



Bladder-sparing protocols in the treatment of muscle-invasive bladder cancer

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Abstract: Bladder-sparing protocols (BSP) have been gaining widespread popularity as an attractive alternative to radical cystectomy (RC) for muscle-invasive bladder cancer. Unimodal therapies are inferior to multimodal regimens. The most promising regimen is trimodal therapy (TMT), which is a combination of maximal transurethral resection of bladder tumor (TURBT), radiotherapy, and chemotherapy. In appropriately selected patients (low volume unifocal T2 disease, complete TURBT, no hydronephrosis and no carcinoma-in-situ), comparable oncological outcomes to RC have been reported in large retrospective studies, with a potential improvement in overall quality of life (QOL). TMT also offers the possibility for definitive therapy for patients who are not surgically fit to undergo RC. Routine biopsy of previous tumor resection is recommended to assess response. Prompt salvage RC is required in non-responders and for recurrent muscle-invasive disease, while non-muscle-invasive recurrence can be managed conservatively with TURBT +/- intravesical BCG. Long-term follow-up consisting of routine cystoscopy, urine cytology, and cross-section imaging is required. Further studies are warranted to better define the role of neoadjuvant or adjuvant chemotherapy in the setting of TMT. Finally, future research on predictive markers of response to TMT and on the integration of immunotherapy in bladder sparing protocols is ongoing and is highly promising.

Keywords: Muscle-invasive bladder cancer; chemoradiation; trimodal therapy (TMT); bladder-sparing protocols (BSP); bladder preservation therapy; transurethral resection of bladder tumor (TURBT)

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Introduction

Bladder cancer is the 10th most common cancer worldwide with an estimated 550,000 new cases and 200,000 deaths in 2018 (1). About 25% of new diagnoses are muscle-invasive bladder cancer (MIBC), which carry a worse prognosis compared to non-muscle invasive disease (2). Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) with bilateral pelvic lymphadenectomy is considered the standard of care for treatment of MIBC by multiple

international guidelines (3-5). However, this is associated with a significant impact on quality of life (QOL) as RC affects continence, sexual function, fertility, and bowel function. Moreover, many elderly individuals, which represents most of bladder cancer patients, may not be surgical candidates due to associated medical co-morbidities (6). Indeed, RC carries a rate of high-grade complications of 20% and a mortality risk of 3-6%, which increases up to 8-14% for patients over 80 years old (7-11). This may explain why approximately 50% of patients with invasive

disease receive no definite treatment (12).

Bladder-sparing protocols (BSP) answer an unmet need to broaden treatment options for patients with MIBC, with the ultimate goal of preserving optimal QOL, avoiding risks of mortality and morbidity of RC while maintaining appropriate oncological control. Multiple regimens are available, including unimodal chemotherapy or radiotherapy, maximal transurethral resection of bladder tumor (TURBT) or partial cystectomy, and multimodal protocols (chemoradiation or trimodal therapy, TMT); the latter being the most promising and the most commonly used approach. It involves a combination of maximal TURBT and concomitant chemoradiation.

Unimodal therapy

It is important to note that all unimodal therapies are inferior to combination therapy or RC and therefore should not be routinely offered alone as a curative intent. This is emphasized in international guidelines (3-5).

TURBT

TURBT alone could be therapeutic only if the tumor is limited to the superficial muscle layer and if repeat biopsies of the previous resection site are negative for invasive tumor (i.e., no residual T1 or higher stage disease). Solsona *et al.* reported on a phase II study for MIBC with 15-year of follow-up on 133 highly-selected patients who were treated with a complete TURBT with negative biopsy post-treatment (13). The 5-, 10- and 15-year overall survival (OS) and cancer-specific survival (CSS) rates were 73.7%, 39.8%, 24.8% and 81.9%, 79.5%, 76.7%, respectively. Their rate of disease progression was 30%, with 7.7% of patients developing metastasis. Of interest, 100% of patients who developed metastasis occurred during the first 36 months post TURBT, and only 30% of patients had local progression from 36 to 180 months (and none after this period). Their follow-up schedule that was developed consists of endoscopic and systemic evaluation every 3 months during the first 3 years, after which systemic evaluation can be omitted and endoscopic interval can be prolonged to every 6 months for 5 years, then annually up to 15 years. Herr reported similar survival rates with 10-year CSS of 76% for 99 patients who received TURBT alone for patients with MIBC (14). Patients with T0 disease on restaging TUR were significantly more likely to survive than patients with T1 disease (82% *vs.* 57%, $P=0.003$).

Optimal characteristics for patients undergoing TURBT alone in MIBC are the following: accessible tumor location, complete resection with a negative restaging TURBT, tumor size <2–3 cm, no multi-focal carcinoma in-situ (CIS), no hydronephrosis, and adequate bladder function (13,14).

Partial cystectomy

In highly selected patients, partial cystectomy alone for MIBC has been reported to provide reasonable oncological outcomes, with the added advantage of accurate staging by lymphadenectomy and full-thickness resection with adequate evaluation of surgical margins compared to TURBT alone. Capitanio *et al.* reported a comparable 5-year OS and CSS for partial cystectomy and RC of 57% and 70% compared to 55% and 69%, respectively, when patients were matched for age, race, TNM stage, tumor grade and number of lymph nodes removed (15). However, the recurrence rates after partial cystectomy reported in the literature have been as high as 38–49% with up to 30% of patients ultimately undergoing RC (15-17).

Ideal candidates are patients with a solitary lesion <3–4 cm, where excision with 2-cm margins is feasible (such as the bladder dome), no concomitant CIS, no need for ureteral reimplantation, and no hypercontractility of the bladder (18). Less than 5% of MIBC population would meet the criteria for partial cystectomy (16).

Chemotherapy

NAC was shown to lead to downstaging in some patients, with 30% to 40% of patients having no residual disease at time of RC (19-21). Herr *et al.* reported on a cohort of 63 patients who refused RC after complete response (CR) following NAC (22). CR was defined as negative post-chemotherapy TUR biopsy and imaging showing radiographic resolution of the tumor. The 5-year OS was 64%; however, the relapse rate was relatively high at 64%, with 38% (24 patients) of recurrence being muscle-invasive. The median time to muscle-invasive recurrence was 16 months. In total, 19 patients (30%) with muscle-invasive relapse died of their disease; however, 10 patients refused RC even after invasive recurrence, where RC could have salvaged oncological outcomes and prevented bladder cancer death. Solsona *et al.* published a phase 2 nonrandomized trial in selected patients with residual microscopic disease after complete TURBT and offered either chemotherapy or RC (23). The 5- and 10-year CSS rate were 65% and 60%, respectively, which was similar to the RC arm. However, a high proportion of patients developed

invasive recurrence or metastasis (29%) and required salvage RC (45%); 10% of patients with initial bladder preservation developed distant metastasis without local recurrence and later died of their disease.

