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Review

Alternatives to radical cystectomy: a bladder-sparing approach in appropriately selected patients

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Radical cystectomy (RC) has historically been the standard treatment for muscle-invasive bladder cancer (MIBC); nonetheless, it is associated with a high morbidity and mortality, with complication rates often exceeding 60%, a relatively high 90-day mortality rate, as well as a significant impact on quality of life (QoL). This substantial burden has generated increasing interest in effective bladder-sparing alternatives. Among these approaches to bladder preservation, trimodal therapy (TMT), comprising maximal transurethral resection of bladder tumour (TURBT) followed by concurrent chemotherapy and radiotherapy (chemoRT) using radiosensitising agents, has become a guideline accepted alternative to RC in appropriately selected patients with MIBC. Additional bladder-sparing strategies, such as TURBT monotherapy or TURBT followed by systemic therapy and surveillance in those patients achieving a complete clinical response, may be alternatives in select settings, although data are limited. Appropriate surveillance after a bladder-sparing approach is paramount to offer timely salvage RC when needed, occurring in approximately 11–16% of contemporary TMT cohorts. QoL outcomes consistently favour TMT over RC, particularly in preserving urinary and sexual function. Severe treatment-related toxicity with TMT is uncommon, with Grade ≥3 adverse events occurring in <10% of cases. In conclusion, bladder-sparing approaches offer a suitable alternative to RC in appropriately selected patients with MIBC, incorporating multidisciplinary care and a commitment to lifelong surveillance.

Keywords

bladder cancer, bladder chemoradiation, bladder preservation, trimodal therapy, transurethral resection of bladder tumour (TURBT)

Introduction

Bladder cancer ranks as the sixth most common cancer in the United States, representing ~4.2% of all newly diagnosed cancer cases. In 2025, an estimated 84 870 new cases of bladder cancer were expected to be diagnosed in the United States, with ~17 420 deaths projected from the disease [1,2]. The median age at diagnosis is 73 years, and 90% of the diagnoses are made in people aged >55 years, affecting predominantly male individuals [3]. About 25% of bladder cancer cases present as muscle-invasive bladder cancer (MIBC), which is associated with poor prognosis and a 5-year mortality rate of about 50–70%. Non-metastatic MIBC is defined as cancer that has invaded the muscle layer of the bladder wall but has not spread to distant organs. The stage is denoted as T2 or higher in the TNM system and is an aggressive disease associated with a higher risk of metastasis as compared to non-MIBC (NMIBC) [4]. The most important prognostic factor in this clinical scenario is the depth of invasion.

The historical 'gold standard' treatment of localised MIBC has been radical cystectomy (RC) with pelvic lymph node dissection following neoadjuvant chemotherapy (NAC). Although this treatment offers a potential cure, it is associated with the risk of significant morbidities like perioperative complications and detriment to the quality of life (QoL). Moreover, the population commonly affected by bladder cancer is elderly and presents with multiple comorbidities. These demographic characteristics represent a challenge in the management of these patients as they may have an elevated risk or might not be suitable for aggressive surgical interventions like a RC. Alternatives to RC with bladder preservation pose an attractive option to achieve an equivalent option for cure in select patients. Trimodal therapy (TMT) with maximal transurethral resection of bladder tumour (TURBT) followed by concomitant chemotherapy and radiotherapy (chemoRT) is now an accepted and guideline-based option for bladder preservation in appropriately selected patients [5]. Although outcomes are under active debate, emerging evidence suggests that bladder preservation may also be achievable in select patients who, after maximal TURBT, achieve a complete clinical response (cCR) to NAC and may effectively be cured with dual-modality therapy. Whatever the approach, bladder

preservation strategies aim to balance goals between adequate oncological control, minimising toxicity, and preservation of QoL.

Rationale for Bladder-Sparing Therapy

A multi-modal organ-sparing approach has been increasingly utilised for organ conservation in various cancers, including laryngeal, anal, breast, oesophageal, and limb sarcomas. However, RC continues to be the most commonly offered treatment option for MIBC. While RC remains effective and may be the best curative option in some cases, it is a major surgical intervention with significant physiological and life-altering consequences. In addition, at least across the United States, many patients, especially those in their seventh, eighth, and ninth decades of life, have been undertreated for MIBC, presenting a treatment void which TMT may fill [6].

