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Position Paper

Eligibility and Endpoints for Clinical Trials in Trimodality Therapy for Bladder Cancer

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Abstract.
BACKGROUND: Trimodality therapy (TMT) is a viable option for muscle-invasive localized bladder cancer, providing an alternative to radical cystectomy in properly selected patients. The approval of novel therapeutics in different stages of bladder cancer treatment has sparked interest in exploring concurrent systemic therapies with radiation in clinical trials to enhance long-term outcomes. Achieving uniformity in trial eligibility criteria and endpoint definitions is imperative in describing clinical significance, comparing trials, and changing standard of care guidelines.
OBJECTIVE: To delineate eligibility criteria and appropriate endpoints for TMT clinical trials in an attempt to achieve uniformity in trial eligibility criteria and endpoint definitions. This will help move the field of bladder preservation forward and improve the current standard of care.
METHODS: An expert panel, comprising individuals with extensive experience in bladder cancer clinical trials, clinical practice focused on bladder cancer treatment, and patient advocacy, was assembled. The panel systematically reviewed phase II/III clinical trials previously published and assessing the role of radiation in definitive therapy with the specific goal of preserving native bladder function during bladder cancer treatment. Recommendations were summarized based on review of these trials and past experiences of the investigators. To ensure a holistic perspective, the summary was further subjected to rigorous reevaluation by a patient advocate, who added valuable insights from a patient's standpoint. The resulting consensus statements were summarized in this publication to contribute to the evolving landscape of bladder cancer research and treatment.

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RESULTS: The eligibility criteria for TMT should be pragmatic to encompass patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, bladder cancer stage T2-T4a N0 ± N1M0, unilateral tumor-associated hydronephrosis, attempted maximal transurethral resection of bladder tumor (TURBT), both pure urothelial carcinoma and/or mixed histologic subtypes (excluding rare and aggressive small cell variants) and patients who are non- cystectomy candidates. Bladder intact event-free survival (BIEFS) is proposed as a suitable endpoint for registration trials designed to compare two different treatment interventions, defined as the time from randomization to muscle-invasive or locoregional recurrence, systemic recurrence, radical cystectomy from any cause, or death from any cause. Overall survival is deemed an appropriate secondary endpoint or a co-primary end point as recent improvements in systemic therapy can produce significant improvement in long-term outcomes. Primary and secondary endpoints should be supported with patient-reported quality of life assessments, when available.

CONCLUSIONS: The standardization of clinical trial design, eligibility criteria, and endpoints is essential for expediting progress in the field. Inclusivity, patient-centricity, and clinically meaningful endpoints will facilitate the analysis, comparison, and meta-analysis of different trials, fostering advancements in bladder cancer treatment.

BACKGROUND

Bladder cancer poses a significant health burden in the United States, with over 80,000 new diagnoses annually with a median age at diagnosis of 73 years [1, 2]. Despite the potential lethality of the disease, treatment patterns in the community reveal a gap in the administration of aggressive and potentially curative therapy to a substantial number of patients. Trimodality therapy (TMT) is emerging as a favorable option not only for patients who are poor surgical or chemotherapy candidates, but also for patients who choose to preserve their native bladder function and want to avoid major life altering surgeries with potential negative impacts on quality of life, sexual and bowel function.

Previous efforts at randomized clinical trials comparing radical cystectomy (RC) to TMT faced many obstacles [3]. Challenges to a randomized trial include patient acceptance of randomization between two very divergent treatment pathways and patient preference for bladder preservation. The decision criteria for suitability for these options are also very distinct. In the absence of a feasible randomized trial, we have high-quality retrospective data from a large, multi-institution propensity score matched and weighted analysis showing in well-selected patients treated at high volume specialty care centers, TMT and RC have similar oncologic outcomes (distant metastasis free survival, cancer specific survival and disease-free survival) [4]. Further, both neoadjuvant chemotherapy followed by radical cystectomy (NAC+RC) or TMT alone are strongly supported by prospective Phase 2 and randomized Phase 3 trials demonstrating favorable long-term outcomes, although not comparative against each other [5–7]. Both of these options (NAC+RC or TMT alone) are now accepted as category I recommendation by National Comprehensive Cancer Network (NCCN) guidelines for patients with stage II and IIIA MIBC.

Past trials exploring TMT had varying eligibility criteria and endpoints, hindering meaningful cross-trial comparisons. This article examines the evolution of eligibility criteria across previous clinical trials, their diverse endpoints, and provides summarized recommendations for future clinical trial designs.

ELIGIBILITY IN CLINICAL TRIALS EVALUATING SYSTEMIC THERAPY COMBINATION WITH TRIMODALITY THERAPY

The goal of eligibility criteria should be to make the trial pragmatic, applicable to the population of patients we serve in our clinic and help facilitate accrual. Clearly, they should bring uniformity to the patient population studied, but at the same time, should not act as an impediment to the enrollment and access to life saving treatment [8] (Tables 1 and 2).

Stage

Prior clinical trials have identified optimal candidates for trimodality therapy as those with clinical stage T2-T4aN0Mo muscle invasive bladder cancer. The risk of micrometastatic disease escalates with higher stage, and patients with node-positive

