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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

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Abstract

Background: Tri-modality therapy (TMT) is a recognized treatment strategy for selected patients with muscle-invasive bladder cancer (MIBC).
Objective: Report long-term outcomes of patients with MIBC treated by TMT.
Design, setting, and participants: Four hundred and seventy-five patients with cT2–T4a MIBC were enrolled on protocols or treated as per protocol at the Massachusetts General Hospital between 1986 and 2013.
Intervention: Patients underwent transurethral resection of bladder tumor followed by concurrent radiation and chemotherapy. Patients with less than a complete response (CR) to chemoradiation or with an invasive recurrence were recommended to undergo salvage radical cystectomy.
Outcome measurements and statistical analysis: Disease-specific survival (DSS) and overall survival (OS) were calculated using the Kaplan-Meier method.
Results and limitations: Median follow-up for surviving patients was 7.21 yr. Five- and 10-yr DSS rates were 66% and 59%, respectively. Five- and 10-yr OS rates were 57% and 39%, respectively. The risk of salvage cystectomy at 5 yr was 29%. In multivariate analyses, T2 disease (OS hazard ratio [HR]: 0.57, 95% confidence interval [CI]: 0.44–0.75, DSS HR: 0.51, 95% CI: 0.36–0.73), CR to chemoradiation (OS HR: 0.61, 95% CI: 0.46–0.81, DSS HR: 0.49, 95% CI: 0.34–0.71), and presence of tumor-associated carcinoma in situ (OS HR: 1.56, 95% CI: 1.17–2.08, DSS HR: 1.50, 95% CI: 1.03–2.17) were significant predictors for OS and DSS. When evaluating our cohort over treatment eras, rates of CR improved from 66% to 88% and 5-yr DSS improved from 60% to 84% during the eras of 1986–1995 to 2005–2013, while the 5-yr risk of salvage radical cystectomy rate decreased from 42% to 16%.
Conclusions: These data demonstrate high rates of CR and bladder preservation in patients receiving TMT, and confirm DSS rates similar to modern cystectomy series. Contemporary results are particularly encouraging, and therefore TMT should be discussed and offered as a treatment option for selected patients.
Patient summary: Tri-modality therapy is an alternative to radical cystectomy for patients with muscle-invasive bladder cancer, and is associated with comparable long-term survival and high rates of bladder preservation.

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1. Introduction

Radical cystectomy (RC) has long been the standard of care for the management of muscle-invasive bladder cancer (MIBC). Modern RC series have demonstrated 5-yr overall survival (OS) rates of 56–66% [1–4]. The morbidity and mortality of RC are well documented [5]. There has been an increasing trend of utilizing organ-preserving therapies in the management of multiple cancers over the past several decades. In bladder cancer, a multidisciplinary approach has led to the development of bladder-sparing approaches using maximal transurethral resection (TURBT) followed by radiotherapy with concomitant radio-sensitizing chemotherapy for MIBC. There are no completed randomized studies comparing RC and TMT, but multiple series have suggested that TMT can yield favorable results in well-selected patients [6–17]. Herein we report the long-term results of an updated analysis from a single institutional experience. To our knowledge, this represents the largest experience of TMT for MIBC.

2. Material and methods

This is a retrospective analysis of 475 patients with MIBC treated at the Massachusetts General Hospital (MGH) and enrolled on prospective institutional or Radiation Therapy Oncology Group (RTOG) protocols, or patients that were treated as per protocol. Further details regarding the protocol design and treatment specifics for each protocol were detailed previously [9–12,15,18–21].

2.1. Patient eligibility and selection

Patients had clinical stage T2-T4aN0M0 urothelial carcinoma of the bladder, and patients treated on protocol were candidates for RC. The decision to pursue TMT was based on patient choice after a multidisciplinary discussion of treatment options. Patients were clinically staged at our institution and underwent a maximally safe TURBT. Patients then received induction concurrent chemotherapy and radiation therapy (RT). After completion of induction therapy, patients underwent a treatment response evaluation with a repeat cystoscopy, tumor site rebiopsy/TURBT, and urine cytology. Patients with a complete response (CR) to induction therapy completed consolidation chemoradiation, whereas those with residual invasive disease were recommended to undergo an immediate RC. Exclusion criteria were as previously described [9–12,18–20,22]. All institutional, state, and federal guidelines were followed. Patients treated on protocol were provided written informed consent approved by the Institutional Review Board prior to their enrollment on protocol.

2.2. Protocol design and treatment

The treatment program for RTOG 8903, MGH 180, MGH 880, MGH 930A, RTOG 9506, RTOG 9706, RTOG 9906, and RTOG 0233 have been described

Table 1 – Protocol design and treatment

Protocol	Neoadjuvant chemotherapy	Induction	Response	Consolidation or cystectomy	Maximum RT dose to tumor (Gy)	Adjuvant chemotherapy	Pts., *n* (%)
MGH 180	MCV 2 cycles	CP + QD RT	CR	CP + RT	64.8	None	52 (11)
MGH 880, RTOG 8903 Arm 1	MCV 2 cycles	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	56 (12)
MGH 880, RTOG 8903 Arm 2	None	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	50 (11)
MGH 930A	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.8	MCV 3 cycles	21 (4.4)
RTOG 9506	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	44	None	15 (3.2)
RTOG 9706	None	CP + BID RT	IR CR	Cystectomy CP + BID RT	64.8	MCV 3 cycles	23 (4.8)
RTOG 9906	None	CP + pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + gem 4 cycles	44 (9.3)
RTOG 0233 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + Pacl + gem 4 cycles	28 (5.9)
RTOG 0233 Arm 2	None	CP + Pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + Pacl + gem 4 cycles	33 (6.9)
RTOG 0524 Group 2	None	Pacl + QD RT	CR	CP + RT	64.8	None	3 (0.6)
RTOG 0712 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + gem 4 cycles	18 (3.8)
RTOG 0712 Arm 2	None	Gem + QD RT	IR CR	Cystectomy Gem + RT	64	CP + gem 4 cycles	14 (2.9)
Per protocol	Varied[a]	Varied[b]	IR CR	Cystectomy Varied[b]	64–66	Varied[c]	118 (25)

BID = twice daily; CP = cisplatin; CR = complete response; Gem = gemcitabine; IR = incomplete response; MCV = methotrexate, cisplatin, vinblastine; MGH = Massachusetts General Hospital; Pacl = paclitaxel; Pts. = patients; QD = once daily; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; 5-FU = 5-fluorouracil.

[a] Ten patients received two cycles of MCV.

[b] Thirty-seven patients received concurrent cisplatin; 34 patients received concurrent paclitaxel; 25 patients received concurrent cisplatin/5-FU; 16 patients received concurrent cisplatin/paclitaxel; four patients received concurrent 5- fluorouracil/mitomycin-C; one patients received concurrent gemcitabine/cisplatin; and one patient received concurrent carboplatin.

[c] 34 patients received adjuvant chemotherapy.

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