Surgical Morbidity

In all of urological oncology surgeries, RC carries some of the highest associated rates of morbidity and mortality, where ~64% of patients experience complications within 90 days, 26% require readmission, and the 90-day mortality rate is ~2.7% [7]. Efforts to mitigate these outcomes through Enhanced Recovery After Surgery (ERAS) pathways and minimally invasive approaches, such as robot-assisted RC (RARC), have not yet yielded substantial improvements in complication and readmission rates [8]. Data from relatively recent randomised clinical trials demonstrate that there is no difference between open and robotic approaches in terms of complication rates or survival [9]. The more recently reported iROC trial (ClinicalTrials.gov identifier: NCT03049410) demonstrated no difference in overall and high-grade complications between open RC (ORC) and RARC with complete intracorporeal urinary diversion; however, there were lower rates of thromboembolic and wound complications with the robot-assisted approach [10]. Furthermore, this trial found that the open approach had a small, but significant increase in the number of days alive and outside the hospital over 90 days, although the clinical significance of this is unclear. For example, the RAZOR trial (NCT01157676), a multicentre phase 3 randomised study, showed no significant difference in overall or major complication rates between RARC and ORC up to 90 days postoperatively. Similarly, readmission rates at both 90 days (24.1% vs 23.1%) and 1 year (29.5% vs 28.5%) were comparable between RARC and ORC. The 2-year progression-free survival (PFS) rates remained nearly identical (72.3% for RARC vs 71.6% for ORC). Notably, the study identified patient frailty, as measured by the simplified Frailty Index (sFI ≥3), as a strong predictor of major complications and readmissions, rather than the surgical approach itself. This emphasises the need for careful patient selection and preoperative optimisation, regardless of the surgical technique [11].

Renal Function

Long-term renal function is another critical consideration. Decreased renal function over time is noted in most patients during long-term follow-up after RC. Approximately 72% of patients experience a reduction in estimated GFR of >10 mL/min/1.73 m^2 by 10 years after surgery, with 56% developing new-onset Stage 3 chronic kidney disease and 3.5% progressing to haemodialysis [12]. Studies of renal function in patients undergoing TMT are underway and will shed more light onto the comparable risks.

Patient's QoL

Trimodal therapy allows patients to maintain a higher level of overall well-being and functional status without compromising oncological outcomes. In a multicentre study, Mak et al. [13] analysed and compared the QoL of patients undergoing TMT and RC. The study found that TMT was associated with better informed decision-making, less life interference from cancer and its treatment, fewer concerns about appearance, better general QoL, higher physical, social, emotional, and cognitive functioning, as well as improved sexual function compared to RC. Additionally, a systematic review and meta-analyses by Ditonno et al. [14] demonstrated significantly higher QoL scores for TMT compared to RC, despite similar oncological outcomes.

Guidelines

Major organisations and guidelines, including AUA, European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN), recognise TMT as a valid alternative for appropriately selected patients with localised MIBC, emphasising the importance of shared decision-making.

The AUA recommends a preserving approach for patients with MIBC who have elected trimodality with organ preservation with maximal TURBT followed by chemotherapy combined with external beam RT (EBRT). The guidelines also mention the ideal candidate as those in whom complete resection is feasible and who have no hydronephrosis and no carcinoma *in situ* (CIS). Furthermore, the guidelines recommend regular surveillance for patients who elect bladder-preserving therapy, including CT scans, cystoscopy, and urine cytology [15].

The EAU recommends offering bladder preservation to patients with MIBC and small solitary tumours, no extensive or multifocal CIS, no tumour-related hydronephrosis, and good pretreatment bladder function. And also consider in patients with contraindications for surgery. These guidelines

also highlight the importance of multidisciplinary team care and long-term bladder monitoring [16].

The NCCN guidelines recognise bladder preservation through TURBT and chemoRT as a Category 1 recommendation for clinical stage T2 tumours and selected T3 and T4 cases [17]. It should be noted that current guidelines do not discuss surveillance alone in patients who have a cCR after NAC.