Table 1
Key eligibility criteria for various clinical trials

Clinical trial	Design/ phase	T stage N (%)			Hydrone-phrosis (%)	TURBT N (%)		Node positive allowed	CIS: N (%)	NAC: N (%)	AC: N (%)	ECOG (%)
		T1	T2	T3/T4		Complete	Incomplete					0, 1 vs 2
RTOG 85-12, 1993 [49]	II	0 (0)	12 (25)	36 (75)	NA	NA	48 (100)	Yes	NA	NA	NA	88 vs 12
RTOG-8802, 1996 [50]	II	0 (0)	22 (24)	69 (76)	20	NA	91 (100)	Yes	NA	91 (100)	No	93 vs 7
RTOG 89-03, 1998 [25]	III	0 (0)	47 (38.2)	76 (61.7)	20	88 (71.5)	35 (28.4)	Yes	NA	Yes	No	NA
RTOG 95-06, 2000 [44]	I/II	0 (0)	26 (76.0)	8 (23.5)	Excluded	26 (76.5)	7 (20.6)	No	No	No	No	NA
RTOG 97-06, 2003 [51]	I/II	0	30 (65.2)	16 (34.8)	Excluded	46 (100)	0 (0)	No	No	No	57	100 vs 0
RTOG 99-06, 2009 [43]	I/II	0 (0)	70 (88)	10 (12)	Excluded	NA	NA	No	No	No	80 (100)	100 vs 0
BCON, 2010 [29]	II	30 (9.2)	214 (65.4)	82 (25.1)	No	126 (38.5)	201 (61.5)	No	NA	NA	NA	NA
BC 2001, 2012 [7]	III	1 (0.3)	297 (82.5)	61 (16.9)	NA	239 (66.4)	100 (27.8)	No	No	118 (32.8)	NA	97 vs 3
RTOG 0233, 2013 [27]	II	0 (0)	88 (94)	5 (6)	NA	93 (100)	0 (0)	No	No	NA	54 (58)	100 vs 0
Giacalone et al., 2017 [15] (MGH experience)	Retro-spective study	0 (0)	317 (66)	158 (33.3)	57 (12.0)	332 (69)	143 (30)	No	116 (24.4)	118 (24.8)	215 (45.2)	NA
RTOG-0712, 2019 [28]	II	0 (0)	64 (97.0)	2 (3.0)	Excluded	NA	NA	No	NA	NA	66 (100)	100 vs 0
Zlotta et al, 2023 [4] (Toronto/MGH/USC experience)	Retro-spective study	0 (0)	1010 (90.3)	109 (9.8)	124 (11.1)	282 (100)	0 (0)	No	223 (79)	159 (56)	NA	77* vs. 23*

Abbreviations: TURBT: Transurethral resection of bladder, CIS: Carcinoma in situ, NAC: Neo-adjuvant chemotherapy, AC: Adjuvant chemotherapy, NA: Not available, N: Number of participants.
*77% of patients had performance status score of 0 compared to 23% who had performance status score of either 1 or 2.

Table 2
Recommended eligibility criteria for future clinical trials evaluating systemic therapy combination with trimodality therapy

Endpoint	Definition
Stage	Clinical stage T2-T4, N0, M0 based on cross sectional imaging preferred MRI, TURBT and examination under anesthesia. N1 patient can be included in clinical trial evaluating neoadjuvant therapy with suitable comparator arm.
Hydronephrosis	Patients with tumor associated unilateral hydronephrosis which is treated should be allowed to enroll.
Neoadjuvant/Adjuvant chemotherapy	Can be allowed if this is a predefined stratification factor
Maximal TURBT	Patients must have maximal TURBT within 70 days of randomization.
Carcinoma in Situ	Patients with diffuse CIS should be excluded. Tumor associated focal CIS is a common occurrence and should not be an exclusion
Kidney function (GFR limits)	Patients with GFR limit >25 ml/min should be eligible
Performance status	ECOG performance status of <2 should be allowed for enrollment.
Histology	Patients with mixed urothelial with squamous/adenocarcinoma/ sarcomatoid/plasmacytoid histology should be allowed. Small cell carcinoma should be excluded.

Abbreviations: TURBT: Transurethral Resection of Bladder Tumor, ECOG: Eastern Cooperative Oncology Group, GFR: Glomerular Filtration Rate, CIS: Carcinoma in Situ, N0: No lymph node metastasis, M0: No distant metastasis, N1: Metastasis in lymph node.

disease are deemed more appropriate for systemic chemotherapy options [6, 9]. This section explores the complexities of staging in determining clinical trial eligibility and provides our recommendations based on these findings.

Staging procedures

Traditional staging procedures for clinical staging of bladder cancer often suffer from high rates of both under- and over-staging [10, 11]. Therefore, we strongly advocate for a comprehensive approach that includes examination under anesthesia, cross-sectional imaging (preferably with MRI), and cystoscopic evaluation. For male patients, biopsy of the prostatic urethra is essential to exclude carcinoma in situ as part of the clinical staging process. We recognize that these procedures are not routinely followed and that pragmatic trials may face eligibility challenges if these are mandated for inclusion. However, the protocol should strongly recommend these procedures, as this will help bring about practice change over time. Additionally, microscopic confirmation of the presence of muscularis propria in the specimen should be mandatory.

Role of MRI

Multi-parametric MRI can aid in more accurate T staging and identifying N1 patients, thus appropriately stratifying or excluding these patients during enrollment [12]. The nuances, pitfalls, and accessibility of using MRI in a clinical trial setting are outside the scope of this article. However, it is important to note that the best time to perform an MRI is prior to the TURBT or at 8 weeks after the procedure. Additionally, the recommended bladder filling of 300 ml is crucial for the most accurate assessment [13]. We also acknowledge the possibility of stage migration with increased use of MRI for clinical staging and radiation planning in future studies.

T2 vs T3/T4

The percentage of patients with cT3-cT4a disease enrolled in TMT trials is less than those with cT2 disease; from the pooled analysis of NRG/RTOG TMT trials 39% had cT3-T4a disease, similarly the pooled MGH TMT data which showed 34% with cT3-T4a disease [14, 15]. Patients requiring a salvage cystectomy following TMT had a higher proportion of cT3-T4a disease, however these patients had a significantly higher rate of initial incomplete TURBT, which likely leads to worse local control [15]. This could also reflect inherent complexity of achieving complete TURBT in patients with cT3-T4a disease. Zlotta, et al reported that oncologic outcomes in patients with both cT2 and cT3-4a disease were not different between RC and TMT. However, their analysis excluded patients with multiple tumors and size larger than 7 cm but included patients with hydronephrosis. The number of T4a alone patients was very small to draw any meaningful conclusions in the highest risk subgroup [16]. We recommend enrolling patients with clinical T stage T2-T4a in trials evaluating muscle invasive bladder cancer.

