Bladder-Sparing Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer

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Abstract: Bladder-sparing therapies for the treatment of nonmetastatic muscle-invasive bladder cancers are included in both American and European guidelines. Numerous treatment approaches have been described, including partial cystectomy, radiation monotherapy, and radical transurethral resection. However, the most oncologically favorable and well-studied regimen employs a multimodal approach that consists of maximal transurethral resection of the bladder tumor followed by concurrent radiosensitizing chemotherapy and radiotherapy. This sequence, referred to as trimodal therapy (TMT), has been evaluated with robust retrospective comparative studies and prospective series, although a randomized trial comparing TMT with radical cystectomy has not been performed. Despite promising reports of 5-year overall survival rates of 50% to 70% in well-selected patients, relatively few patients qualify as ideal candidates for TMT. Specifically, contemporary series exclude patients who have clinical stage T3 disease, multifocal tumors, coexisting carcinoma in situ, or hydronephrosis. Herein, we review all forms of bladder-preserving therapies with an emphasis on TMT, highlighting the rationale of each component, survival outcomes, and future directions.

Introduction

Bladder cancer is the sixth most common malignancy in the United States and accounts for nearly 18,000 deaths per year.[1] Although patients with non–muscle-invasive bladder cancer may be managed with minimally invasive therapies, such as transurethral resection (TUR) and intravesical therapy, the gold standard treatment for nonmetastatic muscle-invasive bladder cancer is neoadjuvant chemotherapy followed by radical cystectomy.[2-4] Radical cystectomy is an inherently morbid operation; recent cystectomy trials have reported that 59% to 69% of patients experience postoperative complications of any grade and 13% to 22% experience high-grade complications.[5-7] Furthermore, removal of the native bladder necessitates urinary diversion in the form of an incontinent urostomy, a continent catheterizable

reservoir, or an orthotopic neobladder, all of which carry substantial quality of life implications. Given these considerations, bladder-sparing alternatives to radical cystectomy are attractive to patients and clinicians alike.

Organ-sparing multimodality approaches have been applied to a variety of malignancies (eg, breast cancer, head and neck cancer, cervical cancer, and anal cancer), and generally involve limited resection or biopsy followed by concurrent or sequential chemoradiation. The organ-sparing approach to bladder cancer follows this paradigm. The best-studied and best-supported approach entails maximal TUR, external beam radiotherapy with concurrent radiosensitizing chemotherapy, and often either neoadjuvant or adjuvant chemotherapy. This multimodal, multidisciplinary approach is commonly referred to as trimodal therapy (TMT).

To date, no prospective randomized trials have established the efficacy of TMT vs radical cystectomy. However, numerous prospective trials and large retrospective series have provided insight into the safety and efficacy of TMT.[8-22] In spite of the lack of data from randomized trials comparing radical cystectomy and TMT, encouraging oncologic outcomes have led to the inclusion of TMT in guidelines from the American Urological Association (AUA), the European Association of Urology (EAU), and the National Comprehensive Cancer Network as an alternative for well-selected patients with muscle-invasive bladder cancer.[2-4]

This review serves as an analysis of contemporary bladder-sparing therapies for nonmetastatic muscle-invasive urothelial carcinoma of the bladder, including TMT, radical TUR alone, partial cystectomy, and radiation monotherapy. Although alternative bladder-sparing approaches are discussed, the primary focus of this review is TMT, including patient selection criteria, common treatment protocols, oncologic outcomes, and toxicities associated with this approach.

Radical Cystectomy as the Benchmark

Oncologic outcomes following radical cystectomy serve as the benchmark against which bladder-sparing treatments must be compared. Cross-trial comparisons between radical cystectomy and TMT outcomes must be made with caution because bladder cancer patients represent a heterogeneous population and trials vary in their selection criteria, the era of treatment, patient demographics, and treating institutions. These discrepancies may limit the utility of comparing these often-disparate patient populations. Similarly, retrospective comparisons of radical cystectomy and TMT outcomes, although valuable, may be confounded by selection bias or discrepancies between clinical and pathologic staging, and must be viewed with an appropriately skeptical eye.[23-25] Regardless, in the absence of randomized comparisons, crude and adjusted comparisons to radical cystectomy outcomes help contextualize the safety and efficacy of TMT.

