Late Pelvic Toxicity After Bladder-Sparing Therapy in Patients With Invasive Bladder Cancer: RTOG 89-03, 95-06, 97-06, 99-06

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A B S T R A C T

Purpose

In selected patients with muscle-invasive bladder cancer, combined-modality therapy (transurethral resection bladder tumor [TURBT], radiation therapy, chemotherapy) with salvage cystectomy, if necessary, can achieve survival rates similar to radical cystectomy. We investigated late pelvic toxicity after chemoradiotherapy for patients treated on prospective protocols.

Patients and Methods

Between 1990 and 2002, 285 eligible patients enrolled on four prospective protocols (Radiation Therapy Oncology Group [RTOG] 8903, 9506, 9706, 9906) and 157 underwent combined-modality therapy, surviving ≥ 2 years from start of treatment with their bladder intact. Rates of late genitourinary (GU) and GI toxicity were assessed using the RTOG Late Radiation Morbidity Schema, with worst toxicity grade (scale 0 to 5) occurring ≥ 180 days after start of consolidation therapy reported for each patient. Persistence of toxicity was defined as grade 3+ toxicity not decreasing by at least one grade. Logistic and Cox regression analyses were performed to evaluate relationship between clinical characteristics, frequency, and time to late grade 3+ pelvic toxicity. Covariates included age, sex, stage, presence of carcinoma in situ, completeness of TURBT, and protocol.

Results

Median follow-up was 5.4 years (range, 2.0 to 13.2 years). Seven percent of patients experienced late grade 3+ pelvic toxicity: 5.7% GU and 1.9% GI. In only one of nine patients did a grade 3+ GU toxicity persist. Notably there were no late grade 4 toxicities and no treatment-related deaths. None of the clinical variables studied predicted for late grade 3+ pelvic toxicity.

Conclusion

Rates of significant late pelvic toxicity for patients completing combined-modality therapy for invasive bladder cancer and retaining their native bladder are low.

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INTRODUCTION

Radical cystectomy remains the gold standard and most common treatment offered for the management of primary muscle-invasive bladder cancer. Such extirpative surgery has resulted in effective local control and is often curative; however, long-term morbidity and reduced quality of life (QOL) due to urinary diversion and impairment of sexual function can be significant.¹⁻³

A large body of experience has accumulated from institutions in North America and Europe suggesting that bladder-sparing approaches may yield favorable results in appropriately selected patients. Modern selective bladder preservation with trimodality therapy, consisting of maximal transurethral

resection of the bladder tumor (TURBT), radiation therapy (RT), and chemotherapy, can achieve complete response rates of 60% to 80%, 5-year survival rates of 50% to 60%, and survival rates with an intact bladder of 40% to 45%.⁴⁻¹¹ Although no randomized comparisons between cystectomy and trimodality therapy exist, long-term data confirm that overall and disease-specific survival rates for patients in bladder-sparing protocols with salvage cystectomy, if necessary, are comparable to outcomes reported in series using primary cystectomy for patients with clinically staged muscle-invasive bladder cancer who are cystectomy candidates.^{1,5,8,12-14}

Successful bladder preservation only has merit if the preserved bladder functions at a level acceptable to the patient. QOL studies demonstrate that

the retained native bladder functions well and sexual function is often maintained.¹⁵ Furthermore, the incidence of cystectomy performed for palliation of treatment-related toxicity has been very low (0% to 2%).^{5,12} However, concern exists regarding the long-term bladder and bowel toxicity of chemoradiotherapy, for which there is limited information.

To evaluate the long-term effects of chemoradiotherapy to pelvic organs, we investigated late toxicity profiles of a large group of patients treated on prospective phase II and III protocols who retained their bladders.

