound, computed tomography, or magnetic resonance imaging. In patients presenting with bone pain or elevated serum alkaline phosphatase levels—potential indicators of bone metastases—bone scintigraphy may be warranted. Follow-up protocols should be personalized based on clinical factors and patient history. In addition, timely reassessment is crucial in patients with suspicious symptoms suggestive of recurrence to facilitate early intervention. Management of treatment-related adverse effects is generally supportive and symptom-directed; in cases of significant toxicity, dose adjustment or treatment discontinuation may be required.

3. Immunotherapy combinations

Three primary traditional bladder-sparing treatment approaches incorporate immunotherapy: immunotherapy combined with CRT, immunotherapy combined with radiotherapy, and immunotherapy combined with chemotherapy.[58,59] Several studies have assessed the efficacy of combining immunotherapy with conventional treatments in bladder-sparing strategies, yielding synergistic effects and promising outcomes.

3.1. Nivolumab

Previous studies have shown that combination therapy with nivolumab and gemcitabine–cisplatin leads to significantly better outcomes in patients with previously untreated advanced urothelial carcinoma compared to gemcitabine–cisplatin alone.[60,61]

A Phase II study explored bladder-sparing treatment for MIBC using gemcitabine, cisplatin, and nivolumab.[62] Patients achieving a clinical CR (cCR) could avoid cystectomy. Of 76 patients, 33 (43%) achieved a cCR, and 32 of them chose not to undergo immediate cystectomy. The positive predictive value of cCR for 2-year metastasis-free survival or <ypT1N0 at cystectomy was 0.97, meeting the study's primary objectives. Common side effects included fatigue, anemia, neutropenia, and nausea. Furthermore, somatic alterations in genes such as *ATM*, *RB1*, *FANCC*, and *ERCC2* did not improve the predictive value of cCR. Immune contexture analyses indicated associations with clinical outcomes. The findings suggest that cCR after this regimen may allow bladder preservation.

In a Phase Ib study, researchers assessed the safety and efficacy of CRT combined with nivolumab and ipilimumab for bladder preservation.[63] Both the nivolumab monotherapy and nivolumab and ipilimumab combination groups demonstrated acceptable levels of toxicity and efficacy.

3.2. Pembrolizumab

Li *et al*.[64] compared the results obtained from the use of pembrolizumab and RC with cisplatin-eligible and cisplatin-ineligible treatments, using a propensity score adjustment based on IPTW. The study found that immunotherapy led to higher response and survival rates, suggesting the potential to establish new neoadjuvant therapeutic standards.

A single-arm Phase II trial assessed the feasibility and safety of combining pembrolizumab with CRT for MIBC.[65]

Twenty-eight patients with cT2–T4aN0M0 MIBC were treated with a regimen of whole bladder radiation, cisplatin, and pembrolizumab. The primary endpoint of feasibility was met, with acceptable toxicity and a high CR rate of 88% at 24 weeks post-CRT. Two-year progression-free survival (PFS) rates were 87% for locoregional PFS and 78% for distant metastasis-free survival, with a median OS of 39 months. The combination of pembrolizumab and CRT showed manageable toxicity and promising early efficacy in treating MIBC.

A retrospective analysis was conducted on 53 MIBC (cT2–T3N0M0) patients initially planned for neoadjuvant pembrolizumab or chemotherapy after maximal TURBT, but later declined RC and radiotherapy.[66] The study found that 43.4% of patients achieved clinical complete remission after neoadjuvant therapy, with a slightly higher remission rate in the pembrolizumab group compared to those in the chemotherapy group (52.1% vs. 36.7%, p=0.26). After a median follow-up of 37.6 months, patients in the pembrolizumab group had improved PFS (median not reached vs. 20.2 months, p=0.078) and OS (median not reached vs. 26.8 months, p=0.027) compared to those in the chemotherapy group. Moreover, patients who achieved clinical complete remission had significantly prolonged PFS (median not reached vs. 10.2 months, p<0.001) and OS (median not reached vs. 24.4 months, p=0.004) compared to those who did not achieve a clinical complete remission. Multivariate analysis confirmed that clinical complete remission after neoadjuvant therapy was independently associated with better PFS and OS. These findings indicate that bladder preservation is a feasible treatment option for selected MIBC patients who opt out of definitive local therapy, particularly for those achieving clinical complete remission post-neoadjuvant therapy. Pembrolizumab offers a promising alternative for patients who are not candidates for chemotherapy. At present, several comparative randomized Phase II trials evaluating the effect of pembrolizumab in combination with CRT are still ongoing.[67]

3.3. Durvalumab

At present, two studies are investigating durvalumab and CRT, enrolling patients with T2–T4M0 MIBC. A Phase II trial evaluated the benefit of adding an immunotherapy drug durvalumab to standard chemotherapy and radiation therapy for treating bladder cancer with regional lymph node involvement.[68] Patients with limited regional lymph node involvement may benefit from an attempt at bladder preservation, along with the use of immunotherapy and systemic chemotherapy. The other study is looking at whether durvalumab can be safely administered as adjuvant therapy after TMT.[69]