Radical cystectomy entails surgical removal of the bladder and the pelvic lymph nodes. In addition, men have the prostate and the seminal vesicles removed and women typically have the anterior wall of the vagina, the cervix, the uterus, the fallopian tubes, and the ovaries removed. Cystectomy may be accomplished in an open fashion or via a robot-assisted laparoscopic approach. Following bladder removal, urinary diversion must be performed using the intestine to form an incontinent urostomy, a continent catheterizable reservoir, or an orthotopic neobladder. Modern cystectomy series report a median postoperative hospital stay of 6 to 9 days, and 13% to 22% of patients experience grade 3 or greater complications perioperatively.[5-7,26,27] In the neoadjuvant chemotherapy era, 5-year overall survival, recurrence-free survival, and cancer-specific survival following radical cystectomy range from 50% to 59%, 57% to 68%, and 65% to 76%, respectively.[27-32]

Trimodal Therapy

TMT regimens vary among trials, but generally consist of maximal TUR followed by external beam radiotherapy and concurrent radiosensitizing chemotherapy with either neoadjuvant or adjuvant combination chemotherapy as well. A mid-chemoradiation "break" of 2 to 3 weeks, although not uniformly employed, is often utilized to evaluate tumor response and improve treatment tolerance. Following mid-treatment evaluation, patients with a complete response are traditionally given the remainder of the planned chemoradiation schedule, whereas nonresponders are referred for early salvage radical cystectomy. A typical TMT regimen schema is shown in Figure 1.

A randomized multicenter trial in the United Kingdom called SPARE (Selective Bladder Preservation Against Radical Excision) was designed to compare radical cystectomy with TMT. Unfortunately, despite being remarkably well planned, organized, and funded, the SPARE trial closed owing to inadequate accrual.[33] The authors cited a low volume of eligible participants, patient reluctance to be randomly assigned, a complex multidisciplinary care pathway, and bureaucratic hurdles that slowed treatment center enrollment as the primary reasons the trial had inadequate accrual. Although randomized data are absent, there is an abundance of prospective, single-arm trials for cystectomy-eligible patients that characterize the safety and oncologic outcomes of TMT, as well as numerous retrospective comparisons of TMT and radical cystectomy.

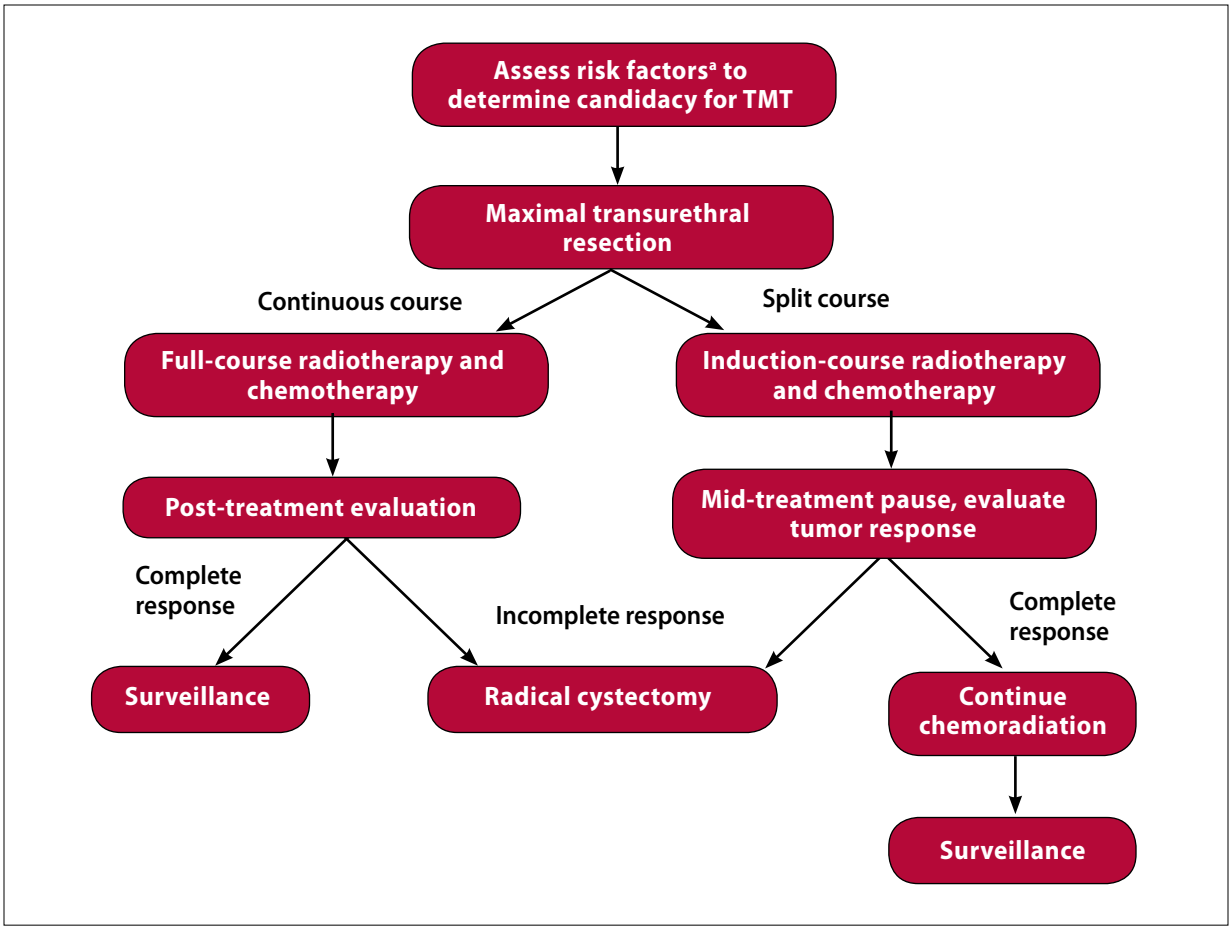

Figure 1. Trimodal therapy treatment schema.