N0 vs N1

The ECOG-ACRIN INSPIRE trial (EA8185), a phase II study of bladder preserving chemoradiation with durvalumab in clinical stage III, node-positive bladder cancer patients, was the first randomized trial to evaluate TMT in clinical node-positive patients.

Unfortunately, this trial closed early due to poor accrual. Retrospective data on TMT in patients with clinical node-positive bladder cancer treated with curative intent showed no difference in OS or PFS between RC and TMT [17]. Node-positive patients had been traditionally excluded from neoadjuvant chemotherapy prior to radical cystectomy trials [5, 6, 18]. Retrospective data from the National Cancer Database (NCDB) demonstrates inferior long-term outcomes for patients undergoing radical cystectomy with clinically node-positive disease who are not pathologically N0 after neoadjuvant chemotherapy [19]. In a suitable design N1 patients can potentially be enrolled in a clinical trial for bladder preservation.

Stage T1

Another area of interest is exploring TMT in patients with high risk T1 non-muscle invasive bladder cancer. There is emerging data to support the use of TMT in select patients with non-muscle invasive disease [20, 21]. The NRG/RTOG 0926 trial evaluated TMT in patients with recurrent high-grade T1 urothelial carcinoma who would otherwise be treated off-trial with salvage cystectomy. In this study of 37 patients, the trial met its prespecified endpoint of cystectomy-free survival, with a 3-year freedom from cystectomy of 88% [22]. NRG GU 014 is a new trial that will be evaluating standard TMT vs. radiation plus pembrolizumab in patients with high-grade T1 disease (recurrent or de novo) as an alternative to cystectomy in patients who meet AUA/SUO guidelines for cystectomy [23].

As we evaluate novel treatment options into the curative treatment of muscle-invasive bladder cancer (immunotherapy or antibody drug conjugates and their combination), trials should continue to include patients with T3/T4 disease. For trials aiming to enhance systemic control in addition to local control it may be appropriate to enroll patients with N1 disease if there is an acceptable comparator arm and patients are stratified by clinical N status. Patients with upper tract disease should be excluded unless they were stage <T1 and or are in remission for two years.

We recommend using clinical stage (T2 vs T3/T4) as a predefined stratification factor in any randomized trial, thus enabling subsequent subset analyses of outcomes in higher-stage patients. Since, higher stage population has poor long-term survival due to regional and distant recurrence regardless of definitive treatment modality [15]. Clinical trials in stage T1 bladder cancer are relatively new area of investigation and therefore we recommend investigators align eligibility with latest AUA/SUO guidelines.

Hydronephrosis

Hydronephrosis had been shown to negatively impact disease-specific survival, overall survival, and Bladder Intact Disease-Free Survival (BIDFS) leading to the exclusion of such patients from trial enrollment beginning with RTOG 9506 [15, 24–26]. A potential explanation for these findings lies in reduced complete response rates due to the tumor's bulk, difficulty in complete resection due to proximity to ureteral orifice and compromised renal function, posing challenges for patients to receive cisplatin-based chemotherapy.

It is, however, recognized that many patients may have baseline unilateral hydronephrosis due to bladder tumor obstructing the ureteral orifice, and this may improve after resection. Therefore, with advancements in transurethral resection of bladder tumor (TURBT) techniques, improved completeness of resection, and progress in radiation therapy (utilizing Intensity-Modulated Radiation Therapy - IMRT and Image-Guided Radiation Therapy - IGRT), coupled with the availability of newer chemotherapy options for patients with compromised renal function (such as 5FU/mitomycin and gemcitabine), eligibility criteria on bladder preservation trials have been expanded to include patients with treated hydronephrosis [7, 16, 27–29]. We recommend excluding patients with bilateral hydronephrosis from trials not offering neoadjuvant chemotherapy as the perceived risk of systemic disease is very high in this patient population [30, 31].

The recent ongoing clinical trials, SWOG/NRG S1806 (randomized clinical trial comparing bladder preservation with CRT vs CRT plus atezolizumab/NCT03775265) and Keynote 992 (randomized trial comparing bladder preservation with CRT vs CRT plus pembrolizumab/NCT04241185/KN 992), have taken a progressive approach by actively enrolling patients with treated unilateral hydronephrosis, setting a precedent for future trials to include this condition as part of their eligibility criteria. We recommend the inclusion of patients with unilateral hydronephrosis in clinical trials.

Neoadjuvant or adjuvant chemotherapy

Despite randomized trials and meta-analyses showing a 5% OS benefit to neoadjuvant chemother-

apy (NAC) prior to RC, early RTOG trials showed no benefit to NAC in combination with TMT and even harm with treatment related deaths. The MRC trial showed 6% overall survival if NAC was given prior to any definitive therapy (RC or RT alone) however it failed to show any improvement in locoregional disease-free survival and no improvement in rate of salvage cystectomy after RT [32]. RTOG 8903 randomized patients to TMT with or without NAC; despite closing early due to unexpected rates of neutropenia, there was no benefit to 2 cycles of MCV NAC prior to TMT [25]. Retrospective analysis from the NCDB has also shown no association of NAC with overall survival in patient treated with RT (HR 1.01; $p = 0.921$) [33]. Moreover, data from Zlotta et al showed that neoadjuvant or adjuvant chemotherapy did not significantly affect MFS rates in patients treated with TMT [4]. That being said, a retrospective experience has shown good efficacy and tolerability with neoadjuvant cisplatin based chemotherapy prior to TMT [34]. The rationale behind this lies in the potential to eliminate micrometastatic disease, especially in more advanced stages such as T3/T4. Notably, evidence from neoadjuvant chemotherapy (NAC) trials in radical cystectomy has shown an overall survival benefit of 5–10% vs radical cystectomy alone, [35] which was primarily driven by benefit observed in higher stage patients. Historically, the distribution of T2 versus T3/T4 patients in TMT clinical trials or series has typically been around 80% versus 20%, respectively. This disproportion may potentially contribute to the observed lack of benefit with neoadjuvant or adjuvant chemotherapy, leaving this question unanswered. An informal online survey was conducted during the SWOG spring meeting (2017) within the Genito-urinary committee regarding the use of neoadjuvant chemotherapy (NAC) prior to trimodality therapy (TMT). Out of 37 members who responded to the questionnaire, 10 (27%) of the investigators routinely use NAC, 12 (32%) sometimes use NAC based on clinical judgment, and 15 (40%) do not use NAC at all. Due to the inconsistency in the use of NAC among this group of investigators, who reflect the choices of treating physicians at comprehensive cancer centers, academic institutions, and community oncology practices, and the conflicting published data, we do not mandate the use of NAC in clinical trials evaluating TMT.