Finally, a more recent retrospective study conducted by Mazza *et al.* reported on 148 patients who elected for active surveillance after clinical CR to TURBT and NAC (24). They reported a 5-year OS of 86%, a relapse rate of 48%, with 23% of recurrence being muscle-invasive. All these patients had a rigorous follow-up regimen and most had a low-risk disease (cT2 disease, solitary and <5 cm tumor, no hydronephrosis and no CIS). They were also offered salvage cystectomy at time of recurrence. In their cohort, 7% of patients developed a local recurrence and then metastasized, which could have potentially been prevented with upfront RC. This is similar to what has been previously reported, with an added mortality risk between 7% and 16% when a patient elect to undergo BSP compared to upfront RC (25).

Radiotherapy

External beam radiotherapy (EBRT) has been shown to lead to complete regression of MIBC in up to 70% of patients, with a sustained local response of 30–50%; however, more than 50% of individuals will develop metastatic disease and 5-year OS is only 20–30% (26). James *et al.* reported a 2-year disease-free survival rate of 54% and a 5-year OS of 35% in their radiotherapy alone group (27). Patients with T3–4 disease, extravesical mass, large tumor size (>5 cm), and hydronephrosis were more likely to have an incomplete response or local recurrence. On the other hand, pre-radiotherapy maximal TURBT and the absence of CIS were good prognostic factors. The development of modern radiotherapy equipment and the introduction of sophisticated computer technology have improved the accuracy of planning and the precision of treatment delivery leading to a decreased radiotherapy toxicity rate. The use of intensity modulated and image-guided EBRT results in less than 10% of major late genitourinary or gastrointestinal toxicities (28,29). Usually, doses of 50 to 70 Gy are given in 1.8 to 2.5 Gy daily fractions over a course of 4 to 7 weeks to the bladder tumor, while 40 to 50 Gy are usually delivered to the pelvic lymph nodes.

Combined chemoradiotherapy has been shown to be significantly superior to radiotherapy alone, with a two-year OS of 56% *vs.* 42% for EBRT (30). Moreover, a Cochrane review from 2002 demonstrated that RC had also a significant OS benefit compared to radiotherapy alone:

36% *vs.* 20% at 5 years (31). Therefore, EBRT alone results in inferior oncological outcomes compared to either RC or multimodal therapy and should not be used alone as primary therapy. However, in frail individuals who are otherwise not candidate for concurrent chemotherapy or RC, cure can still be achievable in patients treated with radiation alone.

Multimodal BSP: TMT

Maximal TURBT

The initial step of any multimodal treatment is a “maximal TURBT”, where as much tumor as possible should be safely resected. The goal is to remove all visible disease without compromising the safety of the procedure. It has been shown in multiple prospective studies that the rate of local control was 20% higher if a complete resection was achieved (32,33). Therefore, patients with large T3/T4 tumors or multifocal CIS, which cannot be completely resected by TURBT, are less likely to be cured by such multi-modal approach (34).

Chemotherapy

Chemotherapy serves two purposes. First, it will act as a sensitizer to radiation by increasing cell kill in a synergistic fashion. Second, it can potentially improve loco-regional control, as up to 50% of patients with MIBC may have occult metastases (4,35).

Several chemotherapy regimens have been used in combination with EBRT. However, only few randomized controlled trials (RCTs) have compared combined chemoradiotherapy *vs.* radiotherapy alone. Supporting evidence from RCTs using the combined approach exists for cisplatin and mitomycin C plus 5-fluorouracil (27,36). Concurrent cisplatin and EBRT was shown to reduce pelvic relapse rate (hazards ratio 0.50, P=0.036) compared to EBRT alone; however, no impact on OS was seen. Multiple other retrospective studies reported similar results (37,38). Concomitant mitomycin C plus 5-FU and radiation was shown to significantly improve locoregional disease-free survival and lower the rate of salvage RC in the BC2001 phase III trial; however, no impact on CSS or OS was demonstrated (5-year OS of 48% in the chemoradiotherapy group *vs.* 35% with radiotherapy alone, P=0.16) (27,39).

Gemcitabine with once daily radiation in a phase 2 randomized trial was recently shown to be well tolerated while producing a high and durable response rate (3-year

CSS and OS were 82% and 75%, respectively), which was comparable to cisplatin plus 5-FU with twice-a-day radiation (40). A randomized trial assessing hypoxia-modifying agents (radiotherapy with concurrent carbogen and nicotinamide) demonstrated a significant improvement in OS and local relapse for combination therapy with a 3-year OS of 59% *vs.* 46% for radiotherapy alone (41). These options are particularly useful when patients are not eligible for cisplatin (42). International guidelines recommend the use of either cisplatin, gemcitabine, or mitomycin plus 5-FU for radiation sensitizing chemotherapy as most evidence exists for these regimens (3-5).

Radiotherapy

Standard radiation regimen usually involves EBRT to the bladder and pelvic lymph nodes for an initial dose of 40 Gy, followed by additional boost to the bladder to 54 Gy and a final boost to the tumor to 64–65 Gy (43). The RTOG 0712 reported on the feasibility of twice daily radiation with 5-FU and cisplatin or once daily radiation with gemcitabine (44). Both regimens were found to have appropriate and comparable oncological outcomes, while the once daily regimen was associated with less grade 3 and 4 toxicities: (55% *vs.* 64%). Over the last few years, radiotherapy regimens using hypofractionated EBRT have been developed, limiting overall treatment duration, and providing similar outcomes in terms of toxicity and disease control (29,40). Total doses ranging from 50 to 52.5 Gy in 20 fractions given over 4 weeks are delivered usually in combination with weekly gemcitabine.

