AUA **Update Series** 2021

Lesson 7 Volume 40

Trimodal Therapy in Muscle Invasive Bladder Cancer Management*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to identify the optimal candidates for trimodal therapy in muscle invasive bladder cancer.

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Release date: March 2021

Expiration date: March 2024

Key Words: organ sparing treatments, chemoradiotherapy, therapeutics, urinary bladder, urologic neoplasms

INTRODUCTION

In Europe and in North America, bladder cancer is the fourth most frequent form of cancer in men and the second most common genitourinary malignancy.[1,2] In Canada, it is the fifth most common cancer after lung, colorectal, breast and prostate neoplasms. Bladder cancer is often characterized by multifocality and field defect and therefore often may require treatment of the whole organ. Radical cystectomy with pelvic lymph node dissection and urinary diversion has been the traditional standard treatment for muscle invasive bladder cancer.[3,4]

However, despite important improvements in surgical technique and perioperative management, RC is still associated with frequent complications and even perioperative mortality.[5,6] The concept of delivering therapy to the entire organ where disease is unifocal in nature has been challenged in the last decades. Although organ sparing approaches in bladder cancer patients who often present with multifocal disease may not be always feasible, a subset of patients are diagnosed with unifocal disease and may benefit. Bladder preservation has been suggested as an alternative to cystectomy in selected patients with MIBC—the goal being to improve long-term quality of life without compromising oncologic outcomes.

Several bladder sparing strategies have been described. These include monotherapies, such as radiation alone, chemotherapy alone and radical transurethral bladder resection, and multimodal approaches (such as TURBT plus chemotherapy, in conjunction with radiotherapy, named trimodality). In general, single modality therapy is not recommended anymore, at least with a curative rather than palliative intent.[3] Recent publications have supported TMT as the bladder sparing modality of choice. Indeed, in selected MIBC patients, it seems to provide similar oncologic outcomes compared to RC,[7] and systematic reviews have supported the rationale of TMT as the bladder preservation of choice in well-selected MIBC patients.[8–10] In this Update, we provide an overview of the available bladder sparing strategies for MIBC focusing on oncologic and functional outcomes.

Evidence acquisition for this review consisted of a comprehensive literature search performed in Medline® and Embase®. The search included articles written in English reporting on bladder sparing strategies in MIBC from 1990 to December 2018. Several combinations, including the following search terms, were used: "bladder preservation," "bladder sparing," "chemoradiotherapy," "trimodality" and "muscle invasive bladder cancer."

TRIMODAL THERAPY

The TMT concept in MIBC includes a combination of complete TURBT followed by RT with radiosensitizing chemotherapy. The primary role of RT after TURBT is to achieve local tumor control in the bladder. The rationale for adding systemic chemotherapy is to enhance the RT effect. Long-term outcomes of the BC2001 phase III multicenter trial have shown improved cancer-specific survival (HR 0.73, 95% CI 0.54–0.99, p=0.043), locoregional control (18% vs 32% at 2 years) and lower rates of salvage cystectomy (11% vs 17% at 2 years) in MIBC patients treated with radiation plus concurrent 5-fluorouracil+mitomycin C at 2 years median followup.[11] Multiple prospective phase II studies have supported those findings (table 1). Reported complete responses range between 60% and 93% depending on the series, with an average of 70%. The only prospective phase III trial reported CR rates of 60%.[12] Thus, approximately 30% of patients who attempted to retain their bladders were not able to do so. Five-year overall survival rates in published trials range from 48% to 65%. In a recent pooled analysis of the Radiation Therapy Oncology Group (RTOG) trials, Mak et al reported a 5-year OS rate of 57% (62% for cT2, 49% for cT3-4).[13] In this pooled analysis, at a median followup of 8 years, similar survival outcomes and response rates among older and younger patients were demonstrated. These findings support the use of this treatment approach in patients younger than 65 years old as well.

Patient selection for bladder preservation. **Patient selection is key to bladder preservation TMT success.** A visibly complete TURBT is associated with a significantly higher rate of CR to TMT as shown in the pooled analysis of 314 patients included in 6 RTOG trials,[13] in the series from Erlangen, Germany,[14] and at Massachusetts General Hospital as reported by Efstathiou et al.[15] Visibly complete TURBT has been associated with better OS, clinical CR rate and bladder intact CSS.[12-14,16,17] An incomplete resection is not an absolute contraindication but may compromise CR and result in worse outcomes.

Presence of hydronephrosis (a surrogate for locally advanced MIBC) has been suggested as a predictor of OS in some series.[12,17] In fact, CRs were observed in 64% of patients without hydronephrosis in both phase III RCTs.[12] Other retrospective series were unable to support those results.[13,14]

Multifocal disease is often an exclusion criterion in TMT trials as it has been associated with a higher risk of tumor recurrence in the bladder (Appendix 1). In general, TMT is not advocated in those with diffuse multifocal disease. Similarly, the presence of multifocal/extensive carcinoma in situ has been associated with lower rates of CR to TMT and higher rates of recurrence after TMT. Fung et al showed that the risk of bladder tumor recurrence was higher in patients with tumor associated CIS (40%) than those without CIS (6%, p=0.075).[18] However, the