PATIENTS AND METHODS

This analysis was based on patients with muscle-invasive bladder cancer enrolled on one of four prospective bladder-sparing Radiation Therapy Oncology Group (RTOG) protocols (89-03, 95-06, 97-06, and 99-06) at 62 participating institutions, undergoing combined-modality therapy and surviving at least 2 years from the start of treatment with their bladder intact. Further details of the eligibility criteria, chemotherapy, RT technique, doses and fields, response criteria and follow-up have been described previously.⁸⁻¹¹

Patient Eligibility and Selection

Eligible patients had clinical stage T2 to T4aNXM0 invasive bladder cancer and were operable candidates for radical cystectomy (protocol 8903 used the 1983 TNM classification system [second edition], protocols 9506 and 9706 used the 1992 system [fourth edition], and protocol 9906 used the 1997 system [fifth edition]). After initial evaluation, which included chest radiograph, intravenous pyelogram, and computed tomography scan, as thorough as possible a TURBT was performed. Subjects were then treated as per protocol with induction chemotherapy and radiation therapy (see Study Design and Treatment and Table 1). An immediate radical cystectomy was recommended for all patients who had less than a clinical complete response (CR), as determined by cystoscopy, cytology, and tumor-site biopsy. The clinical CRs (tumor-site biopsy and urine cytology both negative) received consolidation therapy.

Patients were ineligible for the protocols if there was evidence of distant spread of disease, which included metastases to lymph nodes above the bifurcation of the common iliac vessels, WBC count lower than 4,000/mL (and absolute neutrophil count < 1,800/mL), platelet count lower than 100,000/mL, a serum creatinine level higher than 1.5 to 1.7 mg/mL, a 24-hour creatinine clearance lower than 60 mL/min (lower than 50 mL/min before 1991). All protocols (except for 89-03) excluded patients with tumor-related hydronephrosis. All institutional, state, and federal guidelines were followed. All subjects provided written informed consent before enrollment.

Study Design and Treatment

RTOG 89-03. Between 1990 and 1993, 123 eligible patients were entered onto RTOG phase III protocol 89-03 at 37 participating institutions. Patients were randomly assigned to receive (arm 1, 61 patients) or not receive (arm 2, 62 patients) two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine before 39.6-Gy pelvic RT with concurrent cisplatin in two courses, 3 weeks apart. Patients who achieved a clinical CR received consolidation therapy with 25.2 Gy of additional RT (total dose 64.8 Gy) and one additional course of cisplatin.

Small pelvic radiation treatment fields (similar for all protocols) using a 4-field technique included the whole bladder, bladder tumor, prostate (in men), and adjacent regional pelvic lymph nodes. It extended inferiorly from the lower pole of the obturator, superiorly to include the midsacrum at the S2-S3 junction, and laterally to 1 cm lateral to the bony margin of the pelvis at its widest point.

RTOG 95-06. Between 1995 and 1997, 34 eligible patients were entered onto RTOG phase I/II protocol 95-06 at 11 participating institutions. After initial evaluation and TURBT, patients were treated with induction chemoradiotherapy consisting of cisplatin and fluorouracil (FU) combined with RT

using twice-daily 3-Gy fractions to the pelvis for a total dose of 24 Gy. Patients who achieved a clinical CR received consolidation therapy with the same chemotherapy and 20 Gy of additional RT to the bladder and bladder tumor given in twice-daily 2.5-Gy fractions (total dose 44 Gy to bladder and tumor, 24 Gy to pelvic lymph nodes).

RTOG 97-06. Between 1997 and 1999, 47 eligible patients were entered on RTOG phase I/II protocol 97-06 at 17 participating institutions. After TURBT, induction therapy involved 13 days of concomitant boost RT, 1.8 Gy to the pelvis in the morning followed by 1.6 Gy to the tumor 4 to 6 hours later (40.8 Gy to bladder tumor and 21.6 Gy to regional lymph nodes). For sensitization, cisplatin was given on the first 3 days of each treatment week. Patients having achieved a CR completed consolidation chemoradiotherapy consisting of 1.5 Gy pelvic RT delivered twice-daily to 24 Gy (total dose 64.8 Gy to bladder tumor, 45.6 to pelvic lymph nodes) with sensitizing cisplatin, followed by adjuvant methotrexate, cisplatin, and vinblastine chemotherapy.

