RESEARCH ARTICLE

Radiation-based, multi-modality therapy for elderly patients with muscle-invasive bladder cancer: Utility, Rationale, and Efficacy

Authors
Kimberly R Gergelis MD[1], William G Breen MD[1], and Richard Choo MD[1]

Affiliations
[1]Department of Radiation Oncology, Mayo Clinic, Rochester, MN

Corresponding Author:
Richard Choo MD
Choo.c@mayo.edu

Abstract

Muscle-invasive bladder cancer (MIBC) typically affects older adults, with a median age at diagnosis of 73. Due to its aggressive disease course, definitive treatment is required. With curative-intent treatment, patients with muscle-invasive bladder cancer have an overall survival of ranging from 48-57% with a cancer-specific survival ranging from 52-71% at 5 years.

Radical cystectomy (RC) +/- neoadjuvant chemotherapy (CHT) has been considered a standard of care for MIBC. However, RC carries a high incidence of perioperative complications, including a mortality rate of 1.5-3%. In addition, many elderly patients with bladder cancer suffer from additional comorbidities, prohibiting RC. These patients are often not offered other curative treatment options. Untreated patients with MIBC are at a very high risk of mortality, with five-year overall survival and cancer-specific survival of approximately 5% and 14%, respectively. Tri-modality therapy (TMT), incorporating maximal transurethral bladder tumor resection, radiotherapy, and CHT, is efficacious with a relatively low incidence of major toxicity for MIBC. As a result, TMT has been acknowledged as a viable alternative to RC, and an attractive option for elderly patients who often have major medical comorbidities and/or prefer bladder-preservation.

The object of this review is to discuss the utility, rationale, and efficacy of TMT in elderly patients, which can offer a curative treatment for life-threatening MIBC but also safeguard the quality of life with organ-preservation.

Keywords: Bladder cancer, tri-modality therapy (TMT), radical cystectomy (RC), elderly

1 Introduction

Bladder cancer is the second most common malignancy of the genitourinary tract, representing 4.4% of new cancer cases in the United States in 2021.[1] Elderly patients are disproportionally affected by bladder cancer with a median age at diagnosis of 73.[2] While the majority of bladder cancers present as superficial tumors, 21% are muscle-invasive and non-metastatic at the time of diagnosis, requiring definitive treatment due to their aggressive disease course.[3]

With curative-intent treatment, patients with muscle-invasive bladder cancer (MIBC) have an overall survival of ranging from 48-57% with a cancer-specific survival ranging from 52-71% at 5 years.[4-7] Radical cystectomy (RC) +/- neoadjuvant chemotherapy (CHT) has been considered a standard of care for MIBC in the United States. However, RC carries a high incidence of perioperative complications, including a mortality rate of 1.5-3%.[8, 9] In addition, many elderly patients with bladder cancer suffer from additional comorbidities, prohibiting RC. These patients are often not offered other curative treatment options.[10] Untreated patients with MIBC are at a very high risk of mortality, with five-year overall survival and cancer-specific survival of approximately 5% and 14%, respectively.[7] Over the years, a growing number of studies have reported that tri-modality therapy (TMT), incorporating maximal transurethral bladder tumor resection (TURBT), radiotherapy (RT), and CHT, is efficacious with a relatively low incidence of major toxicity for MIBC. As a result, TMT has been acknowledged as a viable alternative to RC, and an attractive option for elderly patients who often have major medical comorbidities and/or prefer bladder-preservation.

In this review, we describe the utility, rationale, and efficacy of TMT in elderly patients, which can offer a curative treatment for life-threatening MIBC but also safeguard patient quality of life with organ-preservation.

2 Radical Cystectomy +/- Neoadjuvant Chemotherapy for Bladder Cancer

In the United States, RC +/- neoadjuvant CHT is the most commonly utilized curative approach for MIBC.[11] RC involves en bloc resection of the bladder as well as removal of the prostate and seminal vesicles in men or removal of the uterus, ovaries and part of the vagina in women. In addition, a bilateral pelvic lymphadenectomy is generally performed. The options for urinary tract reconstruction include incontinent conduit diversions, continent cutaneous diversions, and orthotopic neobladders.[12]

Neoadjuvant, cisplatin-based CHT is generally added for patients being treated with RC. The phase III SWOG 8710 clinical trial demonstrated that the addition of three cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) increased the likelihood of achieving no residual cancer in a cystectomy specimen, which was associated with improved overall survival. In this study of 307 patients with median age of 63 years, the use of neoadjuvant CHT increased the 5-year overall survival from 43% to 57%.[6] Of note, the 5-year overall survival was significantly worse for patients with ≥ 65 years old than those < 65 years old (42 % vs. 61%, respectively).[13] Although the use of M-VAC did not adversely affect a patient's chance of undergoing RC, nor did it increase the risk of death or complications related to RC, at least one third of patients treated with neoadjuvant M-VAC developed severe hematologic or gastrointestinal effects. As M-VAC is a toxic regimen, especially for frail patients, an alternative neoadjuvant CHT regimen of gemcitabine and cisplatin (GC) has been explored. Dash et al reported similar rates of pathologic complete response in patients treated with four cycles of neoadjuvant GC, compared to historical controls treated with M-VAC. In addition, a higher percentage of patients received all intended cycles of GC, compared to M-VAC.[14, 15] Despite the greater

tolerability of GC, many frail patients are still unable to tolerate neoadjuvant or adjuvant CHT.