ABBREVIATIONS: 5-FU=5-fluoruracil, BCG=bacillus Calmette-Guérin, BO=bladder-only concurrent chemoradiation, CIS=carcinoma in situ, CR=complete response, CSS=cancer-specific survival, CT A/P=computerized tomography of abdomen/pelviscysto=cystoscopy, FCT=fluorouracil plus cisplatin and radiation twice a day, GD=gemcitabine and once daily radiation, MGH= Massachusetts General Hospital, MIBC=muscle invasive bladder cancer, MMC=mitomycin C, NAC=neoadjuvant/adjuvant chemotherapy, NMIBC=non-muscle invasive bladder cancer, OS=overall survival, PFS=progression-free survival, QoL=quality of life, RC=radical cystectomy, RCT=randomized controlled trial, RT=radiotherapy, TMT=trimodal therapy, TCC=transitional cell carcinoma, TURBT=transurethral resection bladder tumor, WP=whole pelvis concurrent chemoradiation

Table 1. Currently published data on TMT for curative intent in MIBC and recurrences rates location after curative intent with TMT and MIBC

References	No. Pts	Followup	Median Age (yrs, range)	Clinical Stage	Radiosensitizing Chemotherapy	RT Dosing (Gy)	NAC	CR Rate (%)
Phase III randomized controlled trials								
James et a[11]	182	70 mos	72.3 (65.1–76.6)	cT2–T4a N0	5-FU, MMC×2	55–64	Yes—57 pts, No—125 pts	Not stated
Shipley et al[12]	62 (arm 2)	60 mos	Not stated	cT2–T4a N0/Nx	Cisplatin×3	64.8	No	55
Phase II prospective clinical trials								
Coen et al[22]	66	5.1 yrs	Not stated	cT2–T4a	FCT vs GD	Various	No	FCT—88, GD—78
Mak et al[13]	468	4.3 yrs	66 (34–93)	cT2–T4a	Various	Various	Yes—151 pts No—317 pts	69
Zapatero et al[41]	80	72 mos	62 (41–76)	cT2–T4a N0	Weekly cisplatin (paclitaxel—5 pts)	64.8	Yes—41 pts, No—39 pts	74
Tunio et al[26]	230	5 yrs	62	cT2–T4a N0/Nx	Weekly cisplatin	65	No	93
Choudhury et al[28]	50	36 mos	67 (48–84)	cT2–T3 N0/Nx	Weekly gemcitabine	52.5	No	88
Kaufman et al[36]	80	49.4 mos	Not stated	cT2–T4a N0	Weekly cisplatin+ paclitaxel×5	64.3	No	81
Gogna et al[42]	113	23 mos	Not stated	cT2–T4a high risk T1	Weekly cisplatin	64	No	70
Housset et al[43]	54	27 mos	66 (37–82)	cT2–T4a N0/N1 (4 pts)	Cisplatin+5-FU×4	44	No	74
Prospective/retrospective single institution studies								
Büchser et al[16]	90	94 mos	63 (41–77)	cT2–T4a	Various	Various	Yes—42 pts, No—48 pts	79
Giacalone et al[17]	475	7.21 yrs	67.3 (60.2–74.6)	cT2–T4a N0M0	Various	Various	Varied	75
Caffo et al[29]	190	44.5 mos	70 (42–87)	cT2–T4a	Gemcitabine based	Various	No	93
Krause et al[44]	473	71.5 mos	65.3 (28–91)	cT2–T4a N0/Nx	Various (RT alone—142 pts)	Various	No	70.4
Perdonà et al[45]	121	66 mos	63	cT2–T4a N0/Nx	Cisplatin (carboplatin—25 pts)	65	Yes	85.7
Weiss et al[46]	112	27 mos	64	cT2–T4a N0/Nx (58 pts) T1 (54 pts)	Cisplatin+5-FU×2	55.8–59.4	No	88.4
Chung et al[47]	340	7.9 yrs	71 (35–91)	cT2–T4	Cisplatin (neoadjuvant CT+RT—57 pts, RT alone—247 pts)	Various	Yes—57 pts, No—283 pts	63.5
Hussain et al[48]	41	51 mos	68 (58–77)	cT2–T4a N0/Nx M0	MMC+5-FU×2	55	No	71
Rödel et al[14]	415	60 mos	67 (31–89)	cT1–T4a	Various (RT alone—126 pts)	Various	No	72

*At 5 years unless otherwise specified.

Salvage Cystectomy Rate	CSS Rate (%)*	OS Rate (%)*	MIBC Rate	NMIBC Rate	Local Recurrence Rate (%)	Pelvic Node Recurrence Rate	Metastatic Rate after CR (%)
6 (11.4%)	67	48	20 (11%)	26 (14.3)	18	9 (5)	Not stated
(25.8%)	Not stated	49	Not stated	Not stated	Not stated	9 (14.5)	39
8 (12%); FCT—3, GD—5	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	FCT—22, GD—16 at 3 yrs
100 (21%)	71	57	13% at 5 yrs, 14% at 10 yrs	31 at 5 yrs, 36 at 10 yrs	Any: 43 at 5 yrs, 48 at 10 yrs	13 at 5 yrs, 16 at 10 yrs	31 at 5 yrs, 35 at 10 yrs
17 (21%)	82	73	–	–	–	–	–
70 (30%)	WP— 47.1, BO— 46.9	WP— 53, BO— 51	WP—20 (57 %), BO—19 (54.3%)	WP—18 (19%), BO—19 (21%)	WP—41, BO—43	WP—5 (43%), BO—16 (46%)	WP—18, BO—18.5
4 (8%)	82 at 3 yrs	75 at 3 yrs	2 (4%)	3 (6%)	10	5 (10%)	4
10 (12.5%)	71	56	8 (12%)	7 (9%)	29	9 (11%)	31
15 (13%)	50	Not stated	11 (14%)	18 (16%)	26	Not stated	9
Not stated	62 at 3 yrs	59 at 3 yrs	2 (5%)	2 (5%)	10	Not stated	15
19 (21%)	81.4	67.1	3 (4%)	11 (15%)	15	Not stated	15
129 (27%)	66	57	76 (16%)	123 (26%)	42	57 (12%)	32
14 (7%)	80.9	59	9 (5%)	19 (10%)	19	Not stated	16
Not stated	Not stated	49	–	–	–	–	–
24 (20.2%)	73.5	67.7	18 (17.6%)	17 (16.7%)	29	Not stated	28
19 (17%)	82 (T2–T4—73)	74 (T2–T4—63)	11 (10%)	13 (12%)	24	Not stated	4
57 (17%)	42	32	50 (15%)	31 (9%)	24	Not stated	7
5 (12%)	68 at 2 yrs	36	2 (5%)	2 (5%)	10	Not stated	17
83 (20%)	56	51	32 (8%)	41 (10%)	26	10 (2%)	Not stated