RTOG 99-06. Between 1999 and 2002, 81 eligible patients were entered on RTOG phase I/II protocol 99-06 at 26 participating institutions. After TURBT, induction therapy involved 13 days of concomitant boost RT, 1.6 Gy to the pelvis in the morning followed by 1.5 Gy to the bladder for the first five sessions (7.5 Gy) then to the tumor for eight sessions (12.0 Gy) in the afternoon (20.8 Gy to pelvis, 28.3 to the whole bladder, and 40.3 Gy to the bladder tumor). Weekly cisplatin and paclitaxel were included as radiation sensitizers. Patients who achieved a clinical CR received consolidation chemoradiotherapy consisting of 1.5 Gy pelvic RT delivered twice-daily to 24 Gy (total dose 64.3 Gy to tumor volume and 44.8 Gy to pelvic lymph nodes) with the same chemotherapy, followed by adjuvant gemcitabine and cisplatin.

Follow-Up

Patients with conserved bladders were actively followed with cystoscopy, biopsy of the tumor site, bimanual examination under anesthesia, and urine cytology every 3 months in the first year, every 3 to 4 months in the second year, every 6 months for 3 years, and then annually. Patients were promptly considered for intravesical therapy for superficial recurrences and salvage radical cystectomy for an invasive recurrence.

Data Collection/Analysis

For the purposes of this analysis examining late pelvic toxicity, patients were included if they met the following criteria: they were eligible for one of the four protocols and they survived two or more years from the start of protocol therapy with an intact bladder. Of the 285 combined eligible patients, 157 were analyzable (Table 1). The remainder either had progressive disease requiring cystectomy and/or died within 2 years after protocol therapy.

Late Pelvic Toxicity

Rates of late GU and GI pelvic toxicity were reported, scored, and collected prospectively in follow-up case report forms as per protocol and according to the RTOG/European Organisation for the Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema (Table 2).¹⁶ The worst toxicity grade (scale 0 to 5) occurring $\geq$ 180 days after the start of consolidation therapy were reported for each patient. Late toxicity was dichotomized as grade lower than 3 and grade $\geq$ 3 in the statistical models. Persistence of toxicity was defined as a grade 3 or higher (grade 3+) toxicity that did not decrease by at least one grade.

Statistical Methods

Logistic regression analyses¹⁷ using the Wald test were performed to evaluate the frequency of late grade 3+ pelvic toxicity with and without adjusting for other covariates. Cox proportional hazards regression¹⁸ using the χ^2 test were performed to model the time to late grade 3+ pelvic toxicity with and without adjusting for other covariates. The following categorical covariates were included in the multiple regression model: age ($\leq$ 65 [reference level]; RL) ν > 65 years), sex (male [RL] ν female), visibly complete TURBT (yes [RL] ν no), tumor grade ($\leq$ 2 [RL] ν $\geq$ 3), clinical stage (T2 [RL] ν T3a-T4a), presence of carcinoma in situ (no [RL] ν yes), and RTOG protocol (89-03 [RL] ν 95-06 ν 97-06 ν 99-06). For the categorical variables, the cut points selected were made before the data were examined. Unadjusted and adjusted

Table 1. RTOG Protocol Design and Treatment

RTOG Protocol	Neoadjuvant CT	Induction/Concurrent	Response	Consolidation/Cystectomy	Adjuvant CT	No. of Eligible Patients	No. of Analyzable Patients
89-03							
Arm 1	MCV 2 cycles	CP + RT	CR	CP + RT	None	61	29
Arm 2	None	CP + RT	IR	Cystectomy	None	62	27
95-06	None	CP + FU + RT	CR	CP + FU + RT	None	34	24
97-06	None	CP + BID RT	IR	Cystectomy	None	47	24
99-06	None	TAX + CP + BID RT	CR	CP + RT	MCV	81	53
			IR	Cystectomy	GEM + CP	81	53
Total						285	157

Abbreviations: RTOG, Radiation Therapy Oncology Group; CT, chemotherapy; MCV, methotrexate, cisplatin, vinblastine; CP, cisplatin; RT, radiation therapy; CR, complete response; IR, incomplete response; FU, fluorouracil; BID, twice daily; TAX, paclitaxel; GEM, gemcitabine.