2.1 Morbidity, Mortality, and Quality of Life after Radical Cystectomy

RC carries a high incidence of perioperative complications with a mortality rate of 1.5-3% in all patients.[8, 9] Due in part to comorbid conditions, the 90-day mortality increases to 6.4%, 10.1%, and 14.8% in patients ages 65-69, 70-79, and 80 or older, respectively.[9]

In addition to a high perioperative mortality rate, it has been reported by Shabsigh et al that more than half of patients experience a perioperative complication within 90 days of RC.[8] Although most complications were Clavien grade 1-2, which comprises the need to use oral medications, bedside intervention, intravenous medications, total parenteral nutrition, enteral nutrition, or blood transfusion, 13% of patients suffered from grade 3-5 complications, which include the necessity of procedures or additional operations, residual disability requiring major rehabilitation, organ resection, or death.[16]

The prevalence and extent of surgical morbidity from RC has been recently reported in a phase III study of 350 patients, comparing open RC versus robot-assisted RC.[17] In this study, the median patient age was 67 years for open RC and 70 years for robot-assisted RC. Only patients that were deemed medically fit for RC and had no history of previous open abdominal or pelvic surgery were eligible for the study. Even in this group of patients with good performance status and medical condition, the 90-day mortality rate was 3% for each type of RC. Modified Clavien-Dindo grade 1-5 adverse events at 90 days were observed in 69% and 67% in the open RC and robot-assisted RC group, respectively. The four most common perioperative complications were urinary tract infection (26% for open RC vs. 35% for robot-assisted RC), ileus (20% vs. 22%), acute renal failure (13% vs. 11%), and sepsis (11% vs. 10%). The rate of serious grade 3-5 adverse events was 22% for each type of RC.

Another factor to consider when determining whether to undertake RC or to pursue an alternative treatment is the potential impact of RC on quality of life, especially for elderly patients who often have multiple medical comorbidities and invariably confront competing mortality risks from other causes. The detrimental effect of RC on quality of life can be considerable in elderly patients. In a study including patients 65 or older enrolled on Medicare Advantage managed care plans with newly diagnosed bladder cancer, the Medicare Health Outcomes Survey (MHOS) was analyzed to evaluate the impact of bladder cancer diagnosis and treatment on health-related quality of life.[18] Patients who underwent cystectomy reported significant declines in physical, mental, and social health-related quality of life (HRQoL) over time compared to control subjects without cancer.

3 Tri-modality therapy

TMT incorporates a TURBT, which is maximal bladder tumor debulking, followed by RT and concurrent CHT.[19] Although not widely utilized in the United States, TMT has been acknowledged as an effective and viable alternative treatment for MIBC in recent years. Attractiveness of TMT stems from three practicalities: 1. It offers a curative treatment for MIBC with organ-preservation, 2. It is generally well-tolerated, even in elderly or frail patients, and its adverse effect on quality of life is at least equal or less than that of RC, 3. Even if a patient suffers a local tumor recurrence after TMT, RC is still available as a salvage treatment.

There has been no phase III study comparing RC with TMT. Thus, the data comparing RC with TMT come from retrospective studies and a systemic review with meta-analysis, and are hampered with

multiple inherent shortcomings. In a retrospective study from the multi-disciplinary bladder cancer clinic of the Princess Margaret Cancer Center, oncologic outcomes were compared between RC and TMT, using a propensity score match.[20] Patients were matched, based on age, gender, clinical T stage, clinical N stage, the presence or absence of concurrent carcinoma in situ, the presence or absence of hydronephrosis, Eastern Cooperative Oncology Group performance status, Charlson comorbidity score, and treatment date. In this matched-cohort analysis of 112 patients (56 treated with RC vs. 56 with TMT) with a median follow-up of 4.51 years, there was no difference in overall survival (64.3% alive in RC vs. 60.7% alive in TMT, p=0.84), and 5-year disease-specific survival (73.2 % for RC vs. 76.6% in TMT, p=0.49).

In addition, over the last 30 years, multiple prospective studies have shown that TMT can yield equivalent long-term disease control and overall survival for well-selected patients, compared to the outcomes of patients treated with RC +/- CHT.[4, 5, 21, 22] In a pooled analysis of 6 RTOG (Radiation Therapy Oncology Group) prospective studies, long-term outcomes of TMT were reported for a cohort of 468 patients with median age of 66 years.[5] With a median follow-up of 4.3 years, 5-year overall and disease-specific survival were 57% and 71%, respectively. The 5-year estimated rates of muscle-invasive local recurrence, non-muscle-invasive local recurrence, and distant metastasis after TMT were 13%, 31%, and 31%, respectively. In a subgroup analysis, elderly patients with age ≥ 75 years had similar rates of completion of RT dose of ≥ 60 Gy, bladder preservation, and disease-specific survival, in comparison with younger patients. This notable result suggests that TMT should be considered for elderly patients who are not medically suitable for RC or desire to pursue organ-preservation.