relationship between CIS and response rates requires further evaluation as one should distinguish CIS found around a muscle invasive tumor and multifocal CIS.

Concurrent sensitizing chemotherapy has been demonstrated in randomized trials to improve outcomes for TMT compared to RT alone,[11] and the ability to tolerate chemotherapy is key. It is noteworthy that non-cisplatin based chemotherapy regimens are efficacious, especially in patients with impaired renal function, a common finding in this patient population.

As a conclusion, a complete TURBT is key in TMT. Indeed, radiotherapy works best on a minimal amount of microscopic residual cells rather than on bulky macroscopic tumors. TURBT is not a surrogate for staging (same for hydronephrosis), but rather because it is an integral part of TMT success. In our experience, 30% to 40% of patients are candidates for TMT, not a majority, but nevertheless a very substantial percentage.

Radiotherapy regimens and followup protocols. **Two main schedules of RT have been reported in TMT protocols—split and continuous.** The split course protocols were developed at Massachusetts General Hospital and adopted in the RTOG trials.[13,17] Induction RT (40–45 Gy) is delivered with concurrent chemotherapy. Following that, response is assessed by cystoscopy with tumor site biopsies. A consolidation chemo-RT (to full dose radiation of 64–66 Gy) is only given to patients with evidence of CR. The continuous course protocols were mainly used at the University of Erlangen[14] and other European institutions. Continuous protocols consist of RT to full dose (64–66 Gy) with concurrent chemotherapy after maximal TURBT. Endoscopic evaluation is performed once treatment is completed. Split protocols decrease the rate of bladder preservation by increasing salvage cystectomy rates. A recent systematic review and meta-analysis did not find significant differences in 5-year OS rates between both protocols, although the continuous protocol might have some advantages regarding CR and lower salvage cystectomy rates.[9] In Toronto, a very stringent protocol, including cystoscopies every 3 months for the first 2 years but without systematic biopsies, resulted in very comparable results.[7] Our followup protocol is shown in Appendix 2. Pathologists are notified that the urine collected is post radiotherapy and this seems useful for their interpretation. Scoping patients after TMT, however, clearly requires experience, and when in doubt, whether on cystoscopy or cytology, we biopsy any suspicious area.

The optimal radiation technique and dose have not yet been standardized. Several studies have focused on accelerated fractionation, but radiation fractionation has not provided a benefit with twice daily treatment compared to once daily fractionation.[17,19–21] In the RTOG 0712, the 2 arms included fluorouracil plus cisplatin+RT twice daily vs gemcitabine+RT once daily.[22] Toxicity and efficacy in the gemcitabine and once daily radiation were more favorable than 5-FU–cisplatin, where up to 65% of patients experienced a grade 3 or 4 related toxicity event. A prospective study reported acceptable toxicity rates in 18 patients receiving whole bladder RT (52 Gy)+tumor boost up to 70 Gy with image adaptation.[23]

Another area of controversy is the radiation field. It has previously been reported that up to 25% to 30% of cT2–T4 N0 patients undergoing RC have positive lymph node metastasis.[24] Moreover, in 12% of patients with locally advanced MIBC, common iliac lymph nodes could be affected.[25] Among node positive patients, 20% to 30% remain alive at 5-year followup. **These results may support the inclusion of pelvic lymph nodes in the radiation field due to understaging concerns.** Tunio et al showed no difference in bladder preservation, CSS and OS rates between whole-pelvis radiation and bladder-only technique covering the bladder with 2 cm margins.[26] It is noteworthy that both groups received cisplatin as radiosensitizer in this series. In addition, side effects were lower in the bladder-only protocol.