odds ratios and hazard ratios were calculated for the logistic regression and Cox proportional hazards regression analyses, respectively, for all covariates with associated 95% CIs and *P* values. All statistical comparisons were two sided and a *P* value lower than .05 was considered significant. SAS (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Pretreatment Characteristics

Between 1990 and 2002, 157 analyzable patients were enrolled and underwent combined-modality therapy on the combined four protocols at 62 participating institutions, surviving ≥ 2 years from start of treatment with their bladder intact. Median age was 65 years (range, 34 to 90 years). Eighty-two percent were male, 95% had transitional cell histology, 71% had stage T2 disease, 15% had associated CIS, and 83% underwent a visibly complete TURBT. Seventeen patients had received either prior intravesical chemotherapy or BCG at time of registration. Pretreatment characteristics are presented in Table 3.

Follow-Up

Median follow-up was 5.4 years (range, 2.0 to 13.2 years) for all analyzable patients, and 6.0 years (range, 2.0 to 13.2 years) for those who were still alive ($n = 99$). Only one patient (in protocol 89-03) was lost to follow-up.

Late Pelvic Toxicity

Of the 157 patients, 34 (21.7%) experienced late grade 1 toxicity. Sixteen patients (10.2%) experienced late grade 2 pelvic toxicity: 15 (9.6%) GU and 3 (1.9%) GI. Two patients developed both late grade 2 GU and GI toxicity. Median time to late grade 2 pelvic toxicity was 31.2 months (range, 9.2 to 137.8 months). Median time to late grade 2 GU and GI toxicity, respectively, was 31.7 months (range, 9.8 to 137.8 months) and 16.3 months (range, 9.2 to 37.9 months).

Eleven patients (7.0%) experienced a late grade 3 pelvic toxicity: nine (5.7%) GU (urinary urgency/frequency, hematuria) and three (1.9%) GI (sigmoid obstruction, proctitis; Table 4). Of note, one patient (on protocol 89-03) developed both a late grade 3 GU and GI toxicity. Median time to a late grade 3 pelvic toxicity was 22.1 months

Table 2. Radiation Therapy Oncology Group Late Radiation Morbidity Scoring Schema

Organ	Grade			
	1	2	3	4
GI	Mild diarrhea	Moderate diarrhea and colic	Obstruction or bleeding requiring minor surgery	Necrosis/perforation
	Mild cramping	Bowel movement > 5 times daily		Fistula
	Bowel movement 5 times daily	Excessive rectal mucus or intermittent bleeding		
GU	Slight rectal discharge or bleeding			
	Slight epithelial atrophy	Moderate frequency	Severe frequency and dysuria	Necrosis/contracted bladder (capacity < 100 mL)
	Minor telangiectasia (microscopic hematuria)	Generalized telangiectasia	Severe generalized telangiectasia (often with petechiae)	Severe hemorrhagic cystitis
		Intermittent macroscopic hematuria	Frequent hematuria	
			Reduction in bladder capacity (< 150 mL)	

Abbreviation: GU, genitourinary.

Table 3. Pretreatment Characteristics of Analyzable Patients in All Studies Combined (n = 157)

Characteristic	No.	%
Sex		
Male	128	82
Female	29	18
Age, years		
≤ 65	81	52
> 65	76	48
Tumor grade		
1	0	0
2	26	16
3	111	71
4	17	11
Unknown	3	2
Tumor histology		
Transitional cell	149	95
Squamous	2	1
Other	6	4
Clinical stage		
T2	111	71
T3-T4a	46	29
Visibly complete TURBT performed		
Yes	131	83
No	25	16
Unknown	1	1
Carcinoma in situ		
No	134	85
Yes	23	15

Abbreviation: TURBT, transurethral resection of bladder tumor.

(range, 8.0 to 98.8 months). Median time to late grade 3 GU toxicity was 18.4 months (range, 9.4 to 98.8 months) and to late grade 3 GI toxicity was 25.8 months (range, 8.0 to 57.8 months). Time to late grade 3+ GU and GI toxicity is graphically displayed in Figure 1.