Current Options for Avoiding RC

Transurethral Resection of Bladder Tumour Alone as Monotherapy

Transurethral resection of bladder tumour as a sole therapy for MIBC is a feasible but uncommon bladder-sparing approach for MIBC. It should be considered only for highly selected patients who are unfit for RC or who strongly desire to avoid it. A key aspect of successful TURBT-only therapy is achieving a maximally complete and safe resection of all visible tumour, including the detrusor muscle, as this is considered the most important factor for oncological control and success of bladder-preserving therapies [18]. The Herr et al. [19] landmark series at Memorial Sloan Kettering Cancer Center demonstrated that in carefully selected patients with T2 MIBC who had no residual tumour on re-resection (pT0 status), long-term outcomes with TUR alone could approach those of immediate RC. In the Herr et al. [19] 10-year study, 99 patients managed with definitive TUR (after a negative restaging TUR) had a 76% disease-specific survival (DSS) rate, statistically similar to the 71% in 52 patients who underwent upfront RC ($P = 0.3$). Notably, patients who truly had no tumour on repeat TUR (T0) fared far better (82% 10-year survival) than those with residual high-grade T1 on re-resection (57% survival). This underlines that TUR-only therapy can be a successful strategy, especially when a vigorous repeat TUR confirms no muscle-invasive disease remains. Similarly, Solsona et al. [20] prospectively followed 133 patients treated with radical TURBT monotherapy for cT2 bladder cancer and observed favourable long-term results: 15-year DSS 76.7%, and PFS 57.8%, supporting the potential for durable cancer control in selected patients.

Transurethral Resection of Bladder Tumour + Systemic Therapy (cCR to Neoadjuvant Therapy)

Another bladder-preservation strategy involves using systemic therapy (chemotherapy and/or immunotherapy) to eradicate any remaining disease after TURBT to address the primary tumour and reserving radical surgery only for those with residual disease. In practice, this often means giving NAC for MIBC, and if a cCR is achieved – i.e., no tumour visible on post-chemotherapy imaging and cystoscopy with biopsy – the patient forgoes immediate RC and is managed with surveillance. This approach builds on the proven benefits of NAC in improving survival in MIBC and the observation that some patients achieve a pathological complete response (pT0) at RC after NAC. For example, in the PURE-01 trial (NCT02736266), neoadjuvant pembrolizumab administered before RC in MIBC resulted in a pathological complete response (pT0) rate of 37% of patients [21]. A recent study examined conservative management in patients with MIBC achieving cCR after NAC. Among 148 patients followed for a median of 55 months, the 5-year DSS rate was 90%, the overall survival (OS) rate was 86%, and the RC-free survival rate was 76%. Although 48% experienced bladder recurrence, only 11% developed muscle-invasive recurrence, and salvage RC was effective in most cases. These results support conservative management with close surveillance as a viable option for carefully selected patients after chemotherapy, emphasising the importance of prompt intervention upon relapse [22]. A recent systematic review confirmed that bladder-sparing strategies after cCR can be effective in selected patients with MIBC. Across 16 surveillance studies, bladder recurrence averaged 43%, mostly non-muscle-invasive, with a mean bladder preservation rate of 73% and a 5-year OS of 64–89%. RT after cCR showed lower recurrence rates (15%) but similar bladder preservation (74%) and 4-year OS of 79% [23]. In summary, TURBT plus systemic therapy is emerging as a promising bladder-preserving strategy in MIBC. In those who achieve a confirmed complete response, long-term survival with an intact bladder is frequently possible, approaching the outcomes of primary RC in contemporary series. The keys to success are strict patient selection, meticulous response evaluation (repeat TURBT and imaging to rule out residual disease), and vigilant surveillance. Patients must commit to frequent cystoscopies and scans, and centres must have a low threshold to perform salvage RC at the first sign of invasive recurrence. In addition, as systemic therapy regimens in MIBC intensify, including the use of antibody-drug conjugates and immunotherapy, we must be mindful of the risks and benefits of an approach that involves neoadjuvant systemic therapy for all, with subsequent selection of local bladder management dependent on response. The potential added toxicity of this approach must be weighed against the now standard of care TMT without neoadjuvant systemic therapy in patients who can be properly selected at the time of diagnosis.

Classic TMT

Patient Selection

Patient selection is a critical component for achieving successful outcomes in bladder preservation strategies. The urologist plays a key role in identifying suitable candidates, performing meticulous TURBTs, and ensuring maximal resection [24]. To determine the ideal candidate for bladder preservation, several patient-related and tumour factors are

Table 1 Patient and tumour selection criteria for bladder preservation TMT.

	Criteria
Patient factors	Favourable baseline bladder function
	Good performance status (ECOG 0–1)
	Ability to tolerate concurrent radiosensitising chemotherapy
	Patient preference for bladder preservation
Tumour factors	Tumours can be completely resected endoscopically
	Tumours without extensive involvement of the bladder wall
	T2 disease. The extent of the tumour wall, rather than the size, remains the determining factor.
	Absence of CIS
	No hydronephrosis
	No lymph node metastases (N0)

ECOG, Eastern Cooperative Oncology Group.

Table 2 Relative contraindications to bladder preservation TMT.

