

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

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ABSTRACT

Purpose. To assess the safety, tolerance, and efficacy of transurethral surgery plus concomitant cisplatin, 5-fluorouracil (5-FU), and radiation therapy in conjunction with selective bladder preservation in patients with muscle-invasive bladder cancer.

Patients and Methods. Thirty-four eligible patients with clinical stage T2-T4a, Nx M0 bladder cancer without hydronephrosis were entered into a protocol aimed at selective bladder preservation. Treatment began with as complete a transurethral resection as possible followed by induction chemoradiation. This consisted of cisplatin 15 mg/m² i.v. and 5-fluorouracil (5-FU) 400 mg/m² i.v. in the mornings on d 1, 2, 3, 15, 16, and 17. On d 1, 3, 15, and 17, radiation was given immediately following the chemotherapy using twice-a-day 3 Gy per fraction cores to the pelvis for a total radiation dose of 24 Gy. Response was evaluated by cystoscopy, cytology, and rebiopsy four weeks later. Patients with a complete response received consolidation therapy with the same drugs and doses on d 1, 2, 3, 15, 16, and 17 combined with twice-daily radiation therapy to the bladder and bladder tumor volume of 2.5 Gy per fraction for a total consolidation dose of 20 Gy and a total induction plus

consolidation dose to the bladder and bladder tumor of 44 Gy. Patients who did not achieve a complete response were advised to undergo prompt cystectomy, as were those with a subsequent invasive recurrence. The median follow up is 29 months.

Results. Of the 34 eligible patients, 26 had a visibly complete transurethral resection. One patient did not complete induction treatment due to acute hematologic toxicity. After induction treatment, 22 (67%) of the 33 patients had no tumor detectable on urine cytology or rebiopsy. Of the 11 patients who still had detectable tumor, six underwent radical cystectomy and five underwent consolidation chemoradiation (one because of refusal to have the recommended cystectomy and four because the treating institutions erroneously assigned them to receive consolidation chemoradiation rather than cystectomy). No patient has required a cystectomy for radiation toxicity. Six patients have died of bladder cancer. The actuarial overall survival at three years is 83%. The probability of surviving with an intact bladder is 66% at three years. A total of seven patients (21%) developed grade 3 or grade 4 hematologic toxicity in conjunction with this treatment.

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Conclusion. This aggressive protocol comprising local surgery plus concurrent 5-FU, cisplatin, and high-dose hypofractionated radiation has been associated with moderately severe hematologic toxicity. Longer

follow-up will be necessary to assess efficacy. Both the 67% complete response rate to induction therapy and the 66% three-year survival with an intact bladder are encouraging. *The Oncologist* 2000;5:471-476

INTRODUCTION

The treatment of muscle-invasive bladder cancer using combined modality therapy with selective bladder preservation or cystectomy based on initial tumor response has been a successful approach reported by several institutions and cooperative groups over the last 10 years [1-7]. These series report a five-year overall survival for patients treated by bladder preservation or prompt cystectomy ranging from 49% to 63%. For all the patients treated on these protocols, 38% to 43% have a five-year survival with an intact bladder. Thus, the overall five-year survival rates are comparable to other series using immediate cystectomy-based approaches in patients of similar age presenting with tumors of similar clinical stage. Also, the majority of the long-term survivors retain their

bladder. However, in a randomized protocol of neoadjuvant chemotherapy in addition to trimodality therapy (transurethral surgery plus concurrent chemotherapy and radiation), the Radiation Therapy Oncology Group (RTOG) reported that only 70% of the patients assigned to the neoadjuvant chemotherapy arm—methotrexate, cisplatin, vinblastine (MCV)—completed the protocol as specified or with only minor deviations. This protocol accrued 126 patients but was terminated prior to its accrual goal of 174 patients because of poor patient tolerance resulting in a low protocol completion rate. In 1993, Housset and colleagues reported encouraging results with regard to bladder preservation and patient compliance with a hypofractionated twice-a-day radiation approach employing concurrent cisplatin and 5-fluorouracil (5-FU) that