If allowing standard NAC or AC as part of study design, then we recommend that it should be a stratification factor. We recommend further investigation in this area, exploring the use of novel chemotherapy, immunotherapy, or combination, considering their demonstrated clinical benefits in patients treated with radical cystectomy and in patients with locally advanced or metastatic disease. Inclusion criteria for such studies should be uniform.

Role of maximal transurethral resection of the bladder tumor

Transurethral resection of the tumor (TURBT) is a critical component of TMT. In long term outcomes of NRG/RTOG trials and large institutional experiences, visibly complete TURBT was associated with increased disease specific survival and overall survival but only on univariate analysis. The benefit was lost in multivariate analysis. However, visibly complete TURBT was associated with improved complete response rates [36]. This could be a result of previously reported pathologic T0 rates of 10–15% for patients treated with RC and no NAC, one must account for this in the design of TMT trials as a so-called radical TURBT itself may be curative. Long term experience from MGH also demonstrated higher rates of salvage cystectomy in patients who had T3/T4 disease (43% vs 30%, $p = 0.007$) and in patients who had incomplete TURBT (43% vs 24%, $p < 0.001$); yet these data also demonstrate that even for patients with T3/T4 disease, disease specific survival was close to 50% at 5 years. BC2001 and MRC trials allowed patients with simple biopsy, incomplete resection, and complete resection to be enrolled on the study. SWOG/NRG S1806 and KN 992 allows patients with TURBT into the muscle which is either characterized by the urologist as grossly complete or incomplete.

We advocate that maximal TURBT is integral to the clinical outcomes of trimodality therapy and understand that this procedure can be challenging in certain clinical situations. Secondly, it may be difficult to perform quality control on adequacy of TURBT as the operative notes may not have complete documentation of the procedure and many patients may be referred from outside practices for enrollment on a clinical trial in a tertiary care center. Allowing patients where the treating urologist had attempted maximal TURBT within last 70 days of randomization is acceptable for enrollment. In addition, we recommend that the trial must mandate repeat office cystoscopy by the treating investigator if the initial TURBT was performed outside the institution to document adequacy and extent of TURBT (SWOG/NRG S1806)

Carcinoma in situ

Carcinoma In Situ (CIS) is a common occurrence concurrent with MIBC, and we advocate for the inclusion of some of these patients in trimodality therapy clinical trials. However, a cautious approach is necessary when CIS is diffuse and remote from the primary tumor. Due to the high rate of recurrence in these patients, as compared to only tumor associated CIS [15], exclusion of patients with diffuse CIS from trials is recommended. Potentially, patients with multifocal CIS could be included while stratifying for this factor. Since CIS is not visible by white light in up to 50% of the time, blue light cystoscopy can be used to better detect CIS but lack of availability at all centers limits its broad application [37]. Mandating bladder-mapping biopsies including prostatic urethra to identify these patients should be considered [37]. Mandating bladder-mapping biopsies including prostatic urethra to identify these patients should be considered.

As the roles of novel chemotherapy, immunotherapy and local agents like drug eluting devices become more established in the treatment of CIS, future studies can explore inclusion of these patients with extent of CIS as a potential stratification factor.

Glomerular filtration rate limits

Classically, cisplatin-eligibility was defined by a GFR requirement of 60 ml/min due to concerns of nephrotoxicity. Based on this, radiosensitizing chemotherapy regimens for patients who are cisplatin-ineligible have been evaluated (gemcitabine(gem), 5-fluorouracil/ mitomycin C(FU/MMC), and carbogen/nicotinamide, allowing for broadened eligibility for TMT.

We believe that there is no discernible difference in clinical outcomes between different radio-sensitizing chemotherapy agents in bladder cancer (gem vs cisplatin vs 5-FU/MMC), and they can be used interchangeably in clinical trials. The ongoing SWOG/NRG S1806 trial, with its built-in stratification on the choice of chemotherapy (Gem vs Cis vs 5FU/mitomycin), is poised to answer this question and provide valuable insights into the comparability of various chemotherapy options in the context of TMT for bladder cancer. Additionally, based on SWOG/NRG S1806 demonstrating feasibility of enrolling patients with a GFR as low as 25 ml/min, we recommend lowering the limit of GFR down to 25 ml/min for eligibility on TMT trials [7].

Performance status

Many earlier trials excluded patients with Eastern cooperative oncology group performance status higher than 1. One of the reasons was the cisplatin chemotherapy was difficult to administer in patients with poor performance status. BC2001, and MRC trials allowed patients with Eastern Cooperative Oncology Group (ECOG) 2 and permitted physicians to decide if their patients can receive full dose cisplatin based neoadjuvant chemotherapy. Patients with bladder cancer who are not good candidates for radical cystectomy can be treated very well with trimodality therapy. SWOG/NRG S1806 and KN992 allowed patients with ECOG 2 performance status to be enrolled but these were stratified to assess its impact on trial endpoints. We encourage investigators to allow patients with ECOG 2 to enroll in TMT trials as these patients will benefit from the intervention and clinical trials help us understand the impact on this subgroup of patients.