Controversy exists on whether partial bladder radiation (with a boost to the tumor region) provides the same outcomes as whole bladder radiation, while sparing normal tissue and decreasing toxicity at the potential cost of missing occult tumor not seen by cystoscopy or imaging. One small retrospective study and another prospective trial did not show neither statistical significance in local recurrence nor OS, but with similar treatment toxicity (45,46). The BC2001 trial also reported on a reduced radiation treatment volume, which aimed to spare the uninvolved bladder (receiving up to 80% of maximum dose) while delivering full dose to the tumor (47). They showed no statistically significant differences in grade 3/4 acute or late toxicity (20% *vs.* 25%, $P=0.48$ and 2.4% *vs.* 5.4%, $P=0.47$, for standard radiotherapy *vs.* reduced volume, respectively). Although both groups had similar 5-year OS (38% *vs.* 44%, respectively), the study could not establish a non-

inferiority outcome of locoregional recurrence-free rate at 2 years (61% *vs.* 64%, $P=0.36$) for the limited volume arm. Therefore, both options seem to have similar efficacy and toxicity rates and may be used for BSP in selected patients. Large multi-institutional RCTs are required to validate these results.

Another area of interest in radiotherapy is the extent of nodal irradiation. Pelvic nodal involvement in muscle-invasive disease is present in at least 30% of patients (48). Furthermore, several studies reported that 20–30% of patients with lymph node metastasis are cured with RC plus pelvic lymphadenectomy (49,50). Thus, at this point, it is recommended to include pelvic nodal radiation in BSP until larger randomized trials can better evaluate the clinical impact of omitting pelvic radiation.

Of interest, two small randomized trials (230 and 60 patients, respectively) compared whole pelvis radiation *vs.* bladder only radiation and reported no difference in neither local disease control nor OS, while decreasing acute toxicities by avoiding nodal irradiation (51,52). The rate of acute grade 3 or 4 toxicity reported by Tunio *et al.* was 13.3% in the bladder-only group compared to 17.6% in the whole pelvis radiation group ($P=0.05$). Arafat *et al.* reported similar rate of acute genitourinary toxicity in both groups, but a significantly higher rate of acute gastrointestinal toxicity (grades 1-4) in the whole pelvis group (93.3% *vs.* 16.7%). Severe RTOG grades 3-4 gastrointestinal toxicity was reported in 6.7% and 0%, respectively. There was no difference in late toxicity between the two groups.

Centers delivering radiotherapy using a “split course” regimen advocate for cystoscopic assessment and biopsy of the previous tumor site or any suspicious lesion after an initial radiotherapy dose of 40 Gy is given (4,53). If incomplete response is observed, patients undergo immediate salvage RC. If no evidence of disease is present, then a consolidative course of radiotherapy is used. A “continuous” regimen is another option used by many centers, where the full dose of radiotherapy is given and cystoscopic evaluation with biopsy is done only 1 to 3 months later (27). No prospective trial comparing these options has been done and no evidence exists that one approach is superior to the other in terms of improving survival or decreasing toxicity.

Patient selection for TMT

As mentioned earlier, patient selection is of paramount importance for successful oncologic control in BSP. Multiple centers have shown improved outcomes as they

Table 1 Ideal selection criteria for trimodal therapy

Ideal TMT patient*	Non-ideal TMT patient (high-risk features)*
cT2	cT3-cT4a disease
Complete TURBT	Inability to perform complete TURBT
No hydronephrosis	Presence of hydronephrosis
No CIS	Presence of extensive CIS
Unifocal tumor	Diffuse and multifocal disease
Good bladder function and capacity	

*, to be considered an ideal TMT, all characteristics need to be present and no high-risk features. TMT, trimodal therapy; TURBT, transurethral resection of bladder tumor; CIS, carcinoma-in-situ.

refined their selection criteria. For example, Giacalone *et al.* (34) improved the 5-year OS for TMT over time from 53% to 75% and diminished their rate of salvage RC from 29% to 16% by being more selective (100% without hydronephrosis, 97% cT2, 82% had maximal TURBT, 81% without CIS, 73% had adjuvant chemotherapy). On their multivariate analysis, T2 disease, CR to chemoradiation, hydronephrosis, and presence of CIS were significant predictors for OS with hazards ratio (HR) of 0.57, 0.61, 1.51 and 1.56, respectively. Complete TURBT was a predictor for bladder-intact disease-specific survival (HR 0.72). Our experience also showed that TMT outcomes were better as we refined our selection criteria in elderly patients: 3-year CSS improved from 38% to 71% (29, 54).

Table 1 lists the oncological factors that define patients as ideal or non-ideal candidates for TMT. The high-risk features associated with worse outcomes with TMT are the following: incomplete/inability to perform maximal TURBT, presence of extensive CIS, hydronephrosis, diffuse multifocal disease, and cT3-cT4a disease. TMT would still be feasible in patients with high-risk features, but chance of cure is significantly diminished.

Outcomes of TMT

CSS and OS

A systematic review performed in 2014 reported a 5-year CSS for TMT ranging from 50% to 82%, and a 5-year OS of approximately 50%, ranging from 36% to 74% (55). Discrepancies in results are expected as patient selection, chemotherapy, radiotherapy regimens, as well as use of neoadjuvant or adjuvant chemotherapy varied in the literature. Pooled analysis from six RTOG bladder-

preservation studies had a 5-year CSS of 71%, a 5-year OS of 57%, and a 21% rate of salvage RC (56). The largest single-center experience reported a 5-year CSS of 66% and a 5-year OS of 57% (34). These results are similar to contemporary RC cohorts reporting a 5-year OS of 57% (50). *Table 2* summarizes major findings of various TMT series.

Similar to TMT, improved outcomes can be seen in patients treated with RC as the selection criteria are refined. Culp *et al.* reported a 5-year OS of 64.8% and a 5-year CSS of 83.5% for low-risk patients (i.e., <cT3b disease, no hydronephrosis, no palpable mass, no lymphovascular invasion on TURBT) who underwent RC (72). Therefore, direct comparison between TMT and RC is difficult, as there is an inherent strong bias of choosing one therapy over the other and patient selection is vastly different. Randomized trials are required to obtain similar patient population to allow comparison of both modalities.