There were no late grade 4 toxicities and no treatment-related deaths. Among the 128 patients who were eligible but not analyzable, there were two grade 4 toxicities (one bowel obstruction and one fistula) and no treatment-related deaths. No cystectomies were performed due to treatment-related toxicity in any of the patients.

Toxicity Persistence

Median duration of a late grade 3 pelvic (GU/GI) toxicity was 7.1 months (range, 4.0 to 33.0 months) before decreasing in sever-

Fig 1. (A) Time to late grade 3+ genitourinary (GU) toxicity; (B) time to late grade 3+ GI toxicity.

ity. In only one (11.1%) of nine patients with late grade 3 GU toxicity did that toxicity persist; while none of the patients had persistent late grade 3 GI toxicity.

Univariate and Multivariate Analyses

None of the clinical variables studied predicted for late grade 3+ pelvic toxicity. Table 5 displays the results for the univariate logistic regression and Cox proportional hazards model. Similar results were observed in multivariate analyses (data not shown).

Table 4. Late Grade 3+ Pelvic Toxicity in RTOG Protocols

RTOG Protocol	Complete Response Rates (%)*	No. of Analyzable Patients	Grade 3+ Toxicity			
			GU		GI	
			No.	%	No.	%
89-03	59	56	4	7	2	4
95-06	67	24	0	0	0	0
97-06	74	24	2	8	1	4
99-06	87	53	3	6	0	0
Total		157	9	5.7	3	1.9

Abbreviations: RTOG, Radiation Therapy Oncology Group; GU, genitourinary.

*Complete response rates are for all eligible patients.

Table 5. Univariate Logistic Regression and Cox Proportional Hazards Model for Late Grade 3+ Pelvic Toxicity

Covariate	Logistic Regression			Cox Proportional Hazards Model		
	OR	95% CI	P	HR	95% CI	P
Sex						
Male	RL			RL		
Female	0.98	0.20 to 4.79	.98	1.32	0.27 to 6.61	.73
Age, years						
≤ 65	RL			RL		
> 65	0.52	0.11 to 2.48	.41	0.88	0.19 to 4.22	.88
Tumor grade*						
1-2	RL			RL		
3-4	0.91	0.18 to 4.47	.91	1.42	0.30 to 6.75	.66
Clinical stage						
T2	RL			RL		
T3-4a	1.42	0.39 to 5.09	.59	1.11	0.28 to 4.41	.88
Tumor histology						
Transitional	RL			RL		
Other	1.99	0.22 to 17.77	.54	—	—	—
Visibly complete TURBT						
Yes	RL			RL		
No	0.48	0.06 to 3.95	.50	—	—	—
CIS						
No	RL			RL		
Yes†	—	—	—	—	—	—
RTOG protocol						
89-03	RL			RL		
95-06†	—	—	—	—	—	—
97-06	1.46	0.32 to 6.66	.63	2.73	0.57 to 13.23	.21
99-06	0.61	0.14 to 2.70	.52	0.85	0.18 to 3.90	.83

Abbreviations: OR, odds ratio; HR, hazard ratio; RL, reference level; TURBT, transurethral resection of bladder tumor; CIS, carcinoma in situ; RTOG, Radiation Therapy Oncology Group.

*Three patients with unknown tumor grade were excluded.

†No analyzable patient has grade 3+ toxicity.

DISCUSSION

Using data from a large group of patients treated on multi-institutional cooperative group prospective protocols with combined-modality therapy for invasive bladder cancer, we found that those who retained their native bladder and survived at least 2 years had a very low incidence of significant late pelvic toxicity. Specifically, the late grade 3 GU and GI toxicity rates were lower than 6% and lower than 2%, respectively. Typically these toxicities occurred within 2 years after therapy, lasted a median of about 7 months, and rarely persisted. Notably, there were no late grade 4 toxicities, no treatment-related deaths, and no cystectomies performed due to treatment-related toxicity.