Several studies have demonstrated that TMT is generally well-tolerated, even among elderly patients or those who are poor surgical candidates due to other medical comorbidities.[11, 23-25] Our group reported a retrospective study of 84 elderly patients who received TMT or RT alone for MIBC. Median patient age in the study was 81 years (range: 70 – 94). Only 29% were considered to have both medical fitness to withstand RC and a surgically resectable bladder tumor; 61% had a surgically resectable tumor but were medically unfit for RC; 7% were both surgically unresectable and medically unfit for RC; 2% were medically fit, but had a surgically unresectable tumor. In this elderly, medically compromised population, 73% (60 patients with concurrent CHT and 1 patient with neoadjuvant CHT) were still able to undergo TMT, while 27% (23 patients) received RT alone.[24]

Another appealing aspect of TMT is the availability of salvage treatment options in the event of post-treatment local tumor recurrence. While TMT offers an opportunity to preserve one's own native bladder, the prospect of having RC as a salvage treatment for post-TMT local tumor recurrence is not lost. This makes TMT particularly appealing to elderly patients who frequently prefer to avoid a major surgical intervention, if possible, in their late life. Local tumor recurrence in the bladder after TMT can be either non-muscle-invasive or muscle-invasive. Non-muscle-invasive local recurrence may not require RC and can be managed with TURBT +/- intravesical therapy.[26] When local tumor recurrence is muscle-invasive, RC is the only viable salvage treatment option. The rate of salvage RC has been reported ranging from 11-42%.[4, 5, 22, 27]

In the phase III BC2001 clinical trial comparing RT alone versus RT + concurrent CHT (RT-cCHT) with fluorouracil (5-FU) and mitomycin C (MMC), the rate of cystectomy at 2 years was 16.8% for the RT group and 11.4% for the RT-cCHT group.[22] Of the 51 patients requiring cystectomy, 41 were for bladder

tumor recurrence and 4 were due to late effects of RT. In a pooled analysis of 6 RTOG prospective studies of TMT, 100 (21%) of a cohort of 468 patients ultimately underwent RC.[5] Of these patients, 62% required immediate cystectomy for incomplete response to induction CHT + RT, 36% required salvage cystectomy for post-TMT tumor recurrence, and 2% had cystectomy for other causes. Among patients undergoing either immediate cystectomy for incomplete response to induction CHT + RT or salvage cystectomy for local recurrence after TMT, the 5-year overall and disease-specific survival were 45% and 60%, respectively.

3.1 Use of Concurrent Chemotherapy in Trimodality Therapy

The BC2001 clinical trial examined the effect of adding concurrent CHT (5-FU and MMC) to RT for MIBC.[22] A total of 360 patients were randomized between RT-cCHT and RT alone. With a median follow-up of 5.8 years, the study reported that the addition of concurrent CHT to RT significantly improved locoregional disease-free survival at 2 years: 67% for the RT-cCHT group vs. 54% for the RT alone (p=0.03). Overall survival at 5 years was 48% for the RT-cCHT vs. 35% for the RT alone. In addition, multiple phase II studies have reported that the addition of concurrent CHT to RT improves locoregional tumor control, compared with historic data of RT alone.[28-37]

Various concurrent CHT regimens have been evaluated over the years. A cisplatin-based combination CHT or 5-FU + MMC have been most widely utilized in current clinical practice. For those patients with significant medical comorbidity such as impaired renal function, alternative CHT regimens containing paclitaxel, carboplatin, or gemcitabine, either alone or combined with other agents have been considered.[28, 33-39]

3.2 Morbidity and Quality of Life with Trimodality Therapy

TMT, which offers an opportunity to preserve one's own native bladder and to avoid a major surgical intervention, comes with its own set of adverse events and potential detrimental effect on quality of life. Acute gastrointestinal (GI) and genitourinary (GU) side effects are expected from RT, since parts of normal organs adjacent to the bladder and/or regional pelvic lymph nodes are exposed to radiation. The addition of concurrent CHT can independently cause hematologic, renal, GI, or neurologic toxicity, and potentially exacerbate RT-related side effects such as diarrhea. Acute grade 3-4 hematologic toxicity of TMT, largely due to the adverse effects of CHT, has been reported at a rate of 17% to 29%.[22, 40, 41] Acute side effects of TMT are most commonly transitory and resolve over 4-8 weeks following the completion of TMT in a majority of patients. Late side effects and the effect on quality of life are, in general, more important concerns to elderly patients who typically desire to maintain good quality of life as much as possible in their late life.