Similarly, James et al in their BC2001 trial did not include pelvic nodes in the radiation field, which included bladder plus 1.5 cm margin, reporting a 5% pelvic nodal recurrence rate.[11] Contemporary radiation protocols for bladder sparing in MIBC include bladder external beam RT (either once or twice a day) and limited pelvic lymph nodes to an initial dose of 40 Gy, with whole bladder boost of 54 Gy and a further tumor boost of 64 to 65 Gy.[4]

Most patients enrolled in the RTOG studies were treated with a 4-field technique. The field edge was placed typically 2 cm away from the bladder volume, which translates into a planning target volume of approximately 1 to 1.5 cm when the beam's penumbra margin is taken into account. Some centers use lipiodol, an agent injected around the base of the tumor resected at TURBT, visible on computerized tomography, to optimize targeting and delivery of radiation therapy as the bladder is mobile, as well as to minimize side effects by avoidance of irradiating normal tissue.[7]

Concurrent radiosensitizing chemotherapy. Concurrent chemotherapy is important to the success of TMT. Several active radiosensitizing drugs, including cisplatin, paclitaxel, 5-FU, MMC and low dose gemcitabine, have been shown to improve RT results. There is a lack of phase III trials comparing radiosensitizing agents in terms of safety and efficacy. **Most published trials have included cisplatin based protocols either alone or in combination with 5-FU and MMC or paclitaxel.**[8] It is well reported in NAC trials before cystectomy that up 50% of candidates may be unsuitable for cisplatin regimen therapies.[27] Age, comorbidities and hydronephrosis might be causes of impaired renal function in those patients. As a result, alternative radiosensitizing agents have emerged. The combination of MMC plus 5-FU concurrent with RT has shown significant improvement of locoregional disease control and lower rates of salvage cystectomy, without increasing the number of adverse events, compared to RT alone.[11] Gemcitabine is a good alternative as a radiosensitizer, as shown in phase I/II trials.[28–30] In addition, the RTOG 0712 trial, as previously mentioned, has demonstrated a CR rate of 78% for gemcitabine and once daily radiation with less toxicity than the 5-FU plus cisplatin and radiation twice a day arm.[22] The completion rates in these trials were 93% in the 5-FU/cisplatin vs 92% in the gemcitabine. Another concurrent chemotherapy regimen includes paclitaxel alone or combined with trastuzumab, described in the RTOG 0524 trial, with CR rates around 70% in both arms at 1-year followup.[31] Completion rates were similar.

Neoadjuvant/adjuvant chemotherapy. It has been shown that the addition of NAC before RC increased OS by 5% compared to RC alone.[32] However, its benefit prior to trimodality in the bladder sparing setting is still controversial. In nonrandomized studies, NAC followed by chemoradiation resulted in encouraging outcomes and tolerability in cisplatin eligible patients. In 57 patients with excellent Eastern Cooperative Oncology Group performance status and stage II disease (65%), stage III disease (25%) and regional nodal metastases (11%), 2-year disease-specific survival rate was 88% (95% CI 78.5–98.1).[33]

A randomized trial compared standard TMT protocol with the inclusion of 2 cycles of NAC.[12] No impact on OS, metastasis-free survival or CR rates was observed by adding NAC. Moreover, the trial was closed prematurely because of poor patient tolerance due to toxicity. A recent systematic review and meta-analysis by Fahmy et al reported similar results when NAC plus TMT was compared to TMT alone.[34] No significant differences were found between both groups in CR (76.2% vs 73%, p=0.33), 5-year CSS (72.4% vs 62.2%, p=0.13) or 5-year OS (53.8% vs 50.4%, p=0.078). Some authors have suggested a selection bias in favor of the TMT population.[8] The role of NAC in clinically localized MIBC (cT2) is currently not fully supported by the evidence in these subgroups.[35]

Some trials have included adjuvant chemotherapy after TMT in their protocols. As expected, there seems to be lower tolerability and completion rates than with NAC.[13] In addition, when adjuvant chemotherapy is used, grade 3 to 4 toxicity rates increased.[22,36,37] In 70 patients with cT2–4a MIBC randomly assigned to fluorouracil plus cisplatin and radiation twice a day or gemcitabine, adjuvant gemcitabine/cisplatin chemotherapy was administered. Although disease-free survival at 3 years reached 80%, toxicity was a concern. Of patients in the fluorouracil arm, 64% experienced treatment related grade 3 and 4 toxicities during protocol treatment, whereas in the gemcitabine arm, this figure was 55%. No phase III trials have been published that report on survival outcomes after adjuvant chemotherapy as primary end point in the TMT population. There is currently no clear established role for the use of NAC or adjuvant chemotherapy for improving survival or local control in TMT bladder sparing approach—some authors advocate a rationale toward its usage in suspicious node positive patients, but further studies are needed in this setting. However, NAC has been shown to have about a 5% benefit in RT patients, where its role is to eliminate metastatic disease, which concurrent chemotherapy with TMT is unlikely to be able to achieve. NAC is currently widely used for patients who are eligible.

ONCOLOGIC OUTCOMES

Medically inoperable patients. Few studies have evaluated the response to bladder sparing approaches of patients unfit for surgery. Hussain et al (SWOG 9312) evaluated 56 inoperable patients (34% with unresectable tumors, 21% unfit for surgery, 45% who refused cystectomy) who received TMT.[38] Overall, treatment was completed in 57% with a CR rate of 49%. The 5-year OS was 32% (20% for unresectable tumors, 31% for unfit patients, 45% for refusing cystectomy). Unfortunately, no detail on the cause of death was reported. Due to the heterogeneity of the above-mentioned population, most phase II/III trials include candidates with resectable disease and no medical contraindications to major surgery.