Two RCTs exist, which directly compare TMT to RC. A small single-centre RCT, which was conducted in Egypt and consisted of 160 patients, showed no difference in OS between RC and TMT (3-year OS of 63% and 61% respectively) (57). No NAC was given and a salvage RC rate of 33% was reported. However, even though the histologic type is not reported, 71% of patients had a history of schistosomiasis, which is associated with higher risk of developing squamous cell carcinoma of the bladder rather than urothelial cell carcinoma. This potentially prevents the applicability of this study to most MIBC patients. Another trial, the SPARE trial aimed to compare RC and BSP in a multicentre RCT setting, but failed to recruit as initially planned (73). In 30 months, only 25 patients were randomized to RC and 20 to TMT. This was mostly caused by clinician and patient preferences for treatment, which prevented proper randomization of treatment allocation

Table 2 Trimodal therapy outcomes based on modern published clinical studies with more than 50 patients

Study	Median follow-up (months)	No. of patients	Inclusion criteria	Neoadjuvant or adjuvant chemotherapy	Concomitant chemotherapy	Radiotherapy	CR rate	Salvage RC	Survival
Prospective phase 3 studies									
AlGizawy <i>et al.</i> [2014] (57)	27	80	T2-3, N0, M0; complete TUR: 60%; hydronephrosis: N/A	None	Cisplatin + gemcitabine (2 cycles)	46 Gy +20 Gy if initial CR	83.8%	32.5%	3-yr OS: 61%; 3-yr CSS: 69%
James <i>et al.</i> [2012] (27)	69.9	182	T2-T4a, N0, M0; complete TUR: 56.6%; hydronephrosis: N/A	NAC: platinum-based (31.3%)	5-FU + mitomycin C	55 Gy or 64 Gy	N/A	11.4%	5-yr OS: 48%
Tunio <i>et al.</i> [2012] (52)	60	230	T2-T4, N0, M0; complete TUR: 76.5%; hydronephrosis: 30%	None	Cisplatin weekly x6	65 Gy	80.7%	21.3%	5-yr OS: 52%; 5-yr CSS: 47%
Shipley <i>et al.</i> [1998] (58)	61	123	T2-T4a, Nx, M0; complete TUR: 71.5%; hydronephrosis: 19.5%	NAC: MVC (50%)	Cisplatin	64.8 Gy (n=62); 39.6 Gy +25.2 Gy if CR (n=61)	58.5%	20.3%	5-yr OS: 49%
Housset <i>et al.</i> [1993] (59)	27	54	T2-T4, N0-N1; complete TUR: 46%; hydronephrosis: 42.6%	None	5-FU + cisplatin	44 Gy	79.6%	27.8% ¹	3-yr OS: 59%; 3-yr CSS: 62%
Phase 2 studies									
Coen <i>et al.</i> [2019] (44)	51.6	66	T2-T4a, Nx, M0; complete TUR: N/A; hydronephrosis: 0%	Adjuvant: GC	5-FU + cisplatin or gemcitabine	40 Gy +24 Gy if initial CR	83.3%	12.1%	3-yr OS: 83.3%
Mitin <i>et al.</i> [2013] (60)	60	93	T2-T4a, Nx, M0; complete TUR: N/A; hydronephrosis: 0%	Adjuvant: GC + paclitaxel (60%)	Paclitaxel + cisplatin (49%); 5-FU + cisplatin (51%)	40.3 Gy + 24 Gy if CR or near CR	67%; 86% ²	5.4%	5-yr OS: 73%
Lagrange <i>et al.</i> [2011] (61)	96	51	T2-T4a, N0, M0; complete TUR: 66%; hydronephrosis: 17%	None	5-FU + cisplatin	45 Gy + 18 Gy if initial CR	N/A	33.3%	8-yr OS: 36%
Choudhury <i>et al.</i> [2011] (40)	36	50	T2-T3, N0, M0; complete TUR: N/A; hydronephrosis: 10%	None	Gemcitabine weekly	52.5 Gy	88%	10%	5-yr OS: 65%; 5-yr CSS: 78%
Kaufman <i>et al.</i> [2009] (33)	49.4	80	T2-T4a, N0, M0; complete TUR: N/A; hydronephrosis: 0%	Adjuvant: paclitaxel + gemcitabine (70%)	Paclitaxel + cisplatin	40.3 Gy + 24 Gy if CR ²	81% ²	12.5%	5-yr OS: 56%; 5-yr CSS: 71%
Gogna <i>et al.</i> [2006] (62)	23	113	T2-T4a, <10 cm tumor; complete TUR: 21.2%; hydronephrosis: N/A	None	Cisplatin weekly	64 Gy	70%	13.3%	5-yr CSS: 50%
Kragelj <i>et al.</i> [2005] (63)	136	84	T1-T4, M0; complete TUR: 66.7%; hydronephrosis: 14.3%	None	Vinblastine weekly	63.8-64 Gy	78%	4.8% ³	9-yr OS: 25%; 9-yr CSS: 51%

Table 2 (continued)

Table 2 (continued)