Histology

Divergent or mixed histology is very well characterized and commonly observed in urothelial carcinoma. In a large retrospective study, of over 448 patients undergoing TURBT, 25% of the patients had mixed histology. Commonly observed components in mixed histology are squamous, glandular, sarcomatoid, micropapillary, small cell and plasmacytoid. These components can be focal, moderate and or extensive admixed within the background of urothelial carcinoma [38]. These cases are considered to clinically behave more aggressively however the treatment paradigm is very similar to pure urothelial carcinoma (NCCN Guidelines). We recommend that patients with divergent mixed histology be included in the clinical trial evaluating trimodality therapy with exception of small cell carcinoma. Patients with pure variant histology should also be excluded from the clinical trial designed for urothelial carcinoma.

ENDPOINTS IN CLINICAL TRIALS EVALUATING SYSTEMIC THERAPY COMBINATION WITH TRIMODALITY THERAPY (TABLES 3 AND 4)

This section discusses the various endpoints utilized in previous phase II/III bladder preservation clinical trials and their nuances. We also provide our recommendations for future clinical trials.

Table 3
Endpoints in various clinical trials

Clinical trial	Phase/Design	Primary endpoint	Secondary endpoints
RTOG 8512, 1993 [49]	II	Complete remission rate	LRFS, DMFS, OS,
RTOG 8802, 1996 [50]	II	Safety	BIS, OS, DMFS, CR
RTOG 89-03, 1998 [25]	II	BIS	OS, Invasive LR, DMFS
RTOG 95-06, 2000 [44]	II	Protocol completion rate	OS, BIS, DMFS
RTOG 97-06, 2003 [51]	II	Protocol completion rate	OS, BIS, CR Rate
RTOG 99-06, 2009 [43]	I/II	Protocol Treatment completion rate	OS, BIS, LRFS, DSS
BCON, 2010 [29]	II	6-month tumor response	OS, RFS < early and late toxicity
BC 2001, 2012 [7]	III	LRDFS	DFS, MFS, Toxicity end points, OS, Rate of RC, Cystoscopic control, Acute toxicity
RTOG 0233, 2013 [27]	II	Protocol Treatment completion rate	OS, BIS
RTOG-0712, 2019 [28]	II	DMFS3	BI-DMFS3
Zlotta et al., 2023 [4] (Toronto/MGH/USC experience)	Retrospective study	MFS	OS, CCS, DMFS, RFFS, DFS

Abbreviations: BIS: Bladder intact survival, OS: Overall survival, DMFS: Distant metastases free survival, CR: Complete response, LR: Locoregional recurrence, DFS: Disease free survival, MFS: Metastases free survival, BI-DMFS3: Blader intact distant metastases free survival at 3 years, CCS: Cancer specific survival, RFFS: Regional failure free survival, LRDFS: Locoregional disease free survival.

Table 4
Endpoint definitions

Endpoint	Definition
Bladder Intact Event Free Survival (BIEFS)	Time to local muscle invasive recurrence, LN recurrence, systemic recurrence, radical cystectomy from any cause, death from any cause
Bladder Intact Disease Specific Survival (BIDSS)	Surviving protocol treatment and bladder cancer with no evidence of distant metastases, nodal recurrence, or nonsalvageable local recurrence with intact native bladder
Bladder Intact Disease-Free Survival (BIDFS)	Time to the earliest of muscle-invasive local recurrence in the bladder, regional pelvic recurrence, DM, bladder cancer–related death, or cystectomy
Disease Specific Survival (DSS)	Surviving protocol treatment and bladder cancer with no evidence of distant metastases, nodal recurrence, or nonsalvageable local recurrence.
Distant Metastasis Free Survival at 3 years (DMFS3)	Time to development of distant metastasis outside pelvis after TMT at 3 years.
Bladder Intact Distant Metastasis Free Survival 3 years (BIDMFS3)	Time to development of distant metastases, undergoing cystectomy, or death from any cause at 3 years
Overall Survival (OS)	Time from registration to death from any cause.
Progression Free Survival (PFS)	Time to local or systemic progression or death.
Regional Failure Free Survival (RFFS)	Local or nodal recurrence within pelvis
Disease Free Survival (DFS)	Regional and distant failure and cancer specific mortality.
Cancer Specific Survival (CSS)	Time to cancer specific mortality
Bladder Intact Survival (BIS)	Time from randomization to cystectomy or death

Abbreviations: LN: lymph node, TMT: trimodality therapy.

Bladder intact event-free survival

Bladder Intact Event-Free Survival (BIEFS) is an innovative endpoint specifically defined for SWOG/NRG S1806. It is a composite endpoint including locoregional muscle-invasive recurrence, systemic recurrence, radical cystectomy, or death from any cause. This endpoint represents a modification of the previously employed Bladder Intact Survival (BIS) [RTOG 8903, 9506, 9706, 0233 and 8802], Bladder Intact Disease-Free Survival (BIDFS) [26], Bladder-Intact Disease Specific Survival (BIDSS) [11], and Bladder-Intact Distant Metastasis Free Survival (BIDMFS) [19]. The modification was necessitated by the challenges of accurately adjudicating the true cause of death in a cooperative group-led clinical trial. To address this, all-cause mortality was included in the endpoint instead of disease-specific mortality. The US Food and Drug Administration (FDA) and Cancer Therapy Evaluation Program (CTEP)/ National Cancer Institute (NCI) provided input on this endpoint definition during the Type B meeting prior to SWOG/NRG S1806 trial initiation. FDA sug-

Table 5
Long-term survival outcomes of various previously reported trimodality therapy trials