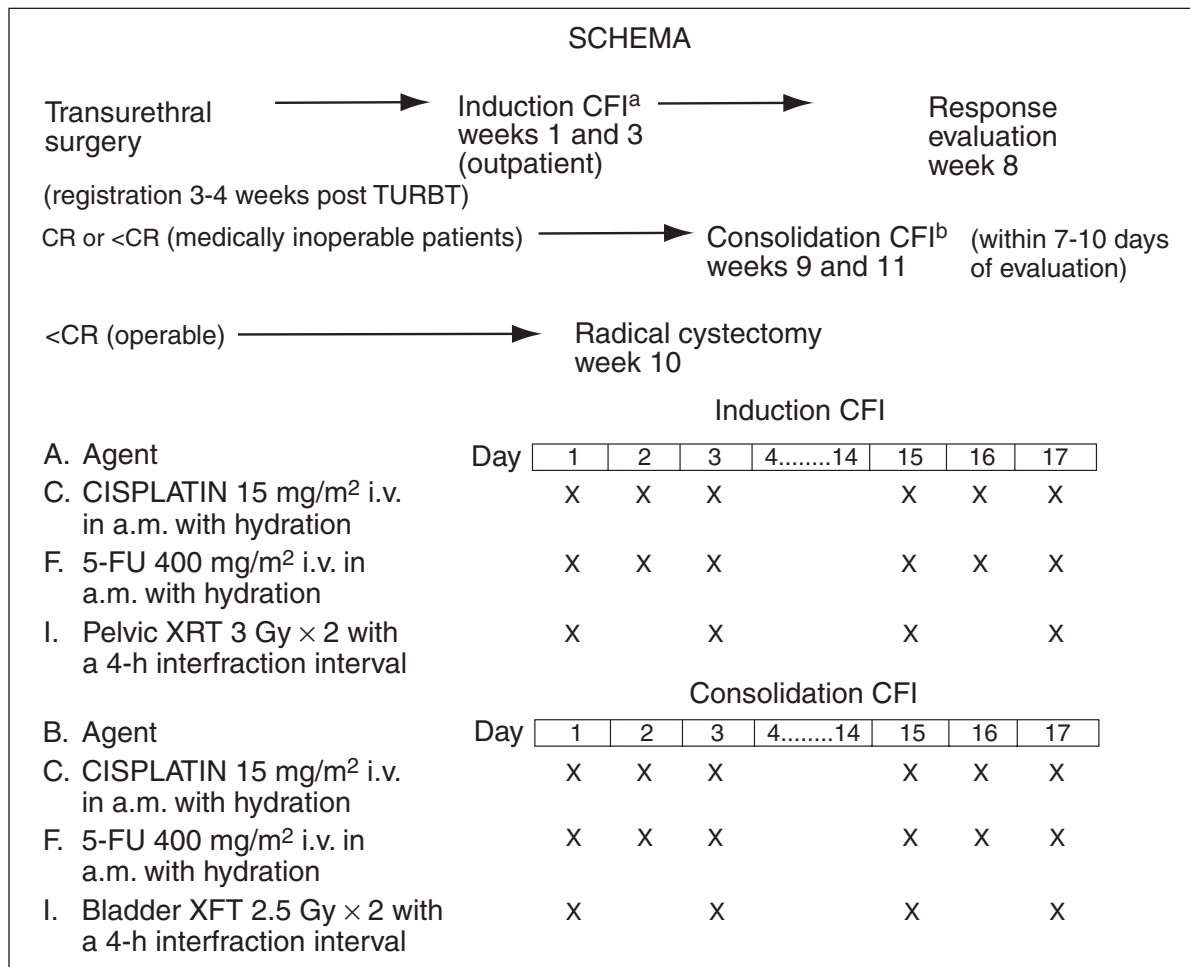


Figure 1. The schema of RTOG 95-06 for the treatment of invasive bladder cancer with combined transurethral resection of the bladder tumor (TURBT) and concurrent radiation therapy and chemotherapy (cisplatin and 5-FU).

