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Platinum Priority – Bladder Cancer

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Long-Term Outcomes of Selective Bladder Preservation by Combined-Modality Therapy for Invasive Bladder Cancer: The MGH Experience

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Abstract

Background: Whether organ-conserving treatment by combined-modality therapy (CMT) achieves comparable long-term survival to radical cystectomy (RC) for muscle-invasive bladder cancer (BCa) is largely unknown.
Objective: Report long-term outcomes of patients with muscle-invasive BCa treated by CMT.
Design, setting, and participants: We conducted an analysis of successive prospective protocols at the Massachusetts General Hospital (MGH) treating 348 patients with cT2–4a disease between 1986 and 2006. Median follow-up for surviving patients was 7.7 yr.
Interventions: Patients underwent concurrent cisplatin-based chemotherapy and radiation therapy (RT) after maximal transurethral resection of bladder tumor (TURBT) plus neoadjuvant or adjuvant chemotherapy. Repeat biopsy was performed after 40 Gy, with initial tumor response guiding subsequent therapy. Those patients showing complete response (CR) received boost chemotherapy and RT. One hundred two patients (29%) underwent RC—60 for less than CR and 42 for recurrent invasive tumors.
Measurements: Disease-specific survival (DSS) and overall survival (OS) were evaluated using the Kaplan-Meier method.
Results and limitations: Seventy-two percent of patients (78% with stage T2) had CR to induction therapy. Five-, 10-, and 15-yr DSS rates were 64%, 59%, and 57% (T2 = 74%, 67%, and 63%; T3–4 = 53%, 49%, and 49%), respectively. Five-, 10-, and 15-yr OS rates were 52%, 35%, and 22% (T2: 61%, 43%, and 28%; T3–4 = 41%, 27%, and 16%), respectively. Among patients showing CR, 10-yr rates of noninvasive, invasive, pelvic, and distant recurrences were 29%, 16%, 11%, and 32%, respectively. Among patients undergoing visibly complete TURBT, only 22% required cystectomy (vs 42% with incomplete TURBT; log-rank $p < 0.001$). In multivariate analyses, clinical T-stage and CR were significantly associated with improved DSS and OS. Use of neoadjuvant chemotherapy did not improve outcomes. No patient required cystectomy for treatment-related toxicity.
Conclusions: CMT achieves a CR and preserves the native bladder in >70% of patients while offering long-term survival rates comparable to contemporary cystectomy series. These results support modern bladder-sparing therapy as a proven alternative for selected patients.

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1. Introduction

Organ conservation by combined-modality therapy (CMT) is commonplace in contemporary oncology, with success in cancer of the breast, anus, larynx, limb, esophagus, and prostate. In primary muscle-invasive bladder cancer (BCa), however, radical cystectomy (RC) still remains the most commonly offered treatment, even though cystectomy can be associated with significant morbidity [1].

Modern bladder-sparing strategies combine maximal transurethral resection of bladder tumor (TURBT) followed by an induction course of concurrent radiation therapy (RT) and sensitizing chemotherapy. An early assessment of treatment response is performed by cystoscopy and rebiopsy. Patients achieving a clinical complete response (CR) continue with consolidation chemotherapy–RT followed by adjuvant chemotherapy. Incomplete responders are advised to undergo immediate cystectomy. Those with conserved bladders are followed by close cystoscopic surveillance, with prompt salvage cystectomy at the first sign of invasive recurrence.

Although no randomized comparisons between cystectomy and CMT exist, a large body of experience has accumulated suggesting that bladder-sparing approaches may yield favorable results in appropriately selected patients [2–10]. General acceptance of bladder-sparing therapy awaits studies that address concerns about limited follow-up and the possibility of high rates of late failure. Here we report long-term overall survival (OS) and disease-specific survival (DSS) data for a large group of patients treated at our institution.

2. Patients and methods

This is an analysis of patients with muscle-invasive BCa enrolled in successive, prospective, institutional or Radiation Therapy Oncology Group (RTOG) bladder-sparing protocols at the Massachusetts General Hospital (MGH). Table 1 summarizes the protocols. These phase 1, 2, and 3 protocols reflect an evolution in the scheduling of chemotherapy–RT and the combination of drugs. Further details of the eligibility criteria, chemotherapy drugs, RT technique, response criteria, and follow-up have been described previously [6–12].

2.1. Patient eligibility and selection

Eligible patients had clinical stage T2–T4aN0M0 transitional cell carcinoma of the bladder and were candidates for RC. After initial evaluation and staging radiology, as thorough a TURBT as possible was performed. Patients were then treated per protocol with induction chemotherapy and RT. Immediate RC was recommended for patients who had less than CR, as determined by cystoscopy, cytology, and tumor-site biopsy. Clinical complete responders received consolidation therapy. Patient exclusion criteria were as previously described [6–12]. All institutional, state, and federal guidelines were followed. All subjects were provided with written informed consent approved by the institutional review board (IRB) before enrollment.

2.2. Protocol design and treatment

2.2.1. MGH 180, MGH 880, and RTOG 8903

Between 1986 and 1993, 151 patients were entered onto phase 1 or 2 protocol MGH 180 and phase 3 protocols MGH 880 and RTOG 8903 [6]. These patients either received (MGH 180) or were randomized (MGH 880, RTOG 8903) to receive (or not) two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) before 39.6-Gy pelvic

Table 1 – Protocol design and treatment

Protocol	Neoadjuvant chemotherapy	Induction or concurrent	Response	Consolidation or cystectomy	Adjuvant chemotherapy	Patients, no. (%)
MGH 180	MCV 2 cycles	CP + RT	CR	CP + RT	None	50 (14.4)
			IR	Cystectomy		
MGH 880, RTOG 89-03 Arm 1	MCV 2 cycles	CP + RT	CR	CP + RT	None	56 (55.4)
			IR	Cystectomy		
MGH 880, RTOG 89-03 Arm 2	None	CP + RT	CR	CP + RT	None	45 (44.6)
			IR	Cystectomy		
MGH 930A	None	CP + 5FU + BID RT	CR	CP + 5FU + BID RT	MCV 3 cycles	21 (6.0)
			IR	Cystectomy		
RTOG 95-06	None	CP + 5FU + BID RT	CR	CP + 5FU + BID RT	None	14 (4.0)
			IR	Cystectomy		
RTOG 97-06	None	CP + BID RT	CR	CP + BID RT	MCV 3 cycles	22 (6.3)
			IR	Cystectomy		
RTOG 99-06	None	CP + Taxol + BID RT	CR	CP + Taxol + BID RT	CP + Gem 4 cycles	45 (12.9)
			IR	Cystectomy		
Per protocol	Varied	Varied	CR	Varied	Varied	95 (27.3)
			IR	Cystectomy		
					Total	**348**

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