Criteria
History of prior pelvic radiation or inflammatory bowel disease
Poor baseline bowel/bladder function.
Large tumour burden involving the majority of the bladder wall
The presence of hydronephrosis
Extensive CIS, especially involving the bladder, neck, or prostatic urethra
Upper tract involvement of tumour
High-grade tumour in bladder diverticulum.

considered. Table 1 presents the clinical selection criteria based on patient and tumour characteristics that favour the use of TMT for bladder preservation. Table 2 outlines the relative contraindications that may exclude patients from consideration of this bladder-sparing approach.

Cross-sectional imaging studies, including contrast enhanced CT urography, MRI, and select use of positron emission tomography, are instrumental in assessing tumour extent and staging to identify the best candidates. Findings such as upper tract involvement, circumferential bladder wall involvement, or large tumour burdens generally indicate that the patient is not a suitable candidate for bladder preservation [25].

Components of TMT

Maximal TURBT

Maximal TURBT resection is a critical component to achieving successful outcomes. This is the first step in the conservative management of MIBC and serves a dual purpose, both diagnostic and therapeutic [26]. The primary objective of this surgical procedure in the context of TMT is to completely remove all visible tumour and not merely provide evidence of muscle invasion, as shown in Fig. 1.

Enhanced cystoscopic tools, such as photodynamic imaging or blue-light cystoscopy, can aid in identifying tumour boundaries, although their use is not mandatory [27]. A complete and aggressive TURBT involves deep resection into the muscular wall to ensure all visible tumour is removed. If necessary, this may include resection at the bladder neck, prostatic urethra, or ureteric orifices. Based on the authors' experience, in cases where the ureteric orifice is resected, ureteric stent placement is recommended to remain in place throughout the course of chemoRT and minimise the risk of ureterovesical junction stenosis. Prior to starting chemoRT, repeat TURBT is often indicated for MIBC, particularly if the initial resection was performed in a low-volume centre. Evidence shows that residual tumours can be found in up to 76% of the re-TURBTs at 2–6 weeks after the first one [28]. Repeating the TURBT ensures complete removal of residual tumour, allows for reassessment through systematic biopsy of the resection site, as well as selected mucosal biopsies of the bladder to rule out diffuse occult CIS [17]. Although there may be some room for recent debate [29], it largely has been accepted that a visibly complete TURBT is a predictor of complete response to induction chemoRT [30].