TMT, trimodal therapy.

[a] Risk factors include extensive carcinoma in situ, hydronephrosis, tumor stage ≥cT3, tumor multifocality, and incomplete transurethral resection.

Treatment Outcomes

Early experience from Massachusetts General Hospital demonstrated promising short-term outcomes, with a complete response rate of 53% and an actuarial 5-year overall survival rate of 48%.[8] These data suggested that TMT had the potential to provide an additional, organ-preserving option to radical cystectomy and served as motivation to refine TMT regimens and patient selection in subsequent trials. Numerous single-institution series, 8 Radiation Therapy Oncology Group (RTOG) protocols, and 2 European trials subsequently explored alternative regimens of TMT for patients who were considered eligible for radical cystectomy.[9-11,15-22] Although numerous regimens were developed, it is important to note that no head-to-head prospective trials have established the superiority of any one TMT regimen over another, and patient populations varied substantially among trials. Rather, treatment toxicity, regimen tolerance and completion, complete response rates, actuarial overall survival, cystectomy rates, and other surrogate outcomes have been utilized to compare the efficacy of various approaches to TMT. The Table displays the TMT regimens and selected outcomes from major published prospective series.

The outcomes of these trials demonstrate general improvement in TMT outcomes over time. The 5-year overall survival rate was between 49% and 75%, and the most recent RTOG trial, 07-12 (Chemotherapy and Radiation Therapy in Treating Patients With Stage II or Stage III Bladder Cancer That Was Removed by Surgery), demonstrated a 3-year metastasis-free survival rate of 78% to 84%.[11] Complete response rates, typically defined as the absence of cystoscopic, pathologic, or radiographic disease, varied from 53% to 88% and also improved over time. The rate of radical cystectomy, which was most commonly used if a patient had either an incomplete response upon mid-treatment evaluation or recurred at a

Table. Selected Components and Outcomes From Prospective Trials of Trimodal Therapy

Trial	Name	N	≥cT3, %	Neoadjuvant Chemotherapy	Continuous or Split Course	Total Radiation Dose	Radiosensitizing Chemotherapy	Adjuvant Chemotherapy	Complete Response, %	Underwent Radical Cystectomy, %	Overall Survival, %
Kaufman,[8] 1993	NA	53	72	Yes (MCV × 2)	Split	64.8 Gy	Cisplatin	No	53	28	5-y: 48
Tester,[9] 1993	RTOG 85-12	48	75	No	Split	64.0 Gy	Cisplatin	No	66	25	3-y: 64
Tester,[15] 1996	RTOG 88-02	91	76	Yes (MCV × 2)	Split	64.8 Gy	Cisplatin	No	75	40	4-y: 62
Shipley,[16] 1998	RTOG 89-03	123	62	Arm 1: Yes (MCV) Arm 2: No	Split	64.8 Gy	Cisplatin	No	59	21	5-y: 49
Kaufman,[17] 2000	RTOG 95-06	34	24	No	Split	44.0 Gy	Cisplatin/ 5-FU	No	67	27	3-y: 83
Hagan,[18] 2003	RTOG 97-06	47	34	No	Split	64.8 Gy	Cisplatin	Yes (MCV)	74	18.60	3-y: 61
Kaufman,[19] 2009	RTOG 99-06	80	12	No	Split	64.3 Gy	Cisplatin/ paclitaxel	Yes (gemcitabine/ cisplatin)	81	12	5-y: 56
Choudhury,[21] 2011	NA	50	16	No	Continuous	52.5 Gy	Gemcitabine	No	88	8	3-y: 75
Lagrange,[20] 2011	GETUG 97-015	51	22	No	Split	53.0 Gy	Cisplatin/ 5-FU	No	92	33	8-y: 36
James,[22] 2012	BC2001	182	15	Yes (33%)	Continuous	55.0 Gy, 64.9 Gy (XRT only)	5-FU/ MMC	No	NR	11	5-y: 48
Mitin,[10] 2013	RTOG 02-33	93	5	No	Split	64.3 Gy	Cisplatin/ 5-FU or paclitaxel	Yes (gemcitabine/ cisplatin/ paclitaxel)	86 (<T2)	5	5-y: 71-75
Coen,[11] 2019	RTOG 07-12	66	3	No	Split	64.0 Gy	Gemcitabine or cisplatin/ 5-FU	Yes (gemcitabine/ cisplatin)	78-88	15	3-y MFS: 78-84