Radiation is highly efficacious in the treatment of symptoms such as hematuria, pain, and sometimes urgency and frequency if the cause is the tumor itself, but less so if the cause is underlying functional/physiological problems. In Toronto, we would treat medically inoperable patients with the same goal as appropriate medically operable patients and in the same manner. It should be stressed that because patients cannot have an operation (anesthesia or medical reasons), this does not mean that they should not benefit from a curative intent treatment with radiation±chemotherapy if they are deemed good candidates for TMT. Radiation is, therefore, not only used palliatively in medically inoperable patients. This is borne out by population data that show a significant portion of MIBC patients never get radiation (or surgery) after their diagnosis, sadly enough.[39,40]

Medically operable patients. CR after TMT has been defined in most series as "no visible tumor on cystoscopy, negative tumor site biopsy and negative urine cytology." Patients with cT2 disease had significantly higher rates of CR compared to cT3–T4a disease (83% vs 63%, p <0.001). In addition, patients who achieved CR after treatment had better OS rates compared to those who did not.[17] Reported CSS rates in published series are presented in table 1.[11-14,16,17,22,26,28,29,36,41–48]

Overall, 5-year CSS rates ranged from 42% to 82%. In a pooled analysis of various RTOG trials, 5-year and 10-year CSS rates of 71% and 65%, respectively, have been reported.[13] In another recent study, including the pooling of 8 different gemcitabine based protocols, 5-year CSS reached 80.9%.[29]

The 5-year OS was 50% in the current review, ranging from 32% to 74% (table 1). Among the different authors and institutions, there is a clear heterogeneity in terms of length and intensity of followup, patient selection criteria and treatment protocols—all aspects that could explain the wide range observed in CSS and OS rates.

Salvage cystectomy in trimodality is reserved for those patients who do not respond to treatment (immediate cystectomy) or develop an invasive recurrence during followup (delayed cystectomy). Literature review also shows a wide range of salvage cystectomy rates, between 7% and 27% (table 1), decreasing due to advancement in chemo-RT treatments and proper patient selection. The MGH group reported a dramatic reduction in risk of salvage cystectomy at 5 years during their 20-year followup (from 42% at the initial period to 16% in their last update).[17]

MIBC recurrence after CR achievement in the TMT series ranges between 4% and 57%. Over 80% of recurrences develop within the first 5 years. This speaks to patient selection criteria. Local recurrence rates within the bladder range between 10% and 43%, and pelvic node recurrence between 5% and 46%. Metastatic rates after CR vary between 4% and 39% (table 1). Of note, salvage cystectomy performed after CR in the MGH long-term series provided worst survival outcomes than early salvage cystectomy.[17]

NMIBC recurrences can also develop. Optimal management is not as clearly defined as it is for MIBC recurrence. Sanchez et al from MGH have recently retrospectively reviewed their outcomes in patients with NMIBC recurrences after CR to TMT.[49] **Of their cohort 342 patients achieved CR, while 85 (25%) developed a NMIBC recurrence after a median follow-up of 9 years.** Median time to recurrence was 1.8 years. A recent pooled analysis of different RTOG trials reported on the incidence of NMIBC recurrences as well (31% at 5 years and 36% at 10 years).[13] For the MGH group, the most frequent type of recurrence was pTis in 41% of cases, followed by pTa in 35% and pT1 in 20%. Eight patients (9%) were managed by immediate salvage cystectomy, 39 (46%) underwent a TURBT with intravesical BCG administration, 35 (41%) underwent TURBT alone, and 2 (2%) underwent TURBT with chemotherapy instillation with nephroureterectomy in 1 patient. It has previously been shown that TURBT plus intravesical BCG instillation is the most popular management for NMIBC recurrences following TMT.[50,51] However, in patients with baseline CIS, Sanchez et al reported an increased risk of NMIBC recurrence.[49] The

10-year CSS rate was slightly lower in patients with NMIBC recurrences (78.4% vs 72.1%, p=0.002). Conversely, 10-year OS was not significantly different among groups (43.6% vs 54.1%, p=0.66). Among 39 patients who received BCG 25 (64%) developed a recurrence. A 3-year recurrence-free survival and PFS after induction BCG of 59% and 63%, respectively, was reported. Of the patients 49% developed some form of toxicity during BCG induction, the most frequent being noninfective cystitis. Zietman et al, in a similar analysis, noted that CSS was not decreased by initial treatment (68% if TURBT and bladder instillation vs 69% in case of immediate salvage cystectomy).[51]

Weiss et al reported similar 10-year OS rates in patients with vs without NMIBC recurrences (72% vs 79%, p=0.78), but a decrease in survival was observed with recurrent NMIBC (50% vs 76% at 10 years, p <0.001).[50] Recent analysis from the Toronto group found a 21% NMIBC recurrence, treated conservatively. All data support that the management of NMIBC recurrences after TMT is similar to standard of care.

TRIMODALITY VS RADICAL CYSTECTOMY

Over the last decade, several retrospective series including TMT have suggested similar oncologic outcomes compared to RC in selected MIBC patients. Definitive comparisons are difficult because of the lack of randomized trials comparing both treatment approaches. The median age of patients undergoing RC is younger compared to those undergoing TMT (66 in our review). Direct comparisons are controversial as TMT studies include cT and cN instead of pT/pN. A well-recognized 15% to 30% upstaging at RC has been described in RC.[52]

The SPARE trial—designed in the United Kingdom—aimed to compare RC and TMT post-NAC. This multi-institutional, prospective, randomized trial included cT2–cT3 N0M0 patients with MIBC fit for either treatment option. The primary end point of the trial was to demonstrate the noninferiority of the TMT in terms of OS. Due to slow recruitment (45 patients randomized within 30 months) and frequent protocol deviations after randomization, the trial was stopped.[53]

Three meta-analyses have been published in the last 4 years, including the TMT vs RC comparison. Both include prospective and retrospective studies. Over 13,000 patients between 1990 and 2013 were included in the first one published in 2015.[54] The 5-year OS was 57% for TMT and 52% for RC (p=0.04). However, when patients receiving RC and chemotherapy (current standard of care) were included, a 53% 5-year OS was observed (p=0.38). Thus, the results were unable to provide support for any inferiority. **In a more recent meta-analysis, Vashistha et al found no differences in 5- and 10-year OS, CSS and PFS rates between TMT and RC.**[55] This meta-analysis included patients until 2016 with more recent treatment techniques.