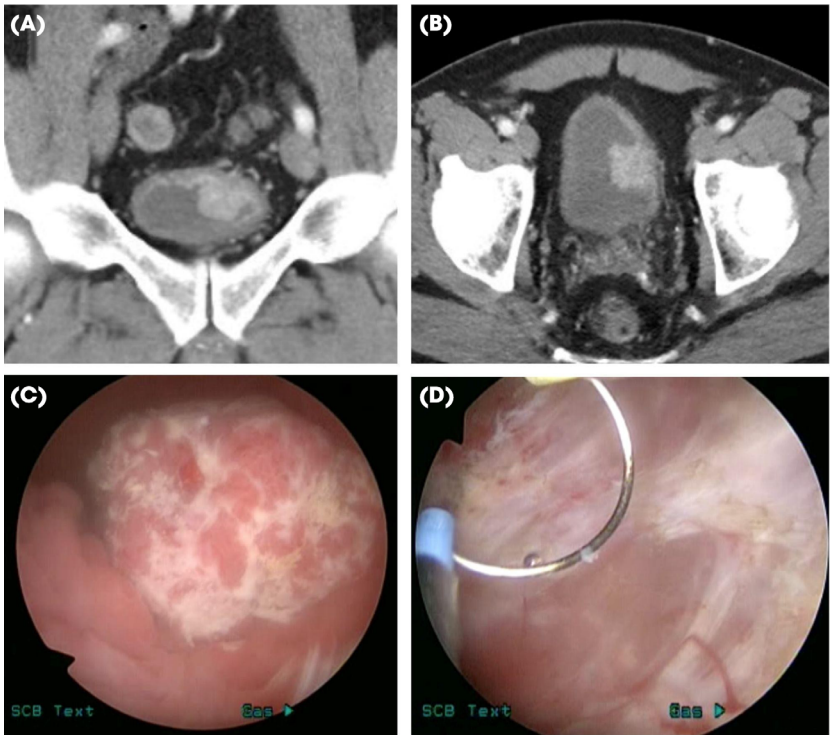
Radiation for TMT

The paradigm for chemoRT begins with a maximal TURBT, followed by definitive RT. Current practice favours single-course RT to a total dose of 55–65 Gy, usually once daily, 5 days a week. Hypofractionated schedules deliver a higher dose per course over a shorter period of time. A hypofractionated schedule of 55Gy in 20 fractions is one standard of care for bladder preservation, although other approaches exist [31]. EBRT is the most common type of RT used in TMT, and although a recent study suggested that whole pelvis, including pelvic lymph nodes may improve outcomes, [32] some debate of this issue continues. Intensity-modulated RT is an advanced form of EBRT that utilises intensity-modulated fields to deliver precise radiation to the tumour, minimising the surrounding tissues' exposure to radiation. Also, image-guided RT enhances precision and improves target visualisation. This technique has fewer side effects and is more effective. More recently, adaptive delivery [33] and treatment with ultra-hypofractionation (ARCHER study NCT07097142) are being investigated. Post-RT cystoscopic reassessment and biopsy determine treatment response [34]. Radiosensitising chemotherapy, with cisplatin, gemcitabine, or a combination of mitomycin C (MMC) and 5-fluorouracil (5-FU), is administered concurrently with RT to enhance the therapeutic effect [35–37].

Chemotherapy

The addition of chemotherapy to RT enhances therapeutic efficacy and improves locoregional disease-free survival

Fig. 1 Case example of a patient with MIBC successfully treated with TMT. (A, B) Coronal and axial CT images demonstrating a bladder tumour before TURBT. (C) Cystoscopic view of the tumour with surrounding papillary mucosal changes. (D) Deep TURBT into the deepest muscular layers of the bladder wall.



compared with RT alone [38]. It is uncommon for patients to be ineligible for concurrent chemotherapy, as even many elderly or frail patients may be able to tolerate radiosensitising chemotherapy alongside RT.

The use of chemotherapy in TMT can be categorised into three primary approaches:

1. Concurrent Chemotherapy

The choice of radiosensitising chemotherapy agents is informed by institutional experience and clinical data. Common agents include cisplatin, paclitaxel, gemcitabine, and combinations such as cisplatin with 5-FU or MMC/5-FU. A single-institutional study demonstrated the benefits of adding chemotherapy to RT. The complete response rate with RT alone was 57% [39]. The addition of radiosensitising chemotherapy, such as cisplatin, increased complete response rates significantly to 81%, and adding cisplatin + 5-FU enhanced complete response rates by 87% [39].

Some of the key trials supporting concurrent chemoRT include the following:

BC2001 (International Standard Randomised Controlled Trial Number: ISRCTN68324339): a phase III trial comparing chemoRT to RT alone in 360 patients with MIBC. The intervention was: RT with or without concurrent MMC and 5-FU. The median follow-up was 69.9 months, and the primary endpoint was loco-regional disease-free survival, with secondary endpoints including OS and toxicity. The results showed that chemoRT provided an improvement in local-regional disease-free survival compared to RT alone (hazard ratio [HR] 0.82, 95% CI 0.63–1.09) with no significant increase in adverse events [35].

Radiation Therapy Oncology Group (RTOG) 0233 (NCT00055601): a randomised phase II study compared two chemoRT regimens (5-FU + cisplatin vs paclitaxel + cisplatin) in 93 patients with MIBC, with all patients receiving adjuvant chemotherapy. The primary endpoints of this study were treatment completion rates, tolerability, and OS. The results showed that both regimens were well-tolerated, with comparable rate of bladder preservation and disease-free survival with intact bladder. This study demonstrated comparable toxicity and efficacy between the two regimens, highlighting the flexibility in chemoRT approaches for MIBC [40].

Subsequently, an RTOG 0712 phase II trial (NCT00777491) compared the University of Michigan scheme of daily RT with twice weekly gemcitabine (27 mg/m^2) to RTOG's twice-daily radiation with 5-FU and cisplatin. Both approaches achieved comparable metastasis-free survival

(MFS) rates, 78% for 5-FU/cisplatin and 84% for gemcitabine. These results support gemcitabine as a viable alternative for patients with renal impairment or contraindications to cisplatin [41].

2 Adjuvant Chemotherapy

The role of adjuvant chemotherapy in TMT remains unclear due to the lack of Level 1 evidence. A retrospective analysis evaluated data from 475 patients accrued to nine Massachusetts General Hospital (MGH)/RTOG trials, with five trials that included adjuvant cisplatin-based chemotherapy (n = 215) and four trials that did not include any adjuvant chemotherapy (n = 260). These data suggest an association between adjuvant chemotherapy and improved DSS in univariate analyses but no association with OS or DSS in multivariate analyses [42].