5-FU, 5-fluorouracil; GETUG; French Genito-Urinary Group; Gy, Gray; MCV, methotrexate, cisplatin, vinblastine; MMC, mitomycin-C; MFS, metastasis-free survival; NA, not applicable; NR, not reported; RTOG, Radiation Therapy Oncology Group; XRT, external beam radiotherapy; y, year(s).

later date with invasive disease (salvage cystectomy), was as high as 40% in earlier experiences[15] but declined over time to 5% to 12% in the most recent series.[10,19,21] Factors that were modified and may account for these improvements include improved patient selection, modifications in radiotherapy dosing, the introduction of image-guided

and intensity-modulated radiotherapy, the movement of combination chemotherapy agents to the adjuvant rather than neoadjuvant setting (to reduce treatment-related toxicity that inhibits patients' ability to receive definitive chemoradiation), and utilization of less nephrotoxic chemotherapeutic agents.

Long-term oncologic outcome data for patients treated by TMT has been provided by several large retrospective series. Massachusetts General Hospital, the University of Erlangen-Nuremberg in Germany, and a pooled analysis of 5 RTOG trials each reported their experience with 475, 415, and 468 patients, respectively.[12-14] Overall survival at 5 and 10 years ranged from 51% to 57% and from 31% to 39%, respectively. Cancer-specific survival at 5 and 10 years ranged from 56% to 71% and from 42% to 65%, respectively. Radical cystectomies were ultimately performed in 20% to 30% of patients originally enrolled in TMT. Interestingly, the Massachusetts General Hospital group performed a subgroup analysis by treatment era and found substantial improvements in 5-year overall survival (75%), cancer-specific survival (84%), and cystectomy rates (16%) in their most recent era of treatment, which ranged from 2003 to 2015. Although many factors may contribute, improved patient selection likely accounts for a substantial portion of the improved outcomes over time.

Patient Selection

The evolution of exclusion criteria and clinical stage of patients included in prospective trials emphasize the significance of patient selection in optimizing TMT outcomes. Common exclusion criteria for TMT include prostatic stromal involvement, neutropenia, leukopenia, thrombocytopenia, and chronic kidney disease. Over time, complete TUR was mandated in inclusion criteria, hydronephrosis was adopted as an exclusion criteria, and the proportion of patients with cT3 or greater disease diminished greatly. For instance, in the era in which Massachusetts General Hospital noted its best outcomes (2003-2015), only 3% of patients had cT3 or greater disease and 0% had hydronephrosis.[12] Multivariable analyses of risk factors associated with worse treatment response have further suggested that incomplete TUR, hydronephrosis, and advanced tumor stage are adverse pretreatment factors.[12-14,16,34] Carcinoma in situ may also be associated with compromised disease-specific survival, although more evidence is necessary to confirm this risk factor.

Ideal patients for TMT who lack any of the listed risk factors may represent a small pool of patients with muscle-invasive bladder cancer. One report estimated that only 10% to 15% of patients who are medically fit for surgery qualify as ideal candidates for TMT.[35] Moreover, reflecting on the reasons why the SPARE trial failed, the authors reported that their inclusion criteria (no hydronephrosis, no extensive carcinoma in situ, and no equivocal adenopathy) restricted eligibility to a smaller field of patients than expected, which made accrual difficult.[33] Among several other reasons, the authors cite this small cohort of potential patients as one of the primary reasons the trial failed. Although improving patient selection may lead to the best TMT outcomes, it may also limit the generalizability of trial results to the bladder cancer population as a whole.

Comparison Studies

Numerous retrospective analyses have been conducted to compare TMT with radical cystectomy, although clear limitations to this approach exist. Selection bias, although inherent to all retrospective studies, may be particularly pronounced in comparisons between TMT and radical cystectomy.[25] Outside of several centers, TMT has often been reserved for patients deemed unfit for radical cystectomy, who may represent an inherently less healthy population. To adjust for this bias, propensity score matching and inverse probability of treatment weighting were utilized by 2 studies that examined data from the Surveillance, Epidemiology, and End Results Program and the National Cancer Database.[36,37] Both identified inferior overall survival in the TMT cohort vs the radical cystectomy cohort (hazard ratios of 1.49 and 1.37, respectively). Opposing these findings, a single-institution, propensity-matched cohort of 224 patients demonstrated equivalent 5-year cancer-specific survival between TMT and radical cystectomy.[38] Moreover, 2 large meta-analyses that included 8 studies and more than 9000 patients identified no discernable statistical difference in outcomes between patients treated by TMT or radical cystectomy.[39,40] Despite statistical adjustments to reduce selection bias, cystectomy and TMT groups have inherent differences that complicate comparisons. In the absence of randomized data, treatment decisions regarding muscle-invasive bladder cancer should be reached by shared decision-making between informed clinicians and patients, which may be best accomplished by multidisciplinary bladder cancer clinics. Although no definitive conclusions can be drawn regarding equivalence to radical cystectomy, the outcomes presented suggest that TMT is a reasonable alternative in well-selected patients.