Study	Median follow-up (months)	No. of patients	Inclusion criteria	Neoadjuvant or adjuvant chemotherapy	Concomitant chemotherapy	Radiotherapy	CR rate	Salvage RC	Survival
Hussain <i>et al.</i> [2001] (64)	N/A	56	T2-T4a, N0/N1; complete TUR: 39.3%; hydronephrosis: N/A; unresectable: 34%	Adjuvant: 5-FU + cisplatin	5-FU + Cisplatin	60 Gy	49%	N/A	5-yr OS: 32%
Fellin <i>et al.</i> [1997] (65)	46	56	T2-T4, N0/Nx, M0; complete TUR: 18%; hydronephrosis: 41%	NAC: MCV	Cisplatin	40 Gy + 24 Gy if CR	50%	46.4%	5-yr OS: 55%; 5-yr CSS: 59%
Tester <i>et al.</i> [1996] (66)	52.8	91	T2-T4a, N0-N2/Nx, M0; complete TUR: 0%; hydronephrosis: 20%	NAC: MCV	Cisplatin	39.6 Gy +25.2 Gy if CR	74.8%	40%	4-yr OS: 62%
Large retrospective studies									
Giacalone <i>et al.</i> [2017] (34)	54.6	475	T2-T4a, N0, M0; complete TUR: 70%; hydronephrosis: 12%	NAC: MCV (25%); adjuvant: varied (45%)	Varied	41.4 Gy +23.4 Gy if CR	75%	29% (at 5-year); 31% (at 10-year)	10-yr OS: 39%; 10-yr CSS: 59%
Krause <i>et al.</i> [2011] (67)	71.5	473	T2-T4a, Nx, M0; complete TUR: 62%; hydronephrosis: N/A	None	Platinum-based (varied)	Median dose: 53.9 Gy; N=142 RTx alone	70.4%	13.3% ⁴	10-yr OS: 30%; 15-yr OS: 19%
Sabaa <i>et al.</i> [2010] (68)	71	104	T2-T3a, N0, M0; complete TUR: 100%; hydronephrosis: 0%	Adjuvant: GC (100%)	Cisplatin weekly	60-65 Gy	78.8%	16.3%	5-yr OS: 59%; 5-yr CSS: 69%
Aboziada <i>et al.</i> [2009] (69)	18	50	T2-T3, N0, M0; complete TUR: 40%; hydronephrosis: 32%	None	Cisplatin weekly	46 Gy +20 Gy if CR or PR	72%	40%	1.5-yr OS: 100%; 1.5-yr CSS: 84%
Perdonà <i>et al.</i> [2008] (70)	66	121	T2-T4, Nx, M0; complete TUR: 81%; hydronephrosis: 8.3%	NAC: MCV	Cisplatin or carboplatin	65 Gy	85.7%	20.2%	5-yr OS: 72%; 5-yr CSS: 79%
Weiss <i>et al.</i> [2007] (71)	27	112	T1-T4, N2, M0; complete TUR: 84.8%; hydronephrosis: 20%	None	5-FU + cisplatin	55.8–59.4 Gy	88.4%	17.0%	5-yr OS: 74%; 5-yr CSS: 82%
Rödel <i>et al.</i> [2002] (37)	36	415	T1-T4; complete TUR: 61.0%; hydronephrosis: N/A	None	Cisplatin +/- 5-FU or carboplatin, N=289	54 Gy; N=126 RTx only	72%	20%	10-yr OS: 31%; 10-yr CSS: 42%

¹, excluding 18 patients (33.3%) who were treated with primary RC after CR to induction treatment; ², CR defined as pT0, Ta, Tis on post induction tumor site biopsy; ³, only 14.3% of patients with persistent or recurrent invasive tumors underwent salvage RC; the other patients refused surgery for tumor dissemination, locally advanced inoperable tumor or poor performance status; ⁴, rate of RC in non-responders. TUR, trans-urethral resection; CR, complete response; RC, radical cystectomy; OS, overall survival; CSS, cancer-specific survival; 5-FU, 5-fluorouracil; N/A, not available; NAC, neoadjuvant chemotherapy; MCV, methotrexate; cisplatin; vinblastine; PR, partial response; GC, gemcitabine + cisplatin; RTx, radiotherapy.

and led to frequent protocol deviations. Conclusions about the non-inferiority of BSP could not be determined as there were too few participants. Unfortunately, it is unlikely that another phase 3 study comparing RC with NAC to TMT will be completed given the adversities encountered in the SPARE trial.

Using the National Cancer Database, two retrospective analysis comparing RC to BSP were performed with propensity score matching (PSM) (74,75). The first study included 6,606 patients who underwent RC and 1,773 who received chemoradiation (CRT). CRT was associated with decreased mortality at 1 year (HR 0.84) but worse outcomes at 2 and 3 years (HR 1.4 and 1.5, respectively). The 5-year OS rate was 38% for RC *vs.* 30% for CRT. The second study included 22,680 patients who were treated with RC and 9,620 patients who underwent BSP, 15.5% being treated with CRT. The reported 5-year OS for RC was 48% compared to 30% for CRT. Most recently, Dafashy *et al.* used the Surveillance, Epidemiology, and End Results (SEER) Medicare database to compare TMT to RC (76). They included 2,963 patients and performed PSM as well as inverse probability of treatment weighting (IPTW). TMT was associated with a significantly decreased CSS (PSM: HR 1.55, IPTW: HR 1.51) and OS (PSM: HR 1.49, IPTW: HR 1.54) compared to RC.

On the other hand, a recent small retrospective study of 112 patients, who also used a more comprehensive PSM to compare RC to TMT found, with a median follow-up of 4.51 years, no differences between OS and CSS ($P=0.63$ and $P=0.49$, respectively) (77). Median OS was 6.61 years, while 5-year CSS was 73.2% and 76.2% for RC and TMT, respectively. However, similar to the other reports, this study is not devoid of limitations. The institution's usual practice is to re-evaluate patient after NAC: if a significant response is observed, TMT is recommended, whereas patients with a poor response would be recommended RC (78). As 35% of patients received NAC, this created an important confounding variable that was not accounted for, positively enriching the TMT group with patients having a favorable tumor profile and subsequent outcome. Kim *et al.* also reported comparable CSS and OS between RC and TMT, with only a decrease in the 5-year local recurrence free survival in the TMT group (79). Finally, a recent meta-analysis comparing RC to TMT, which included 57 studies and more than 30,000 patients, did not show a statistically significant different 10-year OS (35.1% for RC *vs.* 30.9% for TMT, $P=0.32$) or 10-year CSS (50.9% for TMT *vs.* 57.8% for RC, $P=0.26$) between the two treatment options (21).

Apart from the limitations inherent to retrospective reviews using large data base, even applying sophisticated statistical methods, without an upfront properly performed randomized trial, any comparison between RC and BSP is bound to be limited by patient selection, disease extension incorrectly established by clinical investigations, and other unrecognized confounding variables. All in all, even though conflicting results exist in the literature and large multicentre RCT comparing TMT and RC is lacking, TMT can yield comparable oncological outcomes and similar long-term survival rates when patients are appropriately selected (3,4). Moreover, as recent studies have shown that up to 50% of patients do not receive any definitive therapy, TMT should be viewed as a complementary rather than competitive option for patients with MIBC (12).

Recurrence

CR rate post-TMT ranges from 66 to 88% in the literature, depending on selection criteria (21,27,34,56). Among patients with a CR, 12% to 43% will develop a local recurrence. By pooling results of several trials, the RTOG reported a 5- and 10-year rates of muscle-invasive recurrence at 13% and 14%, respectively, and 31% and 36% for non-muscle-invasive recurrence (NMIBC), respectively (56). Median time to recurrence tends to be less than 2 years, but late recurrences in up to 8% of patients more than 10 years after CR have been reported (80). Salvage RC is the standard of care for recurrence of MIBC in surgically fit patients. The average rate of salvage RC reported in the literature ranges from 25% to 30%, with many studies having less than 5 years of follow-up data (81). However, this rate can be reduced with better patient selection as shown by the Massachusetts General Hospital experience, in which the rate of 5-year salvage RC decreased from 42% to 16% (34). Similarly, Hall *et al.* reported a 2-year salvage RC rate of 11% for the TMT group in a randomized controlled trial setting (39).