could be safely given as an outpatient regimen [3]. This treatment regimen (Fig. 1) was judged to be more attractive than one using the same agents but requiring, at that time, 12 days of inpatient chemotherapy to be given concurrently with twice-daily radiation, which had been tested as a single institution approach [8]. The protocol was designed to test the safety, tolerance, and efficacy as well as the protocol completion rate of this selective bladder preservation approach. This protocol targeted a completion rate of 90% as clinically feasible for our cooperative group.

MATERIALS AND METHODS

Patient Selection

Between 1995 and 1997, 35 patients with invasive bladder cancer entered into RTOG 95-06. Thirty-four of the 35 patients were determined to be eligible and are included in this analysis. The range of clinical stage was T2 to T4a Nx M0 without hydronephrosis. Initial evaluation included a chest radiograph, i.v. pyelogram, and/or a computed tomographic scan, and as thorough as possible transurethral resection of the bladder tumor (TURBT). Patients were ineligible for this protocol if there were metastases to lymph nodes or distant metastases, a white count <4,000 per ml and an absolute neutrophil count (ANC) <1,800 per ml, a platelet count <100,000 per mm³, a serum creatinine >1.5 mg/ml, a creatinine clearance of <60 ml/min, hydronephrosis, or a refusal to sign a consent form approved by the institutional review board after the nature of the procedures had been fully explained. Some pretreatment patient characteristics are listed in Table 1.

Chemotherapy/Radiation Treatment Protocol

A schema of the protocol is based on that of *Housset et al.* [3] and shown in Figure 1, which includes the treatment details. In summary, induction chemotherapy/radiation (CFI), was given over a 17-day interval and was followed by an interval of three to four weeks to allow tumor regression. In week 7 or 8 the bladder was re-evaluated cystoscopically. Patients were considered complete responders only if there was no visible mass, no tumor in a tumor site on repeat biopsy, and a negative urine cytology. Complete responders underwent consolidation chemotherapy/radiation (CFI), beginning in week 9 and again the chemoradiation was completed in 17 days. Incomplete responders were advised to undergo a prompt radical cystectomy.

Radiation Therapy

Patients were treated twice daily with at least a 4-h inter-fraction interval on d 1, 3, 15, and 17. During the induction phase, external beam radiation therapy was delivered at 3.0 Gy twice daily to the whole bladder, bladder tumor volume, and

the pelvic lymph nodes. Thus, at the end of the induction phase these structures received 24 Gy in eight fractions over 16 elapsed days. Complete responders and some incomplete responders [5] underwent consolidation therapy which began 7 to 10 days after the re-evaluation cystoscopy. External beam radiation for the consolidation was delivered at 2.5 Gy twice daily to the whole bladder and bladder tumor volume on d 1, 3, 15, and 17. Thus, at the end of the consolidation phase the whole bladder and bladder tumor volume had received 44 Gy in 16 fractions and the pelvic lymph nodes had received 24 Gy in eight fractions.

Systemic Chemotherapy

For both induction and consolidation therapy, 400 mg/m² of 5-FU and 15 mg/m² of cisplatin were administered i.v. before the first radiation treatment on d 1, 2, 3, 15, 16, and 17. Following i.v. hydration at the rate of 500 ml/h, 5-FU was administered by direct i.v. push followed by cisplatin as a 1-h infusion. The first radiation fractionation was between one and two hours following the completion of the chemotherapy. Dose modifications of cisplatin and 5-FU during the consolidation chemotherapy/radiation therapy were made for myelosuppression, for nephrotoxicity, and/or for gastrointestinal toxicity. If a grade III hematologic toxicity developed (platelets <50,000 per mm³ or ANC <1,800 per mm³), then both the chemotherapy and radiation therapy were discontinued for one week and resumed when the ANC returned to \geq 1,800 per mm³ and the platelet count returned to \geq 100,000 per mm³. If the blood counts failed to recover in three consecutive weekly measurements, the patient was considered to be off protocol. If the radiation dose fraction size had to be reduced for diarrhea, additional radiation therapy was given on d 21 and 23 without chemotherapy but using the twice-a-day schedule to ensure a total dose of 44 Gy.