Trimodal Therapy Components

Maximal Transurethral Resection

A maximal TUR is considered the first step in TMT, regardless of the chemoradiation regimen. In a 10-year follow-up of radical TUR as monotherapy for muscle-invasive bladder cancer, Herr and colleagues demonstrated a cancer-specific mortality of 18% in patients who were cT0 on repeat resection, vs 42% in those who were T1.[41] Although these data emphasize that it is critical to render

the bladder disease-free, more than 50% of patients with T2 disease on their initial resection may have residual muscle-invasive disease on repeat TUR.[42] Efforts to reduce under-resection have included taking biopsies of surrounding muscle and perivesical fat, as well as taking a 1- to 2-cm margin of normal-appearing urothelium around the TUR site.[41,43] Radical TUR does carry morbidity, however, as extensive resection into the perivesical fat carries a risk of perforation and may facilitate tumor seeding.[44] As a result, the procedure must be performed in an aggressive yet sensible manner.

Radiosensitizing Chemotherapy

Although the value of concurrent radiosensitizing chemotherapy has been demonstrated by 2 randomized trials,[22,45] the ideal regimen has not been defined. The favorable radiosensitizing properties of concomitant cisplatin have been the best studied, and cisplatin-based doublets are the preferred regimen for patients with adequate renal function in modern series.[10,11,17,19] In a phase 3 randomized trial comparing concomitant radiosensitizing cisplatin and radiotherapy vs radiotherapy alone, Coppin and colleagues demonstrated a significant reduction in pelvic relapse when cisplatin was used as a radiosensitizing agent.[45] Additionally, cisplatin was the primary radiosensitizing agent in 6 prospective RTOG trials.[9,16-18] However, no retrospective or prospective series have shown that radiosensitizing cisplatin improves overall survival. Given the renal impairment found in many patients with muscle-invasive bladder cancer, gemcitabine, mitomycin-C, and 5-fluorouracil (5-FU) have been explored as attractive alternative chemotherapeutic options. In the phase 2 randomized trial RTOG 07-12, Coen and colleagues compared twice-daily radiation with 5-FU/cisplatin vs daily radiation with gemicitabine.[11] Although not powered to compare the 2 arms, both cohorts had distant metastasis-free survival rates greater than 75%, and gemcitabine demonstrated a more favorable risk profile. James and colleagues randomly assigned 360 patients to receive either 5-FU and mitomycin C concurrently with radiation or radiotherapy alone after TUR and demonstrated a significant overall survival benefit in the chemoradiation arm (48% vs 35%).[22] Thus, although cisplatin in combination with 5-FU or paclitaxel may be the preferred chemosensitizing regimen for patients with adequate renal function, gemcitabine monotherapy or 5-FU in combination with mitomycin-C offer patients with renal dysfunction alternative options with similarly encouraging oncologic outcomes.

Adjuvant and Neoadjuvant Chemotherapy

The role of adding systemic chemotherapy to chemoradiation is unclear. Prospective randomized trials have demonstrated that neoadjuvant cisplatin-based chemotherapy confers survival benefit in patients undergoing radical cystectomy.[28] Extrapolation from the cystectomy literature suggests that adding neoadjuvant or adjuvant chemotherapy to standard chemoradiation may treat undetected systemic disease and improve long-term outcomes. However, high-level data supporting additional chemotherapy in TMT are lacking. A phase 3 randomized trial, RTOG 89-03 (Phase III Trial of Neoadjuvant Chemotherapy in Patients With Invasive Bladder Cancer Treated With Selective Bladder Preservation by Combined Radiation Therapy and Chemotherapy), compared patients who received neoadjuvant methotrexate, cisplatin, and vinblastine plus chemoradiation with patients who received chemoradiation alone.[16] Overall survival and distant metastases were not different between the groups, although the neoadjuvant group had significantly more treatment-related toxicity, including 3 deaths from neutropenic sepsis. In the randomized trial comparing 5-FU and mitomycin-C chemoradiation with radiotherapy alone, one-third of the patients in both arms received neoadjuvant cisplatin-based chemotherapy.[22] Although this trial was not designed to characterize the effect of neoadjuvant therapy, subgroup analysis revealed no benefit to neoadjuvant therapy. An alternative approach to neoadjuvant chemotherapy is to deliver combination chemotherapy following chemoradiation (adjuvant chemotherapy). An adjuvant approach prioritizes chemoradiation and may improve the proportion of TMT-enrolled patients who complete therapy.[10] Although the majority of RTOG trials employ adjuvant chemotherapy, the lack of a control arm in these trials limits insight into the efficacy of additional chemotherapy.