Lastly, Wettstein et al have published a rigorous systematic review and meta-analysis on survival outcomes among MIBC patients treated with either TMT or RC.[56] Only 12 studies were finally included for analysis. The pooled results were significantly in favor of RC. However, the authors highlight that results might be driven by large, population based studies. Further research is clearly needed.

As per the above-mentioned issues with direct comparisons, propensity score matching analyses have been published in the literature aiming to control for confounding factors within cohorts. The Fox Chase group analyzed the National Cancer Database, including patients with stage II to III MIBC between 2004 and 2013.[57] The 5-year OS was 48.3% in the RC group vs 29.9% after TMT. RC benefits in OS, compared to TMT, were attenuated when confounding factors were controlled for. Kulkarni et al reported results after propensity score analysis in the Toronto Multidisciplinary Bladder Cancer Clinic.[7] At the time of analysis, extent of TURBT, presence of hydronephrosis, presence of CIS and comorbidities were taken into account. A total of 112 MIBC patients were included after matching. With a median followup of 4.5 years, 5-year CSS was similar between groups (76.6% vs 73.2%). The salvage cystectomy rate in the TMT group was 10.7%. Limitations include the fact that it is a single institution study as well as its retrospective selection bias.

To date, published data comparing TMT and RC should be interpreted with caution due to inherent bias in retrospective comparative studies. Proper RCTs are needed to settle the issue, but unfortunately it does not seem that any is likely to be launched in the near future.

Toxicity and quality of life. TMT aims to preserve the bladder. However, this treatment strategy is not without short- and long-term toxicities. Table 2 summarizes long-term grade 3 to 4 toxicity rates after TMT. We use the Common Terminology Criteria for Adverse Events version 5 terminology.[58] Gastrointestinal toxicity grade 3 ranged between 0.5% and 16%, and similarly for genitourinary toxicity grade 3 (1% to 24%). Very few cystectomies were performed due to toxic side effects. Completion treatment rates average between 80% and 90% depending on the series. Late grade 3 to 4 toxicity rates ranged from 3% to 8% of patients.[11,14]

The major potential benefit of bladder preservation has been improving QoL while preserving bladder function. Unfortunately, out of the several retrospective and prospective series published, very few have performed qualitative evaluation of QoL outcomes through validated questionnaires in patients undergoing TMT protocols. A single institution study has evaluated long-term survivors after TMT.[59] A total of 32 patients underwent urodynamic studies (75% rated as within normal limits) and 48 completed the QoL questionnaires (20% with urinary incontinence, 15% with urinary urgency, 22% with bowel symptoms and 54% with reported erections for intercourse). Similarly, Herman et al published a prospective trial also confirming good bladder functional outcomes after gemcitabine based trimodality.[60] A cross-sectional study by Mak et al compared QoL in survivors of MIBC between those who underwent RC (109 patients) and those who received a TMT bladder sparing approach (64).[61] A total of 6 QoL validated instruments were used. At a median followup of 5.6 years, patients who received TMT had better overall general QoL (by 9.7 points); better physical, socio-emotional and cognitive functions and improved bowel, sexual function and impaired body image. These data support TMT as a good alternative to RC in selected patients. However, they represent a snapshot only of current cohorts.

A French phase II trial prospectively included 53 patients receiving TMT.[62] Patients were assessed for QoL (EORTC QLQ-C30) at baseline and at 6, 12, 24 and 36 months. At 8-year followup, satisfactory bladder function was observed in 67%. This trial reported the only available QoL data that provides a questionnaire timeline analysis. In summary, patient reported outcomes and quality of life are very important end points to report when assessing MIBC treatment options. In Toronto, we use the relatively new Bladder Utility Symptom Scale, which is simple and straightforward for patients and clinicians.[63]