Patients with NMIBC (i.e., Tis, Ta and T1) recurrences can be managed by conservative management (TURBT +/- intravesical BCG) (80,82). Zietman *et al.* initially reported on the Boston experience among patients who developed NMIBC recurrences after CR (82). With updated follow-up and more patients, they recently observed a worse 10-year CSS for patients with NMIBC recurrence compared with those without (72.1% *vs.* 78.4%, $P=0.002$, respectively), but similar OS (43.6% *vs.* 54.1%, $P=0.66$, respectively) (80).

Reported rate of salvage RC in the literature for patients with NMIBC recurrence after CR, which are initially managed by TURBT +/- BCG, is around 25–30% (80,82-84).

It is important to note that only 10 patients with T1 recurrences were managed conservatively in the previously cited studies. As such, until more data is available, it may be more prudent to offer salvage RC in surgical candidates with T1 recurrences.

Salvage RC

Salvage RC is recommended for patients that do not achieve a CR (i.e., non-responders or partial responders) or develop subsequent invasive recurrences after CR following TMT. The overall 5- and 10-year CSS rates for patients undergoing salvage RC in both settings (non-responders and for recurrent tumor) are approximately 50–60% and 40–50%, respectively (17,34,37,56). Reported 5-year and 10-year OS rates are approximately 45% and 20–30%, respectively (17,56). From the limited available data, there appears to be no significant reduction in OS related to delay in cystectomy after TMT for MIBC relapse.

Recent contemporary series comparing salvage RC to primary RC suggest no significant differences in perioperative mortality and major complications rates, with a slight increase in minor complications rate (17,85,86). Interestingly, Eswara *et al.* compared immediate salvage RC (for non-responder, performed after split course assessment) or delayed salvage RC (for MIBC recurrence) (17). Immediate salvage RC had significantly more cardiovascular and hematological complications (i.e., deep vein thrombosis, pulmonary embolism, transfusion, myocardial infarction), while delayed cystectomies had significantly more tissue healing complications (wound infection, fascial dehiscence, ureteral and anastomotic stricture). Moreover, better CSS was seen in the delayed salvage RC group; this difference may be explained by the fact that tumor who initially failed to respond to TMT may have a more aggressive biology and occult distant metastasis.

Nevertheless, appropriate patient counselling about salvage RC is important. Indeed, previous pelvic radiotherapy treatment limits the ability to perform nerve sparing surgery as well as the choice of urinary diversions. Orthotopic neobladder reconstruction, although technically feasible, will be associated with an increased risk of functional complications (such as radiation-induced impaired bowel healing, anastomotic stricture and incontinence) and is not recommended.

Follow-up post TMT

As previously highlighted, since the majority of local recurrences are in the bladder and can occur even 10 years post TMT, long-term regular cystoscopy and imaging is mandated. Multiple follow-up protocols exist and most commonly recommend cystoscopy with urine cytology every 3–4 months during the first year, every 4–6 months in the second year, and every 6–12 months afterwards (56,87). The AUA guidelines recommend cross-sectional imaging of the chest, abdomen and pelvis every 6 months for the first 2 years, and then annually (4).

All the RTOG trials always included post-treatment biopsy and exam under anesthesia to assess response (56). Despite the absence of high level-evidence supporting routine biopsy in the absence of visibly detected tumor on cystoscopy or imaging, we suggest to perform systematic resection of the previous scar in surgical candidates as it is not uncommon for the tumor to re-grow underneath a normal appearing resection scar.

QOL

Even though a goal of TMT is to maintain QOL by avoiding RC-associated morbidities, no studies so far prospectively assessed QOL between the two options. Only one retrospective study compared long-term QOL post TMT versus RC; however, no baseline data were available (88). With a median follow-up of 5.6 years, the authors reported a better general QOL for TMT ($P=0.001$). Patients undergoing TMT also had higher physical, occupational and social role functioning, better emotional and cognitive functioning, better bowel function, fewer bowel symptoms, better sexual function and better body image. However, urinary symptom scores were similar. Pooled analysis from the RTOG prospective trials confirmed that late toxicities were acceptable after TMT: 6% experienced grade 3 genitourinary toxicity, 2% grade 3–4 gastrointestinal toxicity, and <1% of patients required cystectomy for treatment-related effects (89). Using the RTOG criteria, the BC2001 trial reported a grade 3/4 genitourinary toxicity rate of 3.8% at 2 years (47). The overall cumulative grade 3/4 toxicity was 13% at 2 years. Salvage cystectomy was performed in 0.9% of patients due to radiation therapy side effects. Studies reporting acute and chronic toxicity from TMT are reviewed in *Table 3*.

Finally, a small urodynamic study done on 32 long-term survivors post TMT showed that 75% of patients