Radiotherapy

Advances in radiotherapy, including intensity-modulated radiotherapy and image-guided radiotherapy, have improved the ability to precisely target the resected tumor bed while avoiding adjacent normal tissues. Radiation oncologists typically deliver a dose of 55 to 64 Gy in daily fractions of 1.8 to 2.75 Gy over a period of 4 to 6 weeks. Both daily and twice-daily delivery of radiotherapy have been used in prospective trials, without clear superiority of either regimen.[11] Conventional target volumes include the TUR bed, bladder, distal ureters, and proximal urethra (including the prostatic urethra in men). Elective treatment of the pelvic lymph nodes remains an area of controversy, although regional nodes are often included within the standard margins applied for set-up variation and microscopic spread (Figure 2). Partial bladder radiation may be utilized in cases where the lesion/TUR defect is well defined. Partial bladder treatment demonstrates similar efficacy compared with

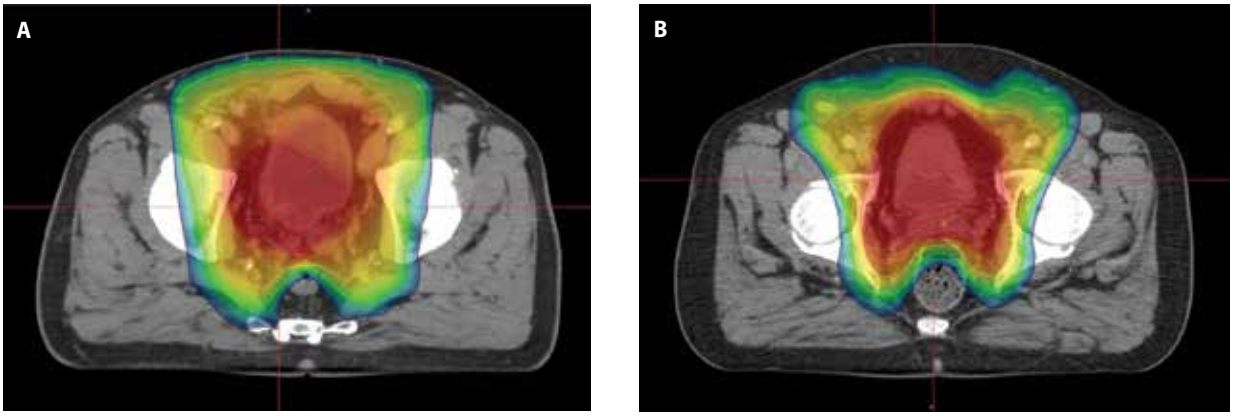

Figure 2. Representative radiation treatment plans relative to anatomy as shown on axial CT images. Colored regions and "isodose lines" represent radiation dose gradients. In partial bladder radiation (**A**), the dose can be targeted to the portion of bladder where the tumor was located (transurethral resection site in bright red outline). Alternatively, the entire bladder can be targeted to address microscopic spread and field effects (**B**). Both plans use intensity-modulated radiotherapy, a dose-painting technique, to treat the internal and external iliac nodes to an intermediate dose.

whole-bladder radiation, while potentially reducing bladder, bowel, and rectal toxicity.[11,16,22,46,47]

Evaluating Tumor Response to Trimodal Therapy

Oncologic surveillance is a key aspect of TMT. AUA guidelines for the treatment of nonmetastatic muscle-invasive bladder cancer[3] emphasize the importance of follow-up in 2 separate statements. The first statement addresses cystoscopic reevaluation mid-treatment to allow for early selection of nonresponders and the second statement addresses post-treatment surveillance. The goal of mid-treatment cystoscopic reevaluation is to detect nonresponders as early as possible to allow for the delivery of definitive treatment in a timely fashion. Additionally, close surveillance after treatment is of utmost importance given the concern for clinical and pathologic staging discrepancies related to understaging.[25,48] The definitions of complete response (T0 staging) after TMT vary slightly, but often include no radiographic evidence of tumor on pelvic computed tomography/magnetic resonance imaging, no cystoscopically visible tumor, no palpable tumor on bimanual exam, negative tumor site biopsy, and, less frequently, negative urine cytology.[10,13,34,49] Although the majority of RTOG trials employ a mid-treatment pause to evaluate tumor response, not all series utilize a break, and the effect of delaying definitive chemoradiation for 2 to 3 weeks is controversial.