3.4. Atezolizumab

A prospective Phase I study evaluated the safety of concurrent atezolizumab, radiation therapy, and gemcitabine in patients with localized MIBC.[70] Eight patients were enrolled, and while the regimen initially used atezolizumab at 1200 mg, three patients developed grade 3 side effects, including two cases of dose-limiting toxicity. As a result, the atezolizumab dose was reduced to 840 mg for the next cohort; yet the study was ultimately terminated due to persistent gastrointestinal toxicity, which was the primary adverse event. The study concluded that the combination of atezolizumab with hypofractionated radiation and gemcitabine resulted in unacceptable gastrointestinal toxicity, warranting caution when considering its use in TMT for MIBC.

Another randomized Phase III trial that evaluated the safety and activity of adding atezolizumab to TMT was inconsistent.[71] A total of 213 patients were included, with 100 in the TMT alone (control) arm and 113 in the TMT and atezolizumab arm. The trial found that hematological toxicities were more common in the atezolizumab arm, but these were generally non-immune related and did not require discontinuation of atezolizumab. Immune-related adverse events, such as pancreatitis, rash, and acute kidney injury, were observed in the atezolizumab arm, but no significant safety concerns were identified. The study demonstrated that adding atezolizumab to TMT was feasible, with no major safety issues, and it is expected to finish accrual in the next two years.

Despite the toxicity associated with combination therapies, neoadjuvant atezolizumab in MIBC is linked to clinical response, with a pathological CR rate of 31% and a 2-year disease-free survival rate of 68%.[72] Cluster of differentiation 8-positive protein expression and serial ctDNA levels were correlated with outcomes, suggesting their potential role in guiding personalized therapy in the future.

4. Target therapies

A total of 68 evaluable patients were treated with daily radiation and either paclitaxel and trastuzumab or paclitaxel alone, based on HER2/neu status.[73] The 1-year CR rate was 72% for patients receiving paclitaxel and trastuzumab, and 68% for those receiving paclitaxel alone. The addition of trastuzumab did not result in a significantly higher incidence of adverse events, and the toxicity was manageable. Notably, the therapeutic efficacy of the paclitaxel–trastuzumab combination in the typically more challenging HER2/neu-positive subgroup was comparable to that of the paclitaxel alone in patients with milder disease.

Another prospective study assessed the safety and efficacy of concurrent radiotherapy and panitumumab

after chemotherapy and pelvic lymph node dissection for invasive bladder cancer.[74] Thirty-one patients were treated with panitumumab and radiotherapy, with 16% experiencing grade 3–4 toxicity. Complete remission was achieved in 94%, and bladder preservation rates were promising. After a median follow-up of 34 months, three patients underwent salvage cystectomy for recurrence. The safety profile was comparable to cisplatin/radiotherapy, suggesting this approach warrants further study.

5. Safety monitoring for novel therapeutic agents

Bladder-sparing strategies that incorporate immune checkpoint inhibitors have demonstrated an overall acceptable safety profile across multiple studies. The combination of pembrolizumab with TMT has been associated with Grade 3–4 adverse events in 22.2–40.0% of patients,[65] with cisplatin dose reductions required in some cases. Commonly reported adverse events include immune-related complications, such as colitis, polymyositis, and nephritis. In a separate study evaluating the addition of nivolumab to TMT, nivolumab monotherapy did not result in any Grade ≥3 serious adverse events.[63] However, combining nivolumab with ipilimumab led to Grade ≥3 serious adverse events in 30–50% patients, predominantly involving immune-mediated and gastrointestinal toxicities. Notably, the incidence of adverse events appeared lower in patient cohorts receiving immunotherapy in conjunction with radiotherapy alone. In this setting, immune-related adverse events occurred in 29.4% of patients, with diarrhea, thyroid dysfunction, and immune-mediated cystitis being the most frequent presentations.

Similarly, the use of atezolizumab combined with radiotherapy has been linked to serious adverse events in 13.3–32.0% patients. These included infections, cardiotoxicity, gastrointestinal disturbances, and genitourinary toxicities. These findings suggest that immunotherapy combined with radiotherapy may represent a more tolerable bladder-sparing approach for frail or elderly patients who are unsuitable for chemotherapy. Comparatively, hematologic toxicity tends to be more prevalent in regimens incorporating chemotherapy, whereas gastrointestinal and urinary toxicities are more commonly observed in radiotherapy-based protocols. As such, individualized treatment planning should incorporate a thorough risk assessment for potential adverse effects based on the patient's clinical status and comorbidities.