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy has been extensively evaluated in surgical series but has shown limited benefit in the context of TMT. For example, RTOG 8903 a randomised phase III study, compared; two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) followed by chemoRT with 39.6-Gy pelvic irradiation with concurrent cisplatin 100 mg/m^2 for two courses 3 weeks apart to chemoRT (same scheme) without neoadjuvant MCV, but found no significant improvement in OS or MFS [43]. In our centre, NAC is typically not used for patients undergoing TMT, except in select cases such as bulky disease, lymphadenopathy, and/or presence of hydronephrosis. Instead, emphasis is placed on concurrent chemoRT to optimise outcomes. However, the utilisation of NAC varies at other centres and remains an area of open debate. As mentioned previously, as neoadjuvant systemic therapy regimens intensify, risk benefit analyses will need to be done to assess if the risk of added toxicity prior to initiating chemoRT will truly improve outcomes.

Oncological Outcomes

The SPARE trial [44], an attempted randomised clinical trial comparing RC to selective bladder preservation failed to accrue, and therefore, consequently no completed randomised clinical trials have directly compared bladder preservation to RC.

Data from experienced institutions, such as MGH, demonstrate that long-term outcomes of bladder preservation are comparable to RC series. For instance, an analysis including 475 patients from 1986 to 2013 showed that complete TURBT was achieved in 70% of cases historically and is significantly higher in contemporary practice (86.1% for the period 2005–2013). Complete response rates to chemoRT were 75% and are now approximately 85–90%, reflecting improvements in patient selection and advances in chemotherapy and RT techniques. Long-term survival outcomes are promising, with 5- and 10-year DSS rates of 66% and 59%, respectively. Notably, and as would be expected, T2 tumours achieve better outcomes than T3/T4 tumours. Contemporary 5-year DSS rates for the period 2005–2013 were 84%, demonstrating advancements in treatment and better patient selection [42].

Some conflicting data from a population-based study that used data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database showed that OS and DSS were better in those patients who underwent RC as compared to those who underwent TMT. Importantly, this analysis demonstrated a greater cost associated with the TMT approach compared to RC. However, in regard to oncological outcomes, when interpreting these data, it is important to note that the median (interquartile range) number of RT fractions was 18 (9–27), and typically >30 are needed for a definitive treatment in a TMT protocol. In addition, patients who were unfit for surgery were not excluded from the analysis, and due to the retrospective nature, these results should be carefully interpreted, as confounding factors, misclassification, and inherent selection bias may be present [45].

In contrast, a comparative study led by Softness et al. [46], which included 2048 patients aged 40–79 years from the National Cancer Database (NCDB) and used propensity-score matching to balance variables between the TMT and RC cohorts, demonstrated no statistically significant differences in OS between the RC and TMT cohorts. Unfortunately, in this NCDB study, DSS could not be assessed. A nationwide study of Veterans Affairs data demonstrated that when traditional TMT per NCCN guidelines was utilised, there was no difference in OS or DSS [47].

In the first propensity-score matched single institutional comparison, Kulkarni et al. [48] reviewed outcomes comparing RC and TMT performed between 2008 and 2013 with a median follow-up of 4.5 years. The findings demonstrated that TMT yielded survival outcomes comparable to those of RC, highlighting the efficacy of bladder preservation in appropriately selected patients. More recently in a multi-institutional propensity-score matched comparative analysis from high-volume centres, Zlotta et al. [49] demonstrated no differences in 5-year MFS, regional failure-free survival, and DSS. In addition, there was no difference when comparing TMT to the subgroup of RC patients who underwent NAC. It is important to note that in the course of this analysis, it was identified that approximately one-third of patients with MIBC, who would be RC candidates, are also appropriate for treatment with TMT. In the absence of a prospective randomised clinical trial, these data present the best comparative analyses to date [48].

Surveillance, Follow-Up, and Recurrences After TMT: NMIBC and MIBC

Surveillance following TMT or chemoRT is critical and highlights the continuing role of the urologist in patient management. The surveillance protocol starts with cystoscopy and biopsy under anaesthesia, which is typically performed 2–3 months following the completion of chemoRT. Surveillance thereafter is similar to protocols for high-risk NMIBC, with cystoscopy and imaging every 3–4 months for the first 2 years, every 6 months until 5 years, and annually thereafter. Cross-sectional imaging for metastatic evaluation, typically using CT continues for 5 years after TMT, and as with high-risk NMIBC continued subsequent long-term upper tract imaging is recommended periodically.