Our findings are consistent with other reports. In a phase II study from the Trans Tasman Radiation Oncology Group employing RT (63 Gy) and weekly cisplatin for bladder preservation, the incidence of significant late grade 3+ urinary toxicity (4%) or bowel toxicity (2%) was low and mainly due to recurrent disease (albeit, their radiation fields were limited to the bladder and did not include the pelvis).¹⁹ In the Erlangen combined-modality therapy series²⁰ which reported on the European experience, chronic urinary and bowel sequelae were seen in 2% and 1.5% of patients, respectively. In cross-sectional studies from Italy and Sweden, about three fourths of patients reported good long-term urinary function and low levels of urinary distress after chemoradiotherapy.^{3,21,22} The prevalence of sexual dysfunction

was lower than after cystectomy, and the prevalence of bowel symptoms was not statistically different. A separate QOL study in patients treated with radical cystectomy and urinary diversion confirmed that bowel issues were not the exclusive problem of radiation-treated patients.³ In a British prospective study using patient-directed QOL questionnaires of 72 patients who had shown a CR to radiation (60 Gy), there was no significant difference in urinary and rectal function as compared to an age- and sex-matched control group who did not receive RT.²³ This is also supported by a phase I study from the University of Michigan, which also demonstrated no significant influence on patient-reported QOL after concurrent RT and gemcitabine for bladder preservation.²⁴ In fact, one multicenter study from France prospectively examined 33 chemoradiotherapy patients who remained alive with tumor-free bladders and documented improvements in bladder function at 6-, 12-, and 24-month intervals, presumably related to primary tumor eradication.²⁵

A study from the Massachusetts General Hospital reported on the QOL and urodynamics of 49 patients who had completed trimodality bladder preservation therapy a median of 6.3 years earlier.¹⁵ In this study, 75% of patients had normally functioning bladders by urodynamic studies. Reduced bladder compliance was seen in 22%, but in only one third of these did it result in distressing symptoms. The urodynamic studies in two of 12 women showed bladder hypersensitivity, involuntary detrusor contractions, and incontinence. The questionnaire showed that bladder symptoms were uncommon, especially

among men, with the exception of control problems. These were reported by 19%, with 11% wearing pads (all women). Distress from urinary symptoms was half as common as their prevalence, with only 6% reporting moderate or higher urinary distress. Bowel symptoms (eg, rectal urgency) occurred in 22%, with only 14% recording any level of distress. Overall global health-related QOL was high. The majority of men retained sexual function, with only 8% reporting dissatisfaction. There was no data available for sexual function among women in this study, although another study reported that the majority of women who underwent bladder preservation therapy showed no decline in their subsequent satisfaction with sexual intercourse.²⁶

While our study has substantial strengths, some potential limitations need to be considered. Firstly, although we reported on a large group of patients treated on prospective protocols with relatively long follow-up, our analyses did not allow for full evaluation of chemoradiotherapy-related late toxicities developing beyond 5 years. Secondly, a standardized and well-accepted late morbidity scoring schema was employed prospectively; however, toxicities were physician- and not patient-reported and thus may have underestimated toxicity and effects on QOL somewhat.²⁷ Nevertheless, adverse events detected by toxicity criteria, such as the RTOG late toxicity system, have been shown to moderately correlate with global QOL scores²⁸ and thus the toxicity instrument used in this study remains important for patient outcome. The RTOG did not collect data on each individual investigator from every institution and thus controlling for each investigator or inter-physician variability is not feasible. Thirdly, our analyses were restricted to analyzable patients, namely those who survived at least 2 years with their bladder intact, and thus may be subject to selection biases. Notably, however, there were no cystectomies performed due to treatment-related toxicity in any of the patients (eligible or analyzable) and no treatment-related deaths. Lastly, although none of the clinical variables stud-

ied predicted for significant late pelvic toxicity, including RTOG protocol, our analyses were limited in their ability to comment on the individual effects of radiation dose, schedule, and treatment volume, as well as specific chemotherapy agents or prior use of intravesical BCG.

In conclusion, in selected patients with muscle-invasive bladder cancer treated with combined-modality therapy who preserve their native bladder, the great majority will retain good long-term bladder and bowel function. Therefore, acceptance of chemoradiotherapy used in modern bladder-sparing therapy with salvage cystectomy if necessary by an experienced multidisciplinary team should not be limited by concerns of high rates of late pelvic toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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