Criteria for Response and Follow-up Procedures

Patients underwent cystoscopy, biopsy of the tumor site, bimanual examination under anesthesia, and urine cytology

Table 1. Pretreatment characteristics

RTOG 95-06	
Histology	
Transitional	33 (97%)
Other	1 (3%)
Grade	
II	5 (15%)
III	24 (70%)
i.v.	4 (12%)
Unknown	1 (3%)
Visibly complete TURBT performed	
No	7 (21%)
Yes	26 (76%)
Unknown	1 (3%)
Palpable mass or induration persistent after the TURBT	
No	29 (85%)
Yes	5 (15%)
T-Stage	
T2	26 (76%)
T3a	5 (15%)
T3b	2 (6%)
T4a	1 (3%)
Age	
<60	14 (41%)
60-69	9 (27%)
70+	11 (32%)
Gender	
Male	27 (79%)
Female	7 (21%)

every three months for the first year and then every six months. Response of the primary tumor was considered a clinical complete response if no tumor was visible on cystoscopy, the tumor-site biopsy was negative, and no tumor cells were found in the urine cytology. Additional therapies such as transurethral resection, intravesical chemotherapy, or cystectomy were initiated at the earliest opportunity if relapse occurred. Uro-dynamic studies were not routinely performed. Median follow-up for the entire group is 29 months (range 7-40) and 30 months for all surviving patients.

Statistical Analysis

The study was designed to accrue a sufficient number of patients to distinguish a 90% protocol completion rate from a 70% protocol completion rate using a one-sided 0.05 test of proportions with an 80% statistical power. This will yield the 95% confidence intervals of the probability of a complete response to be approximately $\pm 20\%$. Accrual to this trial was completed in 25 months.

The protocol completion rate was compared statistically to arm 1 (with neoadjuvant MCV chemotherapy) and arm 2 (without MCV neoadjuvant chemotherapy) of RTOG 89-03 using the chi-square test. Overall and bladder intact survival probabilities were estimated using the Kaplan-Meier

method [9]. Time to distant metastases was estimated using the cumulative incidence method [10].

RESULTS

Thirty-three of 34 patients (97%) completed the induction chemotherapy and radiation therapy per protocol. However, only 26 of the 34 initial patients (76%) completed the whole protocol as planned (Fig. 2). The completion rate of the whole protocol is compromised by four patients whose treating institutions erroneously assigned these patients with residual tumor after induction to receive consolidation chemoradiotherapy rather than cystectomy. Of the 30 patients in whom the protocol was appropriately understood, 26 (87%) completed this planned protocol therapy. The four patients who were correctly assigned their treatment but did not complete the protocol included two complete responders who refused consolidation chemoradiation, one who refused the recommended cystectomy and underwent nonprotocol chemoradiation, and one who was incompletely evaluated for his initial response. The protocol completion rate of this study (76%) was not statistically better than were the rates for either arm of RTOG 89-03 or the study overall. The percentages of patients sustaining a grade III or greater leukopenia, thrombocytopenia, neutropenic