Based on pooled analyses from RTOG studies, as well as individual institutional series, the risk of local subsequent recurrence ranges from 25% to 36% for NMIBC recurrences, while ~14% can progress to MIBC [30,50,51]. Chung et al. [52] evaluated long-term results and factors associated with the risk of relapse in patients treated with TMT for bladder cancer at the Princess Margaret Hospital. In a cohort of 340 patients with a median follow-up of 7.9 years, the researchers found that tumour characteristics associated with recurrence included larger tumour size (>2 cm) and the presence of CIS.

Many cases of NMIBC recurrences can be treated as such with intravesical therapy that can be well tolerated and has reasonable success [50]. Salvage RC is performed in cases of MIBC recurrence or persistent high-risk NMIBC and should be considered in patients who have adverse features such as T1 disease, larger high grade tumours (>3 cm), CIS, lymphovascular invasion, variant histology, multiple recurrences, or poor bladder function. Older data indicate a 5- and 10-year cumulative need for salvage RC of 29% and 31%, respectively; however, more contemporary data suggest that approximately 10–15% of TMT patients will need a salvage RC [42,48]. It is also important to note that DSS rates after salvage RC are comparable to those of primary RC for *de novo* disease, at 64% and 55% at 5 and 10 years, respectively [42]. Furthermore, in patients who undergo TMT, DSS was found to be the same in those who must undergo salvage RC compared to those without any local recurrence [48].

Salvage RC following TMT is associated with a slightly higher complication rate compared to primary RC, although differences are minimal [53]. Pieretti et al. [54] compared salvage RC vs primary RC vs RC after other pelvic RT and found no differences in intraoperative or early complications. Post-TMT salvage RC had slightly higher all late and major late complications compared with primary RC, but there was no difference between the two groups that had RT [54].

Quality of Life

Bladder preservation through TMT is associated with acceptable toxicity and favourable QoL outcomes. The primary rationale for bladder preservation lies in its potential to offer QoL benefits compared to RC. While both approaches have inherent challenges, bladder preservation provides distinct advantages in maintaining urinary and sexual function. Urodynamic studies and QoL analyses of patients with MIBC treated with TMT 20 years ago showed that 78% had compliant bladders with normal capacity and flow parameters, 85% reported no occasional urgency issues, 25% had occasional to moderate bowel control symptoms, and 50% of men maintained normal erectile function following chemoRT [55]. Recent studies support these findings, showing that urinary function is well-preserved in most cases. A German study reported that ~90% of patients expressed satisfaction with their urinary condition post-TMT [56]. A recent meta-analysis demonstrated statistically significant better sexual function outcomes favouring TMT over RC [57]. A systematic review of QoL after TMT that included six studies found that TMT was associated with good general QoL compared to RC, satisfactory urinary function, and satisfactory sexual function. However, the included studies were limited by sample size, variable follow-up, and non-validated instruments [58]. A multi-institutional study analysing 173 patients with MIBC who underwent RC and TMT, and implementing six validated QoL instruments, demonstrated that TMT was associated with markedly better sexual QoL, better informed decision-making, less concerns about appearance, less life interference from cancer or cancer treatment, modestly higher general QoL and bowel function, and similarly urinary scores [13]. Cross-sectional studies comparing TMT and RC outcomes have shown that while urinary function scores are similar, TMT patients report better sexual QoL [59].

Toxicity

Data from large clinical trials demonstrate that severe toxicity (Grade ≥3) following TMT occurs in <10% of cases. Toxicities are generally genitourinary or gastrointestinal; however, advancements in RT delivery have significantly reduced bowel-related complications over time [35. 60]. Radiation cystitis is a potential complication of chemoRT, occurring in 5–10% of patients, although the majority of cases are clinically insignificant, mild to moderate, and often self-limiting [61,62].

Cost (vs RC)

Long-term costs were shown to be significantly higher for TMT than for RC across various studies [14,63,64]. Excess

spending associated with TMT was largely driven by outpatient expenditures. Although initial expenses are higher for RC, TMT is significantly more expensive than RC in the short and long term. However, TMT offered greater effectiveness in terms of cost per quality-adjusted life-year [14]. A Canadian study showed that TMT performed in academic centres was cost-effective compared to RC + NAC, with higher effectiveness at higher costs [65].