Favorable tolerability of TMT is described in the previous section, using our retrospective study as an example.[24] In the phase III trial BC2001, the median age of patients enrolled on the trial was 71.9 years, with a quarter of patients enrolled over the age of 76.2. Despite the advanced age of patients enrolled, greater than 95% of patients were able to complete the prescribed RT, and 96%, 94%, and 80% were able to receive at least 80% of the target MMC, week 1 5-FU, and week 4 5-FU doses, respectively.[22] In this study, acute grade 3 or 4 side effects occurred in 36% in the RT-cCHT group, and 27.5% in the RT alone (p=0.07). These adverse effects were mainly gastrointestinal symptoms. The rate of late grade 3 or 4 adverse events at some time during follow-up was 8.3% for the RT-cCHT group and 15.7% for the RT alone group, using the RTOG grading system. At 1

year following TMT, 3.3% of the RT-cCHT group and 1.3% of the RT alone group had grade 3 or 4 adverse events, and all these adverse events were related to GU symptoms. In our retrospective study of elderly patients of 84 patients, 31% and 5% experienced late grade 2 or 3 GU and GI adverse events, respectively, using the Common Terminology Criteria for Adverse Events version 5; 15% had late grade 3 GU adverse events (urinary incontinence, radiation cystitis, or ureteral obstruction), and 4% had late grade 3 GI adverse events (radiation proctitis and stricture of sigmoid colon). None had late grade 4 or 5 adverse events.[24]

A urodynamic study of 31 patients previously treated with TMT reported decreased bladder compliance in 7 patients; the remaining 24 patients had normally functioning bladders.[42] Of those with reduced bladder compliance, only about one-third reported distressing symptoms. The reported incidence of requiring cystectomy due to severe GU toxicity of TMT is very low with rates ≤ 2%.[22, 27, 32, 38, 40] In the BC2001 study, only 4 patients of a total of 360 patients (1.1%) required cystectomy due to late toxicity from RT.[22]

Quality of life (QoL) considerations are a key driver for the appeal of the organ-preservation approach of TMT, especially for elderly patients. In a cross-sectional study investigating QoL, a total of 226 patients who had undergone TMT or RC for MIBC were surveyed with 6 validated QoL instruments.[43] Among the 173 responders (response rate of 77%), 64 received TMT and 109 had RC. The median interval from diagnosis to questionnaire completion was 9 years for the TMT patients and 7 years for the RC patients. In a multivariate analysis, the TMT patients had better QoL by 9.7 points (out of 100 points) than the RC patients (p=0.001). The TMT patients had significantly better physical, role, social, emotional, and cognitive functioning (p≤0.04), and better bowel function (p=0.02) with fewer bowel symptoms (p≤0.05). TMT was also associated with better sexual function (p≤0.02) and body image (p<0.001). The urinary symptom scores were similar between the two groups. The main limitations of the study are the lack of baseline QoL assessments and potential selection bias, which are inherent shortcomings of a cross-sectional study. Another study compared TMT to RC with a Markov model using decision-analytic modelling.[44] This study reported that TMT had an incremental gain of 0.59 quality-adjusted life years (QALYs), compared with RC. Sensitivity analyses indicated that this gain in QALYs with TMT was largely driven by the QoL differences between TMT and RC.

Patient-reported QoL measures better capture the lasting effects patients experience from treatment, compared to physician-reported toxicities. The BC2001 and BCON clinical trials utilized the Late Effects Normal Tissue Toxicity Force (LENT)-Subjective, Objective, Management, Analytic (SOMA) tool to capture patient-reported late urinary and rectal dysfunction.[45] At two years post-TMT, 25-28% of patients experienced at least one LENT-SOMA bladder or rectal toxicity, with 3-6% of patients experiencing rectal toxicity and 24-25% of patients experiencing bladder toxicity. At five years, at least one late grade 3-4 toxicity was reported in 32-33% of patients, with 3-7% experiencing rectal toxicity and 30-31% experiencing bladder toxicity. BC2001 also collected HRQoL utilizing the Functional Assessment of Cancer Therapy-Bladder (FACT-BL) questionnaire. This study found that HRQoL declined at end of treatment, but recovered to baseline score at 6 months and remained similar or improved from baseline in two-thirds of patients thereafter.[46]

3.3 Commonly Utilized Radiotherapy Fractionations and Treatment Volumes

Several RT fractionation schemes have been explored for MIBC. Currently, the most

commonly utilized RT regimens for curative-intent include conventional fractionation, treating to a total dose of 60-66 Gy in 1.8-2.0 Gy per day fractions, and a moderately hypofractionated regimen of 55 Gy in 20 fractions, delivered daily.[4, 22, 38, 45, 47] The RTOG studies traditionally included the visible tumor, whole bladder, and elective pelvic lymph nodes in the clinical target volume of RT, whereas the clinical target volume of RT in BC2001 was limited to the visible tumor, whole bladder, and a generous planning target volume margin.

3.4 Trimodality Therapy for Elderly Patients

Using the National Cancer Database, Gray et al reported that a high proportion of older patients with MIBC in the United States did not receive definitive therapy.[10] The use of a definitive therapy (RC or RT) progressively decreased with advancing age. Of patients aged 71 to 80 years, 81 to 90 years, and >90 years, only 55%, 35%, and 15% were treated definitively, respectively. It was also noted that the use of RC steadily decreased with advancing age, whereas RT was increasingly used for patients of older age. However, the significant decrease in RC with advancing age was not offset by a proportional increase in the utilization of RT, resulting in a significant shortfall in the utilization of definitive treatment in older patients.