Study	N	Complete response rate	Intact Bladder Disease Specific Survival	Locoregional Relapse Free Survival	Overall Survival
RTOG 8512, 1993 [49]	47	66%	42% (5yr)	45% (5yr)	52% (5yr)
RTOG 8802, 1996 [50]	90	75%	44% (4yr)	45% (4yr)	51% (5yr)
RTOG 89-03, 1998 [25]	123	59%	38% (5yr)	60% (5yr)	49% (5yr)
RTOG 95-06, 2000 [44]	34	67%	66% (3yr)	65% (3yr)	83% (3yr)
RTOG 97-06, 2003 [51]	47	74%	48% (3yr)	73% (3yr)	61% (3yr)
RTOG 99-06, 2009 [43]	81	87%	69% (2yr)	NR	79% (2yr)
RTOG 0233, 2013 [27]	93	NR	NR	NR	73% (2yr)
BC2001 [7]	360	NR	89% (2yr)	82% (2yr)	48% (5yr)
RTOG 0712 [28]	70	82%	NR	NR	72.50% (5yr)
Zlotta et al., 2023 [4] (Toronto/MGH/USC experience)	1119	NR	NR	NR	77% (5yr)

Abbreviations: N: Number of participants; NR: Not reached.

Table 6
Rates of overall survival, disease-specific survival, and bladder Intact disease specific survival over time for trimodality therapy patients treated at MGH [15]

Time period	1986–1995	1996–2004	2005–2013
Number of participants	208	158	109
OS (%)			
5-yr	53	53	75
10-yr	35	35	—
DSS (%)			
5-yr	60	64	84
10-yr	54	56	—
Bladder-intact DSS (%)			
5-yr	40	53	75
10-yr	37	49	—

Abbreviations: OS: Overall survival, DSS: Disease specific survival, MGH: Massachusetts General Hospital.

gested that this is possibly an acceptable endpoint for registrational clinical trial in early bladder cancer but would likely require Oncologic Drugs Advisory Committee (ODAC) review.

The primary focus of BIEFS aligns with the Intent of TMT, which is to preserve the native bladder urinary and sexual function which can impact quality of life. This was the rationale to incorporate salvage cystectomy into BIEFS. BIEFS also accounts for any future systemic therapies administered for subsequent disease progression. Bladder intact Disease-Free survival (BIDFS) which accounts for bladder specific mortality has been previously reported in trimodality trials to trend with overall survival (Tables 5 and 6).

BIEFS holds particular significance for clinical trials designed to assess the efficacy of systemic agents that can influence both local and systemic control, and we strongly recommend adopting BIEFS as the endpoint of choice for practice-changing large phase II and phase III trials in this specific setting. BIEFS has been modified for TMT trials in high-risk T1 disease, with the NRG GU 014 trial incorporating histologically proven recurrent T1 disease or CIS as an additional event of interest.

Overall Survival as a secondary endpoint

In trimodality clinical trials targeting early localized bladder cancer, Overall Survival (OS) may prove unsuitable as the primary endpoint for two key reasons. First, there exists a potential for confounding OS results if there is a higher incidence of radical cystectomy in the underperforming arm, as demonstrated in the BC2001 study. Second, patients progressing with distant metastases may have access to a combination of antibody-drug conjugates and immune checkpoint inhibitors, potentially influencing OS outcomes through a notably high rate of complete response and a significant improvement in median overall survival. Another issue with overall survival is that it may take longer follow up to reach the endpoint and if we notice a strong efficacy signal with alternate endpoints we would like to bring the treat-

ment to our patients. In this context, capturing and potentially stratifying for whether the patient is eligible for radical cystectomy is desirable, given the potential impact of this variable on survival due to advanced age, frailty, and comorbidities. We therefore recommend OS as a secondary endpoint. OS is especially important when maintenance therapy is being investigated after guideline-directed TMT.

Locoregional disease-free survival

Locoregional Disease-Free Survival (LRDFS) is defined as the rate of survival free of recurrence in pelvic nodes or the bladder, with data censored at the first sign of metastases, the occurrence of a second primary tumor, or death. Radical cystectomy was not included as part of the endpoint. LRDFS was the primary end point of BC2001, which compared concurrent chemoradiation to radiation therapy alone for localized bladder cancer [8]. The rationale behind this choice was rooted in the intent of evaluating local control benefits from the addition of radio-sensitizing chemotherapy. Because the doses of chemotherapy used for radio-sensitization are not intended to have a meaningful impact on systemic control, the authors of BC2001 didn't power the study for systemic endpoints (DMFS, OS). The concern over using OS as a primary endpoint was also influenced by the suspicion that patients who received RT alone would have higher rates of salvage cystectomy, thereby potentially diminishing OS differences between the two arms. This was confirmed when no difference was observed in OS at 10 years of follow up in the BC2001 trial [39].

Criticism of LRDFS as a primary endpoint arises from its inclusion of non-muscle-invasive recurrences, which were observed in a third of patients on BC2001. NMIBC recurrences can be effectively managed with intravesical therapy and 10-year OS in those with a NMIBC recurrence does not differ from those without a NMIBC recurrence [40]. Moreover, in recent years, the treatment options for non-muscle-invasive bladder cancer have expanded [41, 42]. We propose that LRDFS should not be used as primary endpoint as it does not include radical cystectomy especially from toxicity and includes NMIBC recurrences which can be managed with intravesical therapies.

The use of Disease-Free Survival (DFS) as a primary endpoint in trials like Checkmate 274, evaluating adjuvant nivolumab, and the inclusion of DFS as a co-primary endpoint in the AMBASSADOR trial, evaluating pembrolizumab in the adjuvant setting after radical cystectomy, indicates a growing acceptance of endpoints other than OS in the evaluation of treatment efficacy. This trend aligns with the rapid development of new therapies and the need for endpoints that are clinically meaningful and provide timely insights into treatment outcomes [9].