Biomarkers and Personalised Therapy

Advances in genomics have introduced the possibility of biomarker-driven management for bladder preservation. Biomarkers may eventually guide treatment selection, predict response to therapies, and inform surveillance strategies. Current research focuses on both tissue-based and liquid biopsy biomarkers. Studies have identified several key biomarkers, including MRE11 and ERCC2, which correlated with improved outcomes following RT-based therapy [66–68], as well as basal and luminal subtypes, with emerging data suggesting that basal subtypes may benefit more from NAC and RT [69–72].

Integration of Immunotherapy With TMT: Rationale for Combining Immunotherapy and ChemoRT

The interplay between the host anti-tumour immune response and RT during TMT is complex and can involve other immune-activating and immune-suppressive effects. For instance, RT can activate the immune system by increasing major histocompatibility complex (MHC) Class I expression, enhancing the presentation of tumour antigens, activating and recruiting the immune cells within the tumour microenvironment, by increasing the release of proinflammatory chemokines such as CXCL16 and interferon gamma, and mediating immunogenic cell death, stimulating dendritic and T cells through damage-associated molecular patterns. In contrast, RT could also suppress the immune response by causing direct lymphocyte toxicity, increasing regulatory T-cell activity, or inducing T-cell exhaustion by upregulating receptors like programmed death 1 (PD-1). For this reason, immune checkpoint inhibitors such as PD-1/programmed death-ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) can mitigate the immunosuppression while preserving the immune activation effects, potentially leading to improved treatment outcomes [73].

Several trials are investigating the role of adding immunotherapy to RT protocols in localised muscle-invasive bladder cancer:

DUART study (NCT02891161): this phase II trial reported high response and disease control rates using concurrent and adjuvant durvalumab with RT in cisplatin-ineligible patients with advanced disease [74].

INTACT trial (SWOG/NRG 1806; NCT03775265): a phase III trial examining chemoRT with or without concurrent and adjuvant atezolizumab in 475 patients with N0 disease. Early safety data show acceptable toxicity profiles, with no immune-related adverse events of Grade ≥3.

KEYNOTE-992 (NCT04241185): a phase III trial evaluating pembrolizumab vs placebo with chemoRT, with cisplatin or 5-FU+ MMC or gemcitabine and RT, both conventional or modern hyperfractionated RT protocols.

Future Directions

Bladder-preservation therapy is increasingly recognised as a viable alternative to RC for appropriately selected patients with MIBC. To further optimise outcomes, ongoing efforts include:

- Prospective validation of biomarkers for personalised treatment selection.
- Refinement of RT protocols, including adaptive delivery and hypofractionated (even ultra-hypofractionated) regimens.
- Integration of neoadjuvant systemic therapy and immunotherapy into TMT and other bladder-sparing approaches, with ongoing trials expected to define its role.
- Multidisciplinary approaches that empower patient autonomy and informed decision-making.

Conclusion

Trimodal therapy can offer comparable survival outcomes to RC while preserving QoL for approximately one-third of patients with MIBC. Advances in RT technology, systemic therapies, and biomarker research continue to enhance its potential. A bladder-sparing approach with dual-modal therapy, involving TURBT and systemic therapy without local RT may be achievable in very select patients; however, more data are needed prior to becoming a standard of care option. No matter the treatment path, it remains clear that a multidisciplinary approach remains essential for shared decision-making, ensuring optimal outcomes and personalised care.

Disclosure of Interests

Dr Jason A. Efstathiou declares consulting fees from Blue Earth Diagnostics, Boston Scientific, AstraZeneca, and Clarity Pharmaceuticals; and participation on advisory boards/DSMBs for Merck, Roivant Pharma, Myovant Sciences, Janssen, Johnson & Johnson, Bayer Healthcare, Progenics Pharmaceuticals, Pfizer, Astellas, Gilead, Lantheus, Angiodynamics, Bioprotect, and MDxHealth. Dr Adam S.

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Abbreviations: cCR, complete clinical response; chemoRT, chemotherapy and radiotherapy; CIS, carcinoma *in situ*; DSS, disease-specific survival; EAU, European Association of Urology; 5-FU, 5-fluorouracil; HR, hazard ratio; MCV, methotrexate, cisplatin, and vinblastine; MFS, metastasis-free survival; MGH, Massachusetts General Hospital; (N)MIBC, (non-)muscle-invasive bladder cancer; MMC, mitomycin C; NAC, neoadjuvant chemotherapy; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; OS, overall survival; QoL, quality of life; (O)(RA)RC, (open) (robot-assisted) radical cystectomy; (EB)RT, (external beam) radiotherapy; RTOG, Radiation Therapy Oncology Group; TMT, trimodal therapy; TURBT, transurethral resection of bladder tumour.