Table 2. Toxicity rates associated with TMT for MIBC

References	No. Pts	Followup	Completion Rates (%)	Gastrointestinal Toxicity Grade 3–4 Immediate/Late	Genitourinary Toxicity Grade 3–4 Immediate/Late	Global Late Toxicity Grade 3–4	Salvage Cystectomy Rate Due to Toxicity (%)
Coen et al[22]	66	5.1 yrs	FCT—93, GD—92	FCT—2 (6%), GD—3 (9%)	FCT—2 (6%), GD—2 (6%)	FCT—8 (25%), GD—5 (16%)	Not stated
Büchser et al[16]	90	94 mos	Not stated	Not stated/6 (7%) grade ≥2	Not stated/22 (24%) grade ≥2		1
Caffo et al[29]	190	44.5 mos	Not stated	20 (10%)/1 (0.5%)	7 (4%)/5 (3%)		Not stated
James et al[11]	182	70 mos	80.2	17 (9.6)/not stated	38 (21.3%)/not stated	10 (8.3%)	Not stated
Zapatero et al[41]	80	72 mos	Not stated	Not stated/5 (16%) grade ≥2	Not stated/18 (22%) grade ≥2		Not stated
Tunio et al[26]	230	5 yrs	WP—93, BO—96	WP—8 (8%)/1 (1%), BO—5 (5%)/0 (0%)	WP—3 (3%)/2 (2%), BO—2 (2%)/1 (1%)		Not stated
Choudhury et al[28]	50	36 mos	92	Not stated	Not stated		2
Kaufman et al[36]	80	49.4 mos	70	Induction 12 (15%), consolidation 4 (5%)/0 (0%)	Induction 3 (4%), consolidation 2 (2%)/3 (4%)		Not stated
Perdonà et al[45]	121	66 mos	95	15 (12.4%)/2 (2%)	14 (11.5%)/4 (3%)		0.8
Weiss et al[46]	112	27 mos	87	34 (30%)/2 (1.4%)	9 (8%)/11 (9%)		1
Gogna et al[42]	113	23 mos	88.5	Not stated/2 (2%)	4 (3.5%)/5 (4%)		0
Hussain et al[48]	41	51 mos	85	4 (10%)/not stated	1 (2%)/not stated		0
Rödel et al[14]	415	60 mos	68	21 (5%)/6 (1.5%)	21 (5%)/5 (3%)		2
Shipley et al[12]	62	60 mos	81	Not stated/3 (5%)	Renal not stated/1 (2%), bladder not stated/5 (8%)		Not stated

Table 3. Ongoing clinical trials including immune checkpoint inhibitors

	No. Pts	Inclusion Criteria	Combination	Primary End Point	Secondary End Point	Expected Date of Accrual
Pembrolizumab:						
NCT02662062	30	cT2–4a TCC, Nx or N0	Pembrolizumab+ cisplatin+RT	% Pts with grade 3 and 4	Efficacy of adding pembrolizumab to standard of care TMT, % pts with metastases, % pts with salvage cystectomy	2024
NCT02621151	54	cT2–T4a TCC N0 M0 TCC	Pembrolizumab+ gemcitabine+RT	Bladder intact disease-free survival at 2 yrs	Safety, CR rates, OS, metastasis-free survival	2026
Durvalumab:						
NCT 03702179 (IMMUNOPRESERVE)	32	cT2–T4a TCC	Durvalumab+ tremelimumab+ RT	% Pts with pathology response	% Pts with bladder preserved at 24 mos, % with salvage cystectomy, disease-free survival, OS, treatment related events	2022
NCT02891161	42	cT3–4N0-2 M0; cTxN1-2M0; cT2N1-2 M0	Durvalumab+RT+adjuvant durvalumab	Dose limiting toxicity, PFS, disease control rate	CR rates, OS, PD-L1 expression	2019
Nivolumab:						
NCT03421652 (NUTRA)	34	cT2–4b N0-1	Nivolumab+RT	PFS	Adverse events, response rate, metastasis-free survival, OS	2020
NCT03171025 (NEXT)	28	cT2–T4a N0 or N+M0; T1 with N+	Adjuvant nivolumab after TMT	Failure-free survival at 2 yrs (locoregional recurrence and distant)	Failure-free survival at 2 yrs	2024
NCT03529890 (RACE IT)	33	cT2–T4 N0	Nivolumab+RT- radical cystectomy	Rate pts who completed at least 2 cycles	Acute toxicity preop, immunorelated toxicities	2022
Avelumab:						
NCT03617913	27	cT2–4a N0M0 TCC	Avelumab+5-FU/MMC/ cisplatin+RT	CR	Adverse events, EORTC-QLQ-30/ BLM 30, PFS, recurrence-free survival	2025
NCT03747419	24	>cT2 TCC cisplatin ineligible	Avelumab+RT	CR at 3 mos	OS, PFS, metastasis-free survival	2021

Molecular markers in TMT. Recent major advances in understanding the molecular landscape of MIBC have led to the identification of new predictive biomarkers that may help guide therapy based on the biology of the tumor. MIBC has been stratified into several molecular subtypes, which could serve for therapeutic selection.[64] In bladder preservation therapy, molecular alterations and genomic signatures as prognostic or predictive biomarkers have also been studied as, similar to radical cystectomy, standard clinicopathological features are often insufficient to accurately predict outcomes or guide therapeutic choices.[65]

DNA repair genes MRE11 or ERCC2, signal transduction genes like EGFR or HER2 immune checkpoint biomarkers like PD-L1, hypoxia or immunological signatures have been studied as prognostic or predictive markers of response to TMT/radiotherapy in MIBC. As an example, the double-strand break repair MRE11 protein (when expression is increased on immunohistochemical staining) leads to decreased DNA repair capacity, and therefore increased radiation sensitivity and subsequently better disease-specific survival. Tumor ERCC mutations lead to decreased nucleotide excision repair capacity but increased cisplatin chemoradiation sensitivity.

Several planned or ongoing clinical trials of bladder preservation therapy for MIBC have incorporated molecular biomarkers into their trial design. The SWOG S1806 trial will randomly assign patients with muscle invasive bladder cancer to chemoradiation with or without the anti-PD-L1 checkpoint inhibitor atezolizumab, and will include transcriptional profiling and comprehensive genomic analysis of all samples.[66]

Very few data have been published on biomarkers in TMT patients. The MGH group reported on the prognostic value of immune and stromal infiltration in MIBC treated with TMT.[67] A higher immune infiltration was associated with better disease specific survival, whereas after NAC and RC the opposite effect is seen.