Distant metastasis free survival

DMFS is defined as the rate of urothelial carcinoma recurrence outside the locoregional area or death from any cause. While valuable for assessing systemic control in treatments like novel chemotherapy or immunotherapy, DMFS alone is not suitable as a primary endpoint. It lacks consideration for local recurrence, radical cystectomy, or toxicity-related complications. Assuming the new intervention under investigation will have minimal impact on local outcomes, DMFS provides crucial insights into the overall effectiveness of the agent in treating bladder cancer, but it should be considered alongside other endpoints for a comprehensive evaluation. We recommend using this as a secondary endpoint.

Bladder intact distant metastasis free survival

Bladder Intact Distant Metastasis Free Survival (BI-DMFS) is defined as the development of distant metastasis, undergoing cystectomy, or death from any cause. Described in NRG/RTOG 0712, this composite endpoint incorporates the impact of invasive bladder events or toxicity leading to radical cystectomy [28]. Not accounting for local non-invasive events or tumor invasive recurrences managed without radical cystectomy, BI-DMFS serves as a valuable endpoint for studying the impact of a systemic agent given neoadjuvantly or adjuvantly with TMT. A trial that demonstrates a 10–15% improvement in BI-DMFS could be potentially practice-changing. However, it may not be an acceptable endpoint for a registration trial due to its limitations. Disease free survival is probably better as discussed below.

Bladder intact disease-free survival

Time to Bladder Intact Disease-Free Survival (BI-DFS) is defined as the time to the earliest of these events: muscle-invasive recurrence in the bladder, regional pelvic recurrence, distant metastases, bladder cancer-related death, or cystectomy. Unlike BI-EFS, BI-DFS excludes death from any cause as

part of the endpoint. Previous NRG/RTOG trials, along with data from MGH patient cohorts, have contributed to the extensive dataset for BI-DFS, making it suitable for analysis in large phase III trials [15, 26]. SWOG/NRG S1806 investigators used the data provided by these previous NRG/RTOG and MGH trials and the BI-DFS endpoint to make assumptions for sample size calculations for the BI-EFS endpoint. If determining the real cause of death in an elderly population is challenging, BI-EFS can be an appropriate primary endpoint.

Bladder intact disease-free survival is a robust endpoint for analyzing therapy efficacy targeting improvements in local or systemic control, de-intensification, or intensification of therapy. It helps control for potential confounding from future therapies and serves as a good alternative to BI-EFS.

Bladder intact survival/Cystectomy free rate

Bladder Intact Survival (BIS) is defined as time from randomization to cystectomy or death from any cause. Cystectomy free rate (CFR) is the proportion of patients who would be cystectomy free and alive at a given point in time. These endpoints were used in early phase II NRG/RTOG studies which were designed to assess completion and safety of new chemotherapy regimens and radiation intensification.

Bladder intact survival or cystectomy free rate does not account for patients who had systemic recurrence and received further systemic therapy without undergoing radical cystectomy. It also allows for the ambiguity of patient refusal to get a cystectomy, even if they have a recurrence. Thus, it may not fully represent the true benefit of a new systemic regimen used along with TMT. With the option of BI-EFS which encompasses more clinically meaningful events, BIS would not be considered an the most optimal endpoint.

Clinical complete response rate

Clinical complete response had been defined by negative cystoscopy, biopsy, cytology, and cross-sectional imaging. This endpoint is defined as the rate of clinical complete response (cCR) at a predefined interval after randomization. It serves as an excellent measure to assess and compare the efficacy of local therapy intensification. However, it is confounded by factors such as the completeness of maximal transurethral resection of bladder tumor (TURBT) and the initial stage of the disease. For instance, a small T2 early papillary lesion may be completely resected, impacting the outcome if not accounted for in stratification.

Historically, RTOG trials had a clinical urologic assessment built in their design to assess response after induction chemoradiation. Patients with complete response would proceed with consolidation radiation to the bladder. This was primarily done in clinical trials performed in United States as urologists were not comfortable to proceed with full radiation if patient was not responding. On the contrary, trials conducted in UK and Europe performed final evaluation 6 months from randomization or 3 months after finishing therapy. Patients who had less than clinical complete response were advised to proceed with radical cystectomy. Currently, there is wider acceptance by urologic community in US for patients to receive their complete treatment and then performing a biopsy 3 months later [25, 28, 43, 44]. This approach was adopted due to an 8% false-negative rate for persistent disease when biopsy was not performed [45]. BC2001 and BCON trials performed biopsies at 6-months post randomization. Those trials struggled to get post-therapy biopsies as physicians and patients were reluctant to undergo additional intervention if there were no suspicious lesions. BCON eventually changed its primary endpoint from CCR to overall survival due to low biopsy compliance [29]. SWOG/NRG S1806 and KN 992 have mandated biopsies at 3 months after finishing radiation, aiming to document complete response within a timeframe sufficient for radiation-related inflammatory changes to settle and achieve full effects on bladder cancer. The compliance rates in these trials will inform the use of biopsies in future studies. Clinical complete response is a good secondary endpoint and could serve as an early post-treatment prognostic marker when evaluating treatment intensification or deintensification treatment strategies. We acknowledge that clinical staging in bladder cancer is discordant from pathologic staging [10, 11].

There is a need to explore non-biopsy-based methods of detecting recurrence, such as with urine cell free DNA, blood ctDNA, and new AI-based models for interpretation of radiology and pathology images. Correlative studies evaluating these novel methods of detection should be included in future clinical trials.