The Mayo Clinic Department of Radiation Oncology reported their experience of 84 elderly patients with 70 years of age or older.[24] As previously mentioned, the median age was 81 years, and only 29% were deemed to have medical fitness to undergo RC, along with a surgically resectable bladder tumor. Sixty-one percent, 29%, and 11% had clinical stage II, III, and IV, respectively. Sixty patients (71%) received concurrent CHT with RT; 1 (1%) received neoadjuvant RT prior to RT; 23 (27%) received RT alone. RT was delivered to the bladder and pelvic lymph nodes in 69%, and to the bladder only in 31%. The common dose-fractionation regimens used were 65 Gy in 35 fractions to the bladder tumor with 45 Gy in 25 fractions to the pelvic lymph nodes, and 55 Gy in 20 fractions to the bladder tumor with 44 Gy in 20 fractions to the remaining bladder. Of the 60 patients receiving concurrent CHT, 20 were unable to complete planned CHT due to a variety of reasons including deteriorating renal function, hematologic toxicity, diarrhea, and fatigue. Two patients were unable to complete RT: one due to unrelated hemorrhagic stroke, and the other due to failure to thrive and GU symptoms. With median follow-up of 5.7 years, disease-specific survival was 80%, 68%, 64%, and 54%, at 1, 2, 3, and 5 years, respectively. Overall survival was 69%, 49%, 42%, and 25% at 1, 2, 3, and 5 years, respectively. Median overall survival was 1.9 years. The progressively larger discordance between disease-specific survival and overall survival over time illustrates that competing mortality risk from causes other than bladder cancer is substantial in these elderly patients with compromised health status. Medical fitness to undergo RC, receipt of CHT, lower T stage, and TURBT were associated with better overall survival. At 5 years, 23 patients (27%) had local recurrence; of these, 12 were muscle-invasive disease, and the remaining 11 were superficial or in situ disease. The rates of pelvis relapse and distant metastasis at 5 years were 9% and 33%, respectively.

In a retrospective study, Boustani et al compared the outcomes of TMT with that of RC in elderly patients.[23] In this study, there were 92 patients (median age: 83 years) treated with RC and 72 patients (median age: 84 years) treated with TMT. With median follow-up of 2.9 years, there was no difference in median overall survival, 1.99 years for the RC group vs. 1.97 years for the TMT group. Also, there was no difference in median progression-free survival, 1.25 years for the RC group vs. 1.52 years for the TMT group. The 5-year overall survival was also similar, 21.7% for the RC

group vs. 24.9% for the TMT group. It is interesting to note that the 5-year overall survival rates of 21.7% in the RC group and 24.9% in the TMT group in this study are similar to that of the Mayo Clinic series (25%). In another retrospective series of 39 elderly patients (median age: 78 years) treated with TMT or RT alone, Tran et al reported overall survival of 43% at 3 years and 29% at 5 years.[11]

4 Immunotherapy for Bladder Cancer

Immune-stimulating treatments for bladder cancer have been utilized for decades, with Bacillus Calmette-Guerin (BCG) intravesicular therapy representing a standard of care treatment for non-muscle invasive bladder cancer since the 1970's.[48, 49] In recent years, immune checkpoint inhibitors of programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1) have demonstrated response rates of 21-29% in patients with metastatic urothelial cancers, and have been incorporated into the National Comprehensive Cancer Network (NCCN) preferred regimens for both cisplatin-eligible and ineligible patients.[50-53]

In patients with metastatic urothelial carcinoma who have already progressed on platinum-based CHT, pembrolizumab, a PD-1 inhibitor, demonstrated an overall survival benefit over further cytotoxic CHT in the phase III, KEYNOTE-045 clinical trial.[52] Importantly, pembrolizumab also resulted in lower rates of grade 3+ toxicity than CHT (15% vs. 49%). Similarly, in the phase III, JAVELIN Bladder 100 clinical trial of 700 patients with metastatic or unresectable locally advanced urothelial carcinoma, avelumab, a PD-L1 inhibitor, improved overall survival as maintenance therapy after cytotoxic CHT, without unexpected increases in toxicity rates.[54]

Elderly patients have been well represented on clinical trials of immune checkpoint inhibitors for bladder cancer. In the phase II, KEYNOTE-052 study of pembrolizumab for patients ineligible for cisplatin-based CHT, nearly half of patients were 75 years or older, with 11% at least 85 years old.[50] As in other cancer types, elderly patients who are unable to tolerate standard cytotoxic CHT may be able to benefit from PD-1 and/or PD-L1 inhibitors.