6. Discussion

Patients with non-metastatic MIBC face two main treatments: RC and TMT, both of which offer similar survival outcomes but differing impacts on health-related quality of life.[75] Although RC offers effective local control of the primary tumor, it is associated with considerable perioperative and long-term complications, including the need for urinary diversion, all of which can significantly impair patients' quality of life. While advances such as robot-assisted surgery and orthotopic neobladder reconstruction have helped to partially alleviate these negative effects, overall long-term quality of life after RC remains suboptimal. In contrast, bladder-sparing approaches, such as TMT, have demonstrated more favorable quality-of-life outcomes. The BC2001 trial reported that although patients with MIBC experienced a temporary decline in the quality of life during CRT, most returned to baseline levels within 6 months post-treatment.[76] Moreover, comparative studies indicate that patients who undergo RC are more likely to suffer a progressive deterioration in psychological, emotional, and social well-being. Notably, even when compared to robot-assisted RC with orthotopic neobladder reconstruction, TMT continues to offer superior quality-of-life outcomes.[77] A qualitative study of 16 MIBC survivors identified key priorities: curing the disease, preserving health-related quality of life, having confidence in the treatment, and considering personal factors such as age and health. In addition, patients highlighted the need for accurate, personalized information and trust in clinicians. Patient decision aids were seen as helpful in supporting shared decision-making, but should complement clinician interactions. In general, RC is preferred for its perceived curative potential, while TMT appeals to those favoring bladder preservation. These findings emphasize the importance of tailored counseling to align treatment with patient preferences.[78]

RC is associated with a significantly higher short-term hospital readmission rate compared to TMT, largely due to the complexity and invasiveness of the surgical procedure. Early post-operative complications—such as infections, ileus, thromboembolic events, and complications related to urinary diversion—are common causes of readmission within the first 30–90 days following surgery. In contrast, although TMT is generally associated with lower short-term readmission rates, certain factors contribute to an increased risk of long-term hospitalization in this group. These include radiotherapy-induced complications, severe urinary tract infections, and tumor recurrence, all of which may necessitate extended or repeated inpatient care.

The cost of bladder-sparing treatment varies widely across countries, influenced by differences in healthcare systems, reimbursement structures, and drug pricing policies. In general, the short-term costs associated with RC are significantly higher than those of TMT, primarily due to the expenses of surgery, hospitalization, and perioperative care. However, the long-term costs of TMT—driven by extended surveillance, supportive care, and potential retreatment—may result in a higher cumulative financial burden over time.

Magee *et al*.[79] reported that the median total cost of RC was $30,577, compared to $18,979 for TMT, demonstrating a significantly higher cost for RC ($p<0.001$). Nevertheless, TMT was associated with higher annual follow-up and care-related costs, although this difference did not reach statistical significance ($p=0.09$). In another study, the overall median cost of TMT exceeded that of RC, mainly due to greater outpatient expenditures, while RC incurred higher inpatient costs.[80]

Furthermore, the incorporation of novel immunotherapies into bladder-sparing regimens may increase financial pressures. A cost-effectiveness analysis by Khaki *et al*.[81] compared neoadjuvant pembrolizumab to cisplatin-based chemotherapy in MIBC patients. They found that pembrolizumab was significantly more expensive, whereas atezolizumab represented a relatively lower-cost immunotherapy option. Given these findings, clinicians must evaluate cost-effectiveness in the context of national healthcare policies, tumor characteristics, and individual patient circumstances. A nuanced approach is essential to balance clinical benefit with economic sustainability in selecting the most appropriate treatment strategy.

As research and clinical evidence continue to advance, the role of bladder preservation in the management of MIBC is likely to grow, leading to more personalized treatment strategies. This evolution will provide patients with an increasing array of options that not only aim for effective cancer control but also prioritize their quality of life, taking into account their preferences and the potential impact of treatments on daily living. With improved understanding of patient-specific factors, such as tumor biology, genetic markers, and immune responses, treatment plans can be better tailored, offering more patients the possibility of bladder-sparing approaches while maintaining strong clinical outcomes. As a result, bladder preservation may become a more widely accessible option for MIBC patients, reducing the need for RC and enabling more individualized care pathways.

7. Conclusion

The TMT approach represents a well-tolerated, potentially curative alternative to RC for selected patients with localized MIBC. Its success hinges on careful patient selection and a coordinated, multidisciplinary approach to maximize oncologic control while preserving bladder function. Advances in predictive biomarkers hold promise for improving patient stratification, enabling more personalized treatment strategies and potentially better long-term outcomes. Nonetheless, several critical challenges remain unresolved—namely, the optimal combination and sequencing of immunotherapeutic agents and chemotherapy, the appropriate duration of immunotherapy, and the most effective drug regimens for bladder preservation. Addressing these uncertainties will require well-designed, large-scale prospective clinical trials to establish standardized, and evidence-based treatment protocols.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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