Toxicity endpoint and quality of life

Given the considerable interest in preserving bladder function, the assessment of toxicity and

patient-reported quality of life becomes paramount in trimodality clinical trials. Radiation introduces potential risks to bladder capacity, and possible increased bladder irritative or obstructive symptoms. Radiation cystitis may induce hematuria and pain, while bowel irritation can manifest as gastrointestinal (GI) symptoms, collectively impacting overall quality of life. Late-grade 3+ physician-reported genitourinary (GU) and GI toxicity from TMT falls within the 1–6% range. Patient-reported toxicity following TMT has also reported excellent social, emotional and bladder functional outcomes. Although the rate of toxicity-related radical cystectomy is notably low [15, 26], it is crucial to recognize that patient-reported quality of life outcome measures would be different for patients treated with trimodality therapy vs radical cystectomy. Consequently, questionnaires designed for assessing surgical outcomes may not be suitable for evaluating radiation-related toxicity [46]. Simultaneously, emerging treatment strategies, while yielding comparable survival outcomes, may significantly differ in terms of short-term and long-term toxicity and quality of life. Therefore, standardizing the evaluation process is critical for meaningful outcome comparisons.

Various standardized quality of life instruments have been employed in trials. The Late Effects of Normal Tissues (LENT) scoring system and the Subjective, Objective, Management, and Analytic scale (SOMA) were specifically crafted to evaluate late toxicity related to radiation treatment, regardless of the treatment site [46, 47]. The FACT-BL and bladder cancer subscale (BLCS) instruments are components of LENT/SOMA scale which were validated on BC2001 trial. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, BLM-30 module, and the Expanded Prostate Cancer Index Composite (EPIC) contain questions tailored for assessing radiation-specific pelvic toxicity, offering a more nuanced evaluation although EPIC has been validated only in the prostate cancer patient population. Investigators should also be mindful that men and women with MIBC may have different QOL outcomes, and therefore the instrument chosen needs to be applicable for both patient populations. We recommend employing one or a combination of these validated questionnaires to assess both toxicity and quality of life. When analyzing QOL results, statistical significance is usually not sufficient. Validated QOL instruments have defined thresholds for clinical significance. That is, when QOL changes or is different by this threshold magnitude or more, then that is deemed to be a difference that meaningfully impacts patients.

A novel endpoint, Quality-adjusted Time Without Symptom or disease or Toxicity of treatment (Q-TWiST), combines disease control and quality of life/toxicity into a single measure [48]. Patient outcomes are categorized into three states: time spent before disease progression without toxicity (ideal), time spent before disease progression with toxicity, and time after disease recurrence or progression until death. Each state is given a weight based on patient preference "utility" scores, with the ideal state given a weight of 1. In an example of a randomized trial, Q-TWiST calculates and compares the amount of time patients in the two arms spend in each state, multiplied by the state weights. The result is a patient-centric outcome that combines both quantity and quality of life.

CLINICAL TRIALS INVESTIGATING DIFFERENT RADIATION TECHNIQUES

Different radiation therapy techniques (including adaptive therapy), fractionation and/or field sizes have the potential to impact local disease control, toxicity, treatment burden, cost, compliance, or ability to receive curative intent treatment due to travel and transportation burdens in this population. Endpoints that focus on these events, such as complete response rate, invasive locoregional recurrence rate (bladder or pelvic node recurrence), rate of radical cystectomy due to any cause, or late GU /GI toxicity, and sexual function [36] would be appropriate for comparing different radiation techniques [36]. Bladder intact event free survival which incorporates many of these endpoints would also be an appropriate primary endpoint for such trial.

CONCLUSIONS

In conclusion, this review discusses key considerations and recommendations for designing and evaluating TMT clinical trials in muscle-invasive localized bladder cancer. The evolving landscape of bladder cancer treatment and expanding indications for TMT as an alternative to radical cystectomy, necessitates a thoughtful approach to trial design. The proposed eligibility criteria encompass a broader patient population, including those with hydronephrosis and more advanced T

stage, reflects a patient-centric perspective that will result in better generalizability. The recommendation to explore neoadjuvant, adjuvant or maintenance novel chemotherapy or immunotherapy acknowledges potential benefit of these strategies in certain high risk clinical scenarios. Future trials should focus on comparing guideline-directed TMT vs combination of novel therapies with TMT or study different radiation schedules within TMT.

The definition and selection of endpoints, such as BIEFS, LRDFS, and DMFS, should be strategically employed to align with the trial's objectives and the preservation of native bladder and other critical genitourinary functions like sexual function. The incorporation of patient reported quality-of-life assessments and considerations of treatment-related toxicity underscore the importance of balancing therapeutic efficacy with the impact on patients' well-being.

Ultimately, achieving uniformity in trial design, eligibility criteria, and endpoints is crucial for advancing the field rapidly. The collaborative effort of multidisciplinary experts, patient advocates, and the integration of novel treatment strategies will optimize bladder cancer management.

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CONFLICT OF INTEREST

SPL is co-editor, and LB, RB and JAS are Editorial Board members of this journal, but they were not involved in the peer-review process nor had access to any information regarding its peer-review.

PS reports the following conflict of interest: Advisory Board: Aveo Pharma, Bayer Health Care, Janssen Research and Development, EMD Soreno, Seattle Genetics, BMS CME/Non-CME - IBCU/ Grand Rounds, Curio, Target Oncology Writing Honorarium: Medscape; LB reports honorarium from up to date, as well as editorial reimbursement from UroToday. GPS reports the following conflict of interest: Advisory Board: EMD Serono, BMS, Merck, Seattle Genetics/Astellas, Janssen, Bicycle Therapeutics, Pfizer, Gilead, Scholar Rock, Eli Lilly/Loxo Oncology, Vial, PrecisCa, Atkis, Kura Oncology, Daiichi-Sankyo, Consultant/Scientific Advisory Board (SAB): Syapse, Merck, Servier, Syncorp, Research Support to institution: EMD Serono, Jazz Therapeutics, BMS Speaker: Seagen, Gilead, Natera, Exelixis, Janssen, Astellas, Bayer, Aveo, Merck, Pfizer CME-certified speaking: Research to Practice, PeerView Institute, Ideology Health, IBCU/Grand Rounds in Urology, Data safety monitoring committee (honorarium): Mereo

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