Immune checkpoint inhibitors are also being evaluated in patients with localized bladder cancer. Recent studies demonstrated the utility of neoadjuvant immunotherapy prior to RC, with pathological complete response rates of 31-42%.[55, 56] In the adjuvant stetting, nivolumab, a PD-1 inhibitor, improved disease-free survival after RC in patients with PD-L1 levels of 1% or more.[57]

Despite the promise of these studies, less than one-third of patients respond to single agent immune checkpoint inhibitors. Patients with higher PD-L1 expression or higher tumor mutational burden appear to have higher response rates to pembrolizumab and avelumab, respectively.[50, 51] These findings demonstrate that biomarkers have potential to select patients who will benefit most from treatment paradigms incorporating immune checkpoint inhibitors. A phase II study demonstrated that dual immune checkpoint inhibition utilizing ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor) with nivolumab (a PD-1 inhibitor) increased the response rate to 38%, at the cost of increased toxicity.[58]

Ongoing studies aim to identify which patients will benefit most from immune checkpoint inhibitors, and how response rates can be improved.

4.1 Immunotherapy Incorporated with TMT

Currently, immunotherapy is not included in the NCCN guidelines for use with RT in TMT setting.[53] However, this approach is receiving extensive study and has potential to improve response rates to TMT and expand curative potential for patients who are not

candidates for typical concurrent cytotoxic CHT.

At least 25 trials incorporating immunotherapy with RT for bladder cancer are currently underway, though few results have been reported to date.[59] A phase II clinical trial recently published in abstract form included 54 patients with MIBC who were ineligible or declined cystectomy, and were treated with one cycle of pembrolizumab prior to TURBT, followed by 52 Gy in 20 fractions of RT with concurrent gemcitabine and pembrolizumab.[60] Median age in this study was 67 years, with patients up to 97 years old enrolled. The protocol treatment was well tolerated with less than 10% of patients discontinuing any treatment. The one-year estimated bladder-intact disease free-survival rate was 77%, a promising result in this patient population. Full publication of this study and others are awaited for further details on efficacy and toxicity, as well as correlative analyses identifying which patients may benefit most from this approach. Selected large randomized clinical trials incorporating immunotherapy with RT for non-metastatic bladder cancer are listed in Table 1.

Table 1: Selected Current Randomized Clinical Trials Incorporating Immunotherapy with RT for Non-Metastatic Bladder Cancer

Study	Drug	Treatment Arm(s)	Enrollment (actual or planned)	Primary Endpoint
NCT04241185 (KEYNOTE-992)	Pembrolizumab	TMT vs. TMT + pembrolizumab	636	BI-EFS
NCT03775265 (SWOG/NRG-1806)	Atezolizumab	TMT vs. TMT + atezolizumab	475	BI-EFS
NCT03768570 (BL13)	Durvalumab	TMT vs. TMT + durvalumab	238	DFS
NCT04216290 (INSPIRE)*	Durvalumab	TMT vs. TMT + durvalumab	114	Clinical CR

BIDFS: Bladder-intact Event Free Survival. DFS: Disease-Free Survival, CR: Complete Response. *Includes patients with clinically lymph node-positive (non-metastatic) disease.

5 Conclusion

Bladder cancer is a disease that primarily affects older adults with challenging medical comorbidities. For patients with MIBC, RC +/- CHT is the most common treatment offered. For patients that are not medically fit to withstand RC, choose not to undergo an extensive surgery, or wish to preserve their own bladder, TMT should be considered as a curative treatment alternative. TMT is well tolerated by even frail patients and rarely results in treatment-related mortality. TMT is a particularly attractive treatment strategy for elderly patients, who often have other major medical comorbidity and face competing mortality risks from other causes, in three aspects: 1. A prospect to receive a curative treatment with an opportunity to have organ-preservation, 2. Favorable tolerability with acceptable and manageable acute and late adverse effects, 3. A prospect of being still able to have cystectomy in the event of local tumor recurrence after TMT. Clinical trials evaluating the role of immunotherapy in the setting of TMT are underway. Further studies will provide insights into the utility of biomarkers to better identify which patients are most likely to benefit from immunotherapy and/or cytotoxic CHT.

References:

1. SEER. Bladder Cancer - Cancer Stat Facts. 2021.
2. Society AC. Key Statistics for Bladder Cancer. 2021.
3. Nielsen ME, Smith AB, Meyer AM, Kuo TM, Tyree S, Kim WY, et al. Trends in stage-specific incidence rates for urothelial carcinoma of the bladder in the United States: 1988 to 2006. *Cancer*. 2014;120(1):86-95.
4. Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm M, Heney NM, et al. Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience. *European urology*. 2017;71(6):952-60.
5. Mak RH, Hunt D, Shipley WU, Efstathiou JA, Tester WJ, Hagan MP, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(34):3801-9.
6. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *The New England journal of medicine*. 2003;349(9):859-66.
7. Martini A, Sfakianos JP, Renström-Koskela L, Mortezavi A, Falagario UG, Egevad L, et al. The natural history of untreated muscle-invasive bladder cancer. *BJU Int*. 2020;125(2):270-5.
8. Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *European urology*. 2009;55(1):164-74.
9. Schiffmann J, Gandaglia G, Larcher A, Sun M, Tian Z, Shariat SF, et al. Contemporary 90-day mortality rates after radical cystectomy in the elderly. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2014;40(12):1738-45.
10. Gray PJ, Fedewa SA, Shipley WU, Efstathiou JA, Lin CC, Zietman AL, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *European urology*. 2013;63(5):823-9.
11. Tran E, Souhami L, Tanguay S, Rajan R. Bladder conservation treatment in the elderly population: results and prognostic factors of muscle-invasive bladder cancer. *American journal of clinical oncology*. 2009;32(4):333-7.
12. Tyson MD, 2nd, Barocas DA. Quality of Life After Radical Cystectomy. *Urol Clin North Am*. 2018;45(2):249-56.
13. Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(14):2781-9.
14. Dash A, Pettus JAt, Herr HW, Bochner BH, Dalbagni G, Donat SM, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer*. 2008;113(9):2471-7.
15. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet (London, England)*. 1999;354(9178):533-40.

16. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery*. 1992;111(5):518-26.
17. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. *Lancet (London, England)*. 2018;391(10139):2525-36.
18. Smith AB, Jaeger B, Pinheiro LC, Edwards LJ, Tan HJ, Nielsen ME, et al. Impact of bladder cancer on health-related quality of life. *BJU Int*. 2018;121(4):549-57.
19. Shipley WU, Prout GR, Jr., Kaufman SD, Perrone TL. Invasive bladder carcinoma. The importance of initial transurethral surgery and other significant prognostic factors for improved survival with full-dose irradiation. *Cancer*. 1987;60(3 Suppl):514-20.
20. Kulkarni GS, Hermanns T, Wei Y, Bhindi B, Satkunasivam R, Athanasopoulos P, et al. Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(20):2299-305.
21. Gofrit ON, Nof R, Meirovitz A, Pode D, Frank S, Katz R, et al. Radical cystectomy vs. chemoradiation in T2-4aN0M0 bladder cancer: a case-control study. *Urologic oncology*. 2015;33(1):19.e1-.e5.
22. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *The New England journal of medicine*. 2012;366(16):1477-88.
23. Boustani J, Bertaut A, Galsky MD, Rosenberg JE, Bellmunt J, Powles T, et al. Radical cystectomy or bladder preservation with radiochemotherapy in elderly patients with muscle-invasive bladder cancer: Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators. *Acta oncologica (Stockholm, Sweden)*. 2018;57(4):491-7.
24. Gergelis KR, Kreofsky CR, Choo CS, Viehman J, Harmsen WS, Lester SC, et al. Outcomes and Profiles of Older Patients Receiving Definitive Radiation Therapy for Muscle-Invasive Bladder Cancer at a Tertiary Medical Center. *Pract Radiat Oncol*. 2020;10(5):e378-e87.
25. Bonet M, Bonfill T, Nuñez M, De Verdonces L, Mur E, Gallardo E, et al. Curative radiation therapy for very elderly bladder cancer patients with localized disease. *Clin Transl Oncol*. 2018;20(7):899-905.
26. Ploussard G, Daneshmand S, Efstathiou JA, Herr HW, James ND, Rödel CM, et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. *European urology*. 2014;66(1):120-37.
27. Rödel C, Grabenbauer GG, Kühn R, Papadopoulos T, Dunst J, Meyer M, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2002;20(14):3061-71.
28. Coen JJ, Zhang P, Saylor PJ, Lee CT, Wu CL, Parker W, et al. Bladder Preservation With Twice-a-Day Radiation Plus Fluorouracil/Cisplatin or Once Daily Radiation Plus Gemcitabine for Muscle-Invasive Bladder Cancer: NRG/RTOG 0712-A Randomized Phase II Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2019;37(1):44-51.
29. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, et al.

Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998;16(11):3576-83.

30. Hagan MP, Winter KA, Kaufman DS, Wajsman Z, Zietman AL, Heney NM, et al. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. *International journal of radiation oncology, biology, physics*. 2003;57(3):665-72.

31. Kaufman DS, Winter KA, Shipley WU, Heney NM, Chetner MP, Souhami L, et al. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist*. 2000;5(6):471-6.

32. Kaufman DS, Winter KA, Shipley WU, Heney NM, Wallace HJ, 3rd, Toonkel LM, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*. 2009;73(4):833-7.

33. Mitin T, Hunt D, Shipley WU, Kaufman DS, Uzzo R, Wu CL, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. *The Lancet Oncology*. 2013;14(9):863-72.

34. Weiss C, Engehausen DG, Krause FS, Papadopoulos T, Dunst J, Sauer R, et al. Radiochemotherapy with cisplatin and 5-fluorouracil after transurethral surgery in patients with bladder cancer. *International journal of radiation oncology, biology, physics*. 2007;68(4):1072-80.

35. Housset M, Maulard C, Chretien Y, Dufour B, Delanian S, Huart J, et al. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1993;11(11):2150-7.