Table 3 Rates of severe acute and late toxicity during trimodal therapy

Study	Median follow-up (months)	No. of patients	Grade ≥3 acute toxicity	Grade ≥3 late toxicity	Protocol and completion rate	Treatment discontinuation due to toxicity	RC due to radiation toxicity
Coen <i>et al.</i> [2019] (44)	51.6	66	48% hematologic; 7.6% GI; 6.1% GU; 1.5% death	N/A	64.3 Gy with 5-FU + cisplatin or gemcitabine alone, adjuvant GC; completed: 53%	3%	0%
Ararat <i>et al.</i> [2016] (51)	24	60	3.3% GI; 5.0% GU	None	64 Gy with cisplatin + paclitaxel, adjuvant PC; completed: N/A	N/A	0%
AlGizawy <i>et al.</i> [2014] (57)	27	80	6.3% hematologic; 2.5% GI; 7.5% GU	9.7% GI (Grade ≥2); 17.7% GU (Grade ≥2)	66 Gy with GC; completed: 72.5%	10%	0%
Mitin <i>et al.</i> [2013] (60)	60	93	Induction: 26.9%; consolidation: 32% (3.2% GI, 5.4% GU); adjuvant chemotherapy: 80.2% (2.5% GI, 2.5% GU); 1.1% death	Radiotherapy induced: 8.6% (- 1.1% GI, - 5.4% GU); unrelated: 29% (- 1.1% GI, - 7.5% GU)	64 Gy with paclitaxel + cisplatin or 5-FU + cisplatin, adjuvant GC + paclitaxel; completed: 60.2%	9.7%	N/A
James <i>et al.</i> [2012] (27)	69.9	182	36.0%: 9.6% GI, 21.3% GU	1-yr: 3.3% (all GU); 2-yr: 4.6%	55 or 64 Gy with 5-FU + MMC; completed: 80.2%	N/A	1.1%
Tunio <i>et al.</i> [2012] (52)	60	230	Overall: 15.5%: 1% hematologic, 6.5% GI, 2.5% GU	0.5% GI; 1.5% GU	65 Gy with cisplatin; completed: 94.5%	7%	N/A
Choudhury <i>et al.</i> [2011] (40)	36	50	8% GI; 4% death	2% GU requiring RC; 2% GI requiring bowel resection	52.5 Gy with gemcitabine; completed: 92%	8%	2%
Efsthathiou <i>et al.</i> [2009] (89)	64.8	157	1.3% death ¹	7%: 1.9% GI; 5.7% GU	Varied protocol; completed: N/A	N/A	0.2% ¹
Perdonà <i>et al.</i> [2008] (70)	66	121	15.7% hematologic; 12.4% GI; 11.5% GU; 9.9% other	4.1% GU; 1.7% GI (Grade 4)	65 Gy with cisplatin or carboplatin, NAC; MCV; completed: 95.0%	3.3%	0.8%
Weiss <i>et al.</i> [2007] (71)	27	112	29.5% hematologic; 30.4% GI; 8.0% GU	10.7% GU; 1.4% GI	55.8-59.4 Gy with 5-FU + cisplatin; completed: 72%	1.8%	0.9%
Gogna <i>et al.</i> [2006] (62)	23	113	Overall: 23%: 13.3% hematologic, 3.5% GU	4% GI ² ; 2% GI	64 Gy with cisplatin; completed: 86.7%	5.3%	0% ²
Rödel <i>et al.</i> [2002] (37)	36	415	28% hematologic; 9% GI; 5% GU; 0.2% death	1.5% GI; 4.3% GU, 2% requiring RC	54 Gy with cisplatin +/- 5-FU or carboplatin; completed: 68%	N/A	2%
Hussain <i>et al.</i> [2001] (64)	N/A	56	Overall: 54.5%: 14.5% hematologic, 18.2% GI, 7.3% neuropathy	N/A	60 Gy + cisplatin and 5-FU, adjuvant cisplatin + 5-FU	8.9%	N/A
Fellin <i>et al.</i> [1997] (65)	46	56	23.2%, all chemotherapy-related	1.8% GI ³ ; 1.8% GU ³	64.8 Gy + cisplatin, NAC: MCV	N/A	0%
Tester <i>et al.</i> [1996] (66)	52.8	91	Overall: 28.6%: 15.4% hematologic, 7.7% GU, 3.3% GI	6.6% GI; 7.7% GU	64.8 Gy + cisplatin, NAC: MCV	21%	1.1%

¹, updated results from Giacalone *et al.* were published in 2017 (including 475 patients) and reported a treatment-related death rate of 1.3% and a cystectomy rate for treatment-related toxicity of 0.2% (34); ², all patients were found to have significant persistent/recurrent bladder cancer and were subsequently managed by salvage RC; ³, late complications were related to salvage radical cystectomy only. RC, radical cystectomy; GI, gastrointestinal; GU, genitourinary; N/A, not available; 5-FU, 5-fluorouracil; GC, gemcitabine + cisplatin; PC, paclitaxel + cisplatin; MMC, mitomycin C; RC, radical cystectomy; NAC, neoadjuvant chemotherapy; MCV, methotrexate, cisplatin, vinblastine.

had a normal functioning bladder, with most other patients experiencing decreased bladder compliance (90); 36% of men had normal erections and another 18% had weaker erections but sufficient for intercourse. One ongoing trial looking to prospectively assess the QOL of patients after BSP will shed light on the subject by limiting existing limitations of retrospective design and interpretation biases (NCT02688348).

Overall, TMT is well tolerated. Long-term requirement for cystoscopy and follow-up as well as the acceptance to forgo a neobladder reconstruction in the event that a patient needs salvage RC is important to consider when counselling patients about this treatment option.

Cost of TMT

Williams *et al.* recently published on the comparison of costs of RC and TMT (91). Using the SEER Medicare database, they showed that median cost was higher for TMT at 90 days (\$83,754 *vs.* \$686,892), 180 days (\$187,162 *vs.* \$109,078) and 365 days (\$289,142 *vs.* \$148,757). When performing inverse probability of treatment-weighted propensity score models analyses, TMT was associated with a median increased cost of \$136,935 at 1 year after diagnosis. Outpatient care, radiology, medication expenses and pathology/laboratory costs contributed to the higher costs associated with TMT. No data on QOL was reported. Extrapolating these cost figures to a similar group of patients in 2017 would result in excess spending of \$468 million with TMT. However, the review involved a longer time span (2002 to 2011), limited data were available on the quality of the radiotherapy and the cost of the management of potential associated medical comorbidities, likely to be significantly more present in TMT patients, were not taken into consideration in the final cost calculation.

Neoadjuvant and adjuvant chemotherapy in TMT

Extrapolation from the surgical literature, where neoadjuvant cisplatin-based chemotherapy shows improvement in OS, led to the interest of studying neoadjuvant and adjuvant chemotherapy when using BSP and TMT in particular. However, there is no clear data supporting its role and its use remains controversial. The Medical Research Council showed in an international phase III trial that neoadjuvant cisplatin, methotrexate and vinblastine for patients treated with cystectomy and/or radiotherapy increased 10-year OS from 30% to 36%,

with a statistically significant 16% reduction in the risk of death (92). However, patients in the bladder-sparing group only received radiotherapy alone, and not TMT. On the other hand, randomized trials in head and neck and cervical cancer showed decreased survival with NAC followed by radiotherapy compared to radiotherapy alone, which challenges if extrapolation from surgical literature can confidently be applied (93,94).