For those with a complete response (T0), additional consolidative chemoradiation is typically recommended. Patients undergoing mid-treatment evaluation who have a partial response with residual noninvasive disease (Ta or Tis) can be managed by salvage cystectomy or continued TMT followed by close surveillance.[10,14,50,51] Mitin and colleagues showed that bladder tumor recurrence rate, salvage cystectomy rate, and survival outcomes were similar between those with a complete response or a partial response after treatment with induction TMT followed by consolidation therapy. Patients with muscle-invasive disease at reevaluation are recommended to undergo radical cystectomy if medically fit for surgery.

Management of Tumor Recurrence After TMT

Post-treatment surveillance strategies include frequent cystoscopic and radiographic evaluations, examination under anesthesia, and tumor site and random bladder biopsies. Urine cytology can also play a complementary role.[3,12,14,16,34,38,51-54]

Superficial, non–muscle-invasive recurrences represent the most common type of recurrence after TMT.[4,22,55] According to both AUA and EAU guidelines, non–muscle-invasive recurrences can be managed conservatively via TUR, intravesical therapy, and close surveillance. Zietman and colleagues noted that 26% (32/125) of patients who initially responded to TMT recurred with 57 noninvasive lesions; 67% were in the same region of the bladder as the original lesion.[56] The majority of these noninvasive lesions were successfully managed conservatively with TUR with or without intravesical chemotherapy. Ten patients with recurrences underwent delayed salvage cystectomy for extensive high-grade noninvasive disease or progression to muscle-invasive disease. Given and colleagues and

Shipley and colleagues also reported initial management of non–muscle-invasive bladder cancer recurrence with conservative therapy, leading to disease-free bladders.[16,55]

Muscle-invasive recurrences after TMT should be managed by salvage cystectomy if patients are medically fit for surgery. Encouragingly, patients whose disease recurs with muscle-invasive tumors and who undergo salvage cystectomy may still achieve reasonable outcomes, with disease-specific survival rates at 5 and 10 years after salvage cystectomy of 58% and 44%, respectively.[12] Additionally, Shipley and colleagues reported similar disease-specific survival for those who underwent early (after initial incomplete response to TMT) vs delayed (after muscle-invasive recurrence) salvage cystectomy.[34]

Treatment-Related Adverse Effects and Quality of Life After Trimodal Therapy

TMT, although believed to confer less morbidity than radical cystectomy, is not without toxicity, which may occur at any point during treatment. Complete transurethral resection of bladder tumor, referred to as "radical" or "maximal" TUR, risks bladder perforation in an attempt to leave no residual disease behind.[57] Small extraperitoneal perforations, which are common (and often intentional) during radical TUR,[41] may be managed by prolonged catheter drainage, whereas intraperitoneal perforations typically require laparotomy and repair. After the initial radical TUR, patients may experience toxicity from chemoradiation and/or neoadjuvant/adjuvant combination chemotherapy. The most recent TMT trials, which utilized a variety of radiosensitizing chemotherapeutic agents and combination chemotherapy regimens, reported acute grade 3 or 4 toxicity in 36% to 85% of cases.[10,11,22] Hematologic toxicity was most common, followed by genitourinary and gastrointestinal toxicity. Although adverse events were common during the chemoradiation portion of TMT, acute toxicity was most common following combination chemotherapy. Late-onset grade 3 or 4 gastrointestinal and genitourinary sequelae of chemoradiation include hemorrhagic cystitis, irritative voiding symptoms, bladder contraction and dysfunction, radiation proctitis, and constipation, and may occur in 6% to 11% of patients after TMT.[50,58]

Following TMT, patients consistently report improved quality of life as compared with radical cystectomy patients, particularly in sexual function domains.[59,60] After TMT, patients report some degree of long-term distress from gastrointestinal or genitourinary symptoms in 32% and 26% of cases, respectively. Zietman and colleagues performed urodynamics in 32 patients who underwent TMT; 22% had decreased bladder compliance and 75% had normal bladders as measured by urodynamics.[61]

Overall, toxicity after TMT is common and is most often related to chemotherapy agents, but long-term sequalae are relatively uncommon and patients generally report better quality of life.