36. Lagrange JL, Bascoul-Mollevi C, Geoffrois L, Beckendorf V, Ferrero JM, Joly F, et al. Quality of life assessment after concurrent chemoradiation for invasive bladder cancer: results of a multicenter prospective study (GETUG 97-015). *International journal of radiation oncology, biology, physics*. 2011;79(1):172-8.

37. Gogna NK, Matthews JH, Turner SL, Mameghan H, Duchesne GM, Spry N, et al. Efficacy and tolerability of concurrent weekly low dose cisplatin during radiation treatment of localised muscle invasive bladder transitional cell carcinoma: a report of two sequential Phase II studies from the Trans Tasman Radiation Oncology Group. *Radiother Oncol*. 2006;81(1):9-17.

38. Efstathiou JA, Spiegel DY, Shipley WU, Heney NM, Kaufman DS, Niemierko A, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *European urology*. 2012;61(4):705-11.

39. Tester W, Caplan R, Heaney J, Venner P, Whittington R, Byhardt R, et al. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy

Oncology Group phase II trial 8802. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1996;14(1):119-26.
40. Choudhury A, Swindell R, Logue JP, Elliott PA, Livsey JE, Wise M, et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(6):733-8.
41. Perdonà S, Autorino R, Damiano R, De Sio M, Morrica B, Gallo L, et al. Bladder-sparing, combined-modality approach for muscle-invasive bladder cancer: a multi-institutional, long-term experience. *Cancer*. 2008;112(1):75-83.
42. Zietman AL, Sacco D, Skowronski U, Gomery P, Kaufman DS, Clark JA, et al. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. *The Journal of urology*. 2003;170(5):1772-6.
43. Mak KS, Smith AB, Eidelman A, Clayman R, Niemierko A, Cheng JS, et al. Quality of Life in Long-term Survivors of Muscle-Invasive Bladder Cancer. *International journal of radiation oncology, biology, physics*. 2016;96(5):1028-36.
44. Royce TJ, Feldman AS, Mossanen M, Yang JC, Shipley WU, Pandharipande PV, et al. Comparative Effectiveness of Bladder-preserving Tri-modality Therapy Versus Radical Cystectomy for Muscle-invasive Bladder Cancer. *Clin Genitourin Cancer*. 2019;17(1):23-31.e3.
45. Choudhury A, Porta N, Hall E, Song YP, Owen R, MacKay R, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. *The Lancet Oncology*. 2021;22(2):246-55.
46. Huddart RA, Hall E, Lewis R, Porta N, Crundwell M, Jenkins PJ, et al. Patient-reported Quality of Life Outcomes in Patients Treated for Muscle-invasive Bladder Cancer with Radiotherapy ± Chemotherapy in the BC2001 Phase III Randomised Controlled Trial. *European urology*. 2020;77(2):260-8.
47. Huddart RA, Hall E, Hussain SA, Jenkins P, Rawlings C, Tremlett J, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). *International journal of radiation oncology, biology, physics*. 2013;87(2):261-9.
48. Brandau S, Suttmann H. Thirty years of BCG immunotherapy for non-muscle invasive bladder cancer: a success story with room for improvement. *Biomed Pharmacother*. 2007;61(6):299-305.
49. Rentsch CA, Birkhauser FD, Biot C, Gsponer JR, Bisiaux A, Wetterauer C, et al. Bacillus Calmette-Guerin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. *Eur Urol*. 2014;66(4):677-88.
50. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389(10064):67-76.
51. Vuky J, Balar AV, Castellano D, O'Donnell PH, Grivas P, Bellmunt J, et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Cancer. *J Clin Oncol*. 2020;38(23):2658-66.
52. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for

Advanced Urothelial Carcinoma. *N Engl J Med*. 2017;376(11):1015-26.
53. Bladder Cancer NCCN.org: National Comprehensive Cancer Network; 2021 [4.2021:[Available from: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
54. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med*. 2020;383(13):1218-30.
55. Bandini M, Gibb EA, Gallina A, Raggi D, Marandino L, Bianchi M, et al. Does the administration of preoperative pembrolizumab lead to sustained remission post-cystectomy? First survival outcomes from the PURE-01 study(). *Ann Oncol*. 2020;31(12):1755-63.
56. Powles T, Kockx M, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. *Nat Med*. 2019;25(11):1706-14.
57. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med*. 2021;384(22):2102-14.
58. Sharma P, Siefker-Radtke A, de Braud F, Basso U, Calvo E, Bono P, et al. Nivolumab Alone and With Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma: CheckMate 032 Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg Expansion Cohort Results. *J Clin Oncol*. 2019;37(19):1608-16.
59. Daro-Faye M, Kassouf W, Souhami L, Marcq G, Cury F, Niazi T, et al. Combined radiotherapy and immunotherapy in urothelial bladder cancer: harnessing the full potential of the anti-tumor immune response. *World J Urol*. 2021;39(5):1331-43.
60. Balar AV, Milowsky MI, O'Donnell PH, Alva AS, Kollmeier M, Rose TL, et al. Pembrolizumab (pembro) in combination with gemcitabine (Gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIBC): A multicenter phase 2 trial. *Journal of Clinical Oncology*. 2021;39(15_suppl):4504-.