Studies to determine if treatment response can be predicted by gene expression profiling should be encouraged. Several novel systemic therapies are currently being tested, either monoclonal antibodies or immune checkpoint inhibitors. The recently published phase I/II RCT RTOG 0524 evaluated the addition of trastuzumab to paclitaxel in patients with her2/neu positive MIBC as a radiosensitizing agent.[31] Phase I/II trials are currently accruing patients with MIBC on TMT protocols. Table 3 illustrates some of the ongoing clinical trials including immune checkpoint inhibitors.[68–70]

The underlying biological rationale is that radiotherapy may enhance the generation of antigen specific immune responses. Checkpoint blockage immunotherapy added to radiation has improved local control in different tumor types.[71]

While radiotherapy might stimulate the induction of local immune responses by anti-PD-1 treatment, active immune stimulation within the tumor microenvironment might maximize radiation induced antitumor immunity. Radiotherapy might increase response rates by creating a more permissive tumor microenvironment through increasing PD-L1 expression on tumor cells and the accumulation of activated effector cells. In the NMIBC space, combination therapy using PD-1/PD-L1 blockade with radiotherapy has been proposed in BCG unresponsive tumors.[72] Several clinical trials such as the ADAPT-BLADDER trial, the BTCRC-GU15-023 study[73] and the NCT03775265 (SWOG/NRG 1806) study are underway that include different immune checkpoint inhibitors.[74]

CONCLUSIONS

TMT, consisting of maximum transurethral bladder tumor resection followed by radiotherapy with concurrent chemotherapy, has emerged as the most robust bladder sparing approach. No randomized studies comparing radical cystectomy and TMT are available. However, nonrandomized studies performed in carefully selected patients with MIBC suggest that the 2 treatment options may provide similar long-term outcomes while maintaining an excellent quality of life. Proper patient selection is key for TMT success. The best candidates for TMT are patients with low volume T2 tumors, no or minimal unilateral hydronephrosis, no extensive multifocal CIS and good bladder function. Biomarkers studies could identify subgroups of patients more likely to benefit. They could also guide the use of combination therapies, including targeted therapies or immunotherapy, which might act synergistically with radiotherapy.

Like any treatment, TMT is not without limitations. These include the risk of bladder recurrences (although often non-muscle invasive and manageable conservatively) requiring a stringent and frequent followup, and progression of the disease outside of the retained bladder. Optimizing chemo-RT regimens and establishing the role of NAC within the current TMT protocols remain unmet needs.

MIBC management is rapidly changing and data on bladder sparing approaches are accumulating. Even the cost-effectiveness of RC vs TMT is now scrutinized in our financially constrained times.[75]

DID YOU KNOW?

- Bladder preservation strategies should include trimodal therapy with complete TURBT, concurrent radiosensitizing chemotherapy and pelvic radiation (split or continuous).
- Patient selection for bladder preservation strategies is key to optimizing patient outcomes.
- Comparisons between RC and TMT seem to provide a noninferiority survival perspective.
- Quality of life of patients with TMT is currently poorly assessed, which precludes further conclusions.

Appendix 1. Clinical features for ideal TMT candidates

cT2–cT3
No hydronephrosis or minimal unilateral hydronephrosis
No multifocal CIS
Unifocal tumor <7 cm
Complete TURBT
Good bladder function and capacity

Appendix 2. Example of Toronto followup schedule post-TMT

End of TMT	3 Mos	6 Mos	9 Mos	12 Mos
Yr 1	Cysto+CT A/P/chest, bone scan	Cysto+CT A/P/chest	Cysto	Cysto+CT A/P/chest
Yr 2	Cysto	Cysto+CT A/P/chest	Cysto	Cysto+CT A/P/chest
Yr 3		Cysto		Cysto+CT A/P+chest x-ray
Yr 4		Cysto		Cysto+CT A/P+chest x-ray
Yr 5		Cysto		Cysto + CT A/P+chest x-ray

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Study Questions Volume 40 Lesson 7

1. A 76-year-old otherwise healthy diabetic woman with a creatinine of 1.8 mg/dl with gross hematuria presents with a 5 cm bladder tumor and positive cytology. She undergoes a visibly complete TURBT and the pathology shows a high grade tumor with muscle invasion as well as multifocal CIS. She does not want to undergo cystectomy. The clinical feature that increases her risk of recurrence if she were treated with TMT is
   a. >75 years of age
   b. creatinine 1.8 mg/dl
   c. CIS
   d. tumor size

2. The average radiation dose applied to the bladder and pelvis during TMT for bladder preservation is
   a. 45 Gy
   b. 55 Gy
   c. 67 Gy
   d. 75 Gy

3. The ideal radiation technique and dose in terms of improved oncologic outcomes and reduced toxicity for TMT is
   a. not yet determined
   b. a split schedule
   c. accelerated fractionation
   d. whole-pelvis radiation

4. The most common reason for salvage cystectomy after TMT for curative intent is
   a. hematuria
   b. overactive bladder syndrome
   c. MIBC recurrence
   d. salvage cystectomy is never performed after TMT

5. A 66-year-old man is noted on surveillance cystoscopy 1 year after TMT for MIBC to have a <5 mm solitary papillary tumor not at the site of any prior resection. Urine cytology is negative for malignant cells. The next step is
   a. surveillance
   b. TURBT
   c. TURBT and BCG instillation
   d. radical cystectomy