The RTOG 89-03 compared neoadjuvant cisplatin, methotrexate and vinblastine with concurrent chemoradiotherapy to only concurrent chemoradiotherapy (58). There were no significant differences in OS or distant metastases, but there were more treatment-related deaths in the arm receiving NAC, highlighting the risks associated with systemic chemotherapy. Moreover, only two-thirds of patients completed their treatment per protocol due to poor tolerability. Similar results were reported in the recent meta-analysis comparing NAC with TMT *vs.* TMT alone (21). Nevertheless, all the published studies comparing these regimens have been underpowered and potentially used suboptimal regimens (such as 2 cycles of systemic chemotherapy instead of 4).

As for adjuvant chemotherapy, no survival data from phase 3 trials have been published in the TMT setting. Phase 1 and 2 studies looking at adjuvant chemotherapy after TMT report a lower tolerability and completion rate, with only 45–70% of patients completed treatment per protocol (33,95). Severe toxicity (grade 3 or 4) also seemed to be more common than in the neoadjuvant setting.

To conclude, although there exists clinical rationale to use neoadjuvant or adjuvant chemotherapy with TMT, well-designed large RCTs are required to elucidate their role with TMT. Appropriate counselling to patients regarding probable higher toxicity rate is advised if such therapy is considered.

Predictive markers of response to TMT

Biomarkers were developed with the hope to be able to prognosticate and predict response to therapy in order to best guide treatment options for patients with MIBC. Multiple biomarkers have currently been studied in the context of BSP for MIBC (96). MRE-11, a DNA-damage signaling protein, is the only biomarker that was shown in multiple studies to be a predictive factor associated with survival following radiotherapy for bladder cancer (97–99). Low tumor MRE11 expression was associated with worse CSS compared to high expression. However, manual MRE11

scoring was not validated across centers and later failed to show significant differences in CSS (100). Better staining methodology with automated digital scoring needs to be developed for MRE-11 to become a robust and reproducible biomarker for radiotherapy success in MIBC. Yang *et al.* developed a 24-gene hypoxia signature and reported a prognostic and predictive value for local relapse-free survival for patients receiving radiotherapy and predicted a benefit from the addition of the carbogen and nicotinamide (hypoxia modification) to radiotherapy (101). However, no studies have currently evaluated chemoradiation therapy with hypoxia modification.

Transcription profiling is also emerging as a potential tool to guide patient selection and treatment choice. A recently published study, examining gene expression profiling of patients treated with TMT or NAC plus RC, reported that higher immune infiltration and higher IFN-gamma gene expression were associated with a significantly improved CSS after TMT (102). In comparison, higher stromal gene expression was associated with a significantly worse CSS and OS in the NAC plus RC cohort.

Song *et al.* highlighted the potential for personalized treatment in patients with MIBC (103). They developed a putative algorithm where patients with high expression of a predictive biomarker for TMT would be offered TMT, while patients with low expression of the biomarker would be offered RC. Nevertheless, even though promising results have been reported with molecular biomarkers, none are routinely used in the clinical setting and prospective clinical trials are required to validate these findings before their implementation in clinical practice.

Tetramodal bladder-preservation therapy

One Japanese center has published on a BSP where partial cystectomy is added to TMT. The goal is to overcome the following limitations of TMT: subclinical residual disease in the original MIBC site and the lack of regional lymph nodes resection. Their protocol consists of debulking TURBT followed by 40 Gy of irradiation with concomitant cisplatin. Patients with solitary MIBC with no involvement of bladder neck or trigone and no residual disease (or minimal NMIBC disease) after chemoradiation were offered consolidative partial cystectomy with pelvic lymph node dissection (104). Recently, Kijima *et al.* published on their updated results on 107 patients with 5-year OS and CSS rates were 93% and 91%, respectively (105); 9% of patients had residual muscle-invasive disease and 2% had lymph node metastasis

on pathology, while 18% of patients experienced local recurrence, including 4% with MIBC. They also reported favorable bladder function with satisfactory bladder capacity and QOL based on SF-36 scores. Nevertheless, this approach is still considered experimental and further studies are required to investigate and evaluate reproducibility of these results.

Current and future directions

Recent development of immune checkpoint inhibitors targeting programmed death-1 (PD-1) and programmed-death ligand-1 (PDL-1) showed improved survival in the 2nd line setting of metastatic urothelial carcinoma after cisplatin-based chemotherapy and were also approved in 1st line for patients unfit for cisplatin chemotherapy. There is a biologic rationale in combining immunotherapy with current BSP. Our recent preclinical findings support the combination of immunotherapy and BSP in achieving maximal tumor inhibition and potentiating abscopal anti-tumor effects (106). This idea is highly promising given recent data from a phase III trial comparing durvalumab after definite chemoradiotherapy to chemoradiotherapy alone for locally advanced non-small-cell lung cancer, showing significantly longer OS and progression-free survival for the immunotherapy arm (107). Multiple phase I to III trials using immune checkpoint inhibitors as neoadjuvant or adjuvant therapy in combination to radiotherapy or TMT for patients with bladder cancer have currently been approved and are ongoing (NCT03768570, NCT03171025, NCT03171025, NCT03491930, NCT02621151, NCT03747419, NCT03775265, NCT03617913).

We foresee a significant increasing use of TMT in the management of MIBC. Optimization of chemoradiotherapy and BSP is still an ongoing goal and controversies remain. Areas of further research includes: (I) the role of pelvic nodal radiation on outcomes, (II) the cost-effectiveness of TMT, (III) the role of neoadjuvant and adjuvant chemotherapy, (IV) the impact of immunotherapy (neoadjuvant, concurrent or adjuvant), (V) the management of T1 recurrences after TMT, and (VI) the prospective validation of predictive biomarkers to guide therapy for MIBC patients, and its implementation in clinical practice.

Conclusions

BSP and most specifically TMT with prompt salvage RC

has been shown to give oncological outcomes comparable to upfront RC, with an improvement in QOL. It can therefore be considered as an attractive alternative to RC in appropriately selected patients or surgically unfit patients. Appropriate patient counselling and multi-disciplinary approach is of paramount importance for successful results. Identification and prospective validation of novel predictive biomarkers are needed to help us better guide therapy and look promising to improve current oncological outcomes in BSP.

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