Practice Patterns and Challenges With Uptake of Trimodal Therapy

Per the AUA guidelines, bladder-preserving therapy should be considered a primary option for patients with muscle-invasive cancer. Despite encouraging oncologic outcomes, there is reluctance among urologists to provide TMT in lieu of primary radical cystectomy. The lack of randomized trials comparing radical cystectomy and TMT may be one significant barrier to implementation. The aforementioned studies comparing treatment modalities are fraught with challenges inherent to retrospective reviews and often reach conflicting conclusions. Unfortunately, developing a large randomized trial for complex interventions requiring multidisciplinary investment is extremely complicated and is unlikely to be completed, as evidenced by the well-funded and well-organized SPARE trial.[33] An additional concern with TMT is the potential need for salvage cystectomy following chemoradiation and the risk of complications related to surgery.[62] Although salvage cystectomy may be a technically demanding operation, recent retrospective series have demonstrated acceptable morbidity and mortality after the procedure.[63,64] Additionally, although cost may not be the most influential factor when considering primary treatment options for muscle-invasive bladder cancer, TMT is estimated to cost substantially more per patient than radical cystectomy over time.[37] Finally, the logistics and feasibility of developing a TMT protocol outside of a large academic referral center may pose a challenge as well. We recognize that in community-based settings, delivery of multidisciplinary care as required for TMT may be difficult. In these settings, it may be prudent to have a single provider serve as the champion for a TMT protocol. This individual would be the primary physician providing care for the bladder cancer patient, and could serve as a quarterback to help coordinate the different aspects of TMT. As an example, if a urologist were to serve as the central advocate for TMT in a community-based setting, he or she could perform the radical TUR, discuss the treatment options with the patient, and refer the patient to radiation oncology for radiotherapy if appropriate. The urologist would remain intimately involved in the patient's care, and would simultaneously arrange a follow-up visit for endoscopic evaluation either during or after completion of radiotherapy. Then, based on the endoscopic and radiographic responses, the urologist would determine the need for salvage therapy.

Alternative Bladder-Sparing Treatment Approaches to Muscle-Invasive Bladder Cancer

Although TMT is the most extensively studied and supported bladder-sparing option for muscle-invasive bladder cancer, alternative options include radical TUR alone, partial cystectomy, and radiation monotherapy. These options lack comparative data to establish safety and efficacy and are not considered first-line by AUA or EAU guidelines. Encouraging outcomes with these approaches must also be viewed with the understanding that enrolled patients are often carefully selected and may not represent outcomes achievable in the general population of patients with muscle-invasive bladder cancer. Without comparative data, these modalities must be used selectively, with shared decision-making between the clinician and patient.

The best known of these options is radical TUR. Solsona and colleagues published the longest follow-up of patients with muscle-invasive bladder cancer treated by radical TUR monotherapy.[65] Five-year cancer-specific survival was 81.9% among 133 patients who were rendered cT0 after TUR. Similarly, Herr and colleagues demonstrated a 10-year disease-specific survival of 76% among patients treated with radical TUR alone.[41] Selecting appropriate tumors, specifically relatively small (<2-3 cm), solitary cT2 tumors without additional risk factors, is crucial to success with radical TUR monotherapy.

For surgical candidates with solitary tumors in favorable locations, partial cystectomy is an attractive organ-sparing option. Historically, unacceptably high recurrence rates and morbidity prevented uptake of this approach.[66] Contemporary series, however, report significantly improved outcomes with more stringent patient selection, such as limiting enrollment to those with solitary tumors located at the bladder dome without carcinoma in situ. In carefully selected patients, 2 retrospective series achieved a 5-year overall survival of 67% to 69%.[67,68] A general rule of thumb is that partial cystectomy should only be considered for patients with a single tumor at a single point.

Finally, radiation monotherapy without concurrent chemotherapy is an option for selected patients. The role of radiosensitizing chemotherapy has been confirmed by 2 randomized studies,[22,45] and this treatment should be added to radiation when possible. Additionally, patients with chronic kidney disease may be able to use alternative, less nephrotoxic chemotherapeutic radiosensitizing agents. Therefore, radiation monotherapy may be best utilized as a palliative or salvage option for nonsurgical elderly patients with significant comorbidities that prevent the use of radiosensitizing chemotherapy.

Future Directions

Newer trials are investigating the combination of immunotherapy and chemoradiotherapy. In addition, emerging data on biomarkers such as MRE11 and ERCC1/2 could be used in clinical practice to help select ideal candidates for TMT. High expression of the MRE11 protein is associated with improved outcomes, including cancer-specific survival, among patients treated with definitive radiation compared with surgery.[69] Similarly, loss of ERCC1/2 expression is associated with better chemoradiation response.[70] The phase 3 SWOG/NRG 1806 trial (Chemoradiotherapy With or Without Atezolizumab in Treating Patients With Localized Muscle Invasive Bladder Cancer) is investigating TMT with or without atezolizumab (Tecentriq, Genentech) and will have a biomarker validation component that should help integrate immunotherapy biomarkers into clinical care decisions.

Conclusion

Bladder-sparing TMT is a well-studied alternative to radical cystectomy for select patients with nonmetastatic muscle-invasive bladder cancer. Although no randomized trial exists to establish equivalence to radical cystectomy, numerous prospective series demonstrate encouraging outcomes and, perhaps not surprisingly, patients tend to favor an organ-sparing approach over radical cystectomy. In the future, randomized trials may help clarify the comparative efficacy of these treatment options, although obstacles to complete such trials are significant. In the meantime, multidisciplinary clinics with urology, oncology, and radiation oncology representation may be best suited to help patients navigate these complex treatment decisions.

Disclosures

The authors have no relevant disclosures.

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