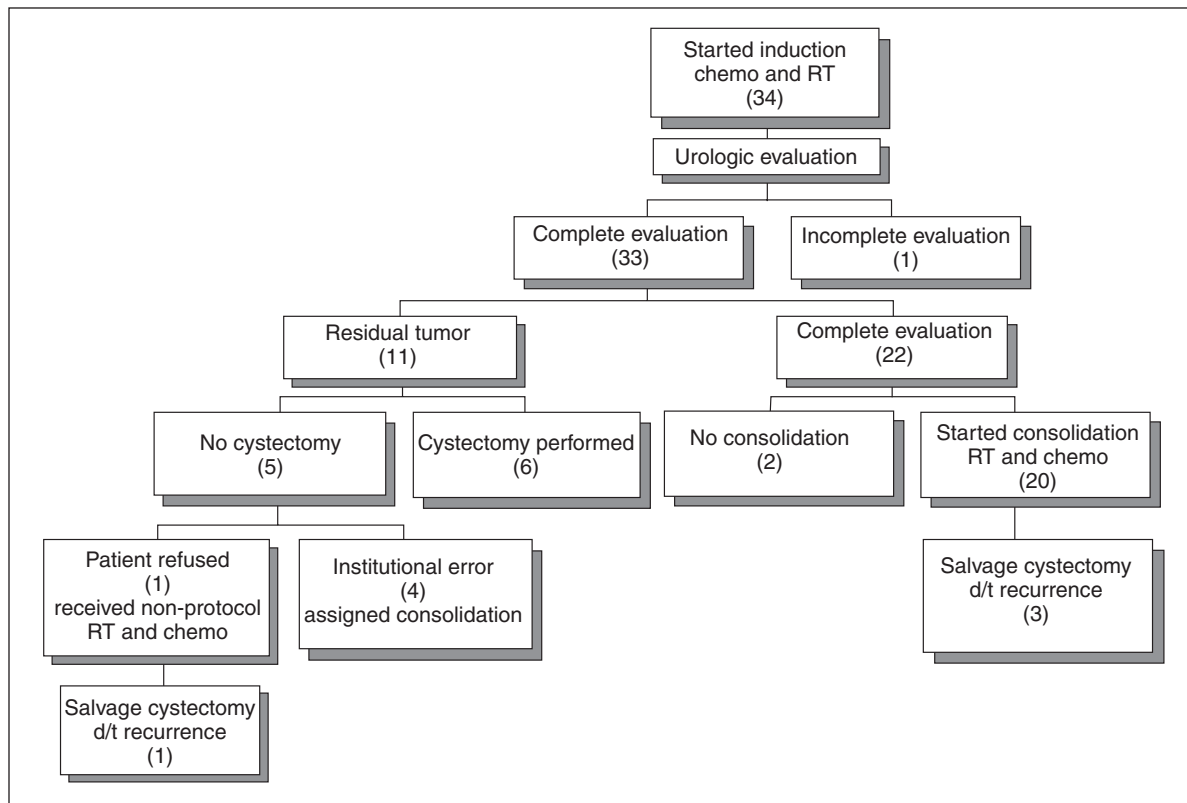


Figure 2. Schema of patient protocol compliance.

Table 2. Grade 3 treatment-related toxicity (*n* = 34)

RTOG 95-06	
Toxicity	Percent
Bladder	6%
Hematological	18%
GI	15%
Other	3%

Table 3. Late toxicity following treatment (*n* = 34)

Grade 3	
Bladder	6%
Hematological	12%
Rectum	6%
Small bowel	3%
Other	3%
Grade 4	
Hematological	3%
Rectum	3%
Small bowel	3%

fever, infection, nausea/vomiting, or bladder irritation during the protocol are shown in Table 2. One patient suffered grade 4 leukopenia during the induction chemoradiotherapy. During the chemoradiation, the following grade 3 toxicities were reported: in the bladder in two patients, in the rectum in two patients, and the small bowel in one patient. No grade 4 toxicities were recorded.

The percentage of patients sustaining late morbidity reported during the follow-up phase of this study is shown in Table 3. Grade 3 toxicities were reported in two patients for bladder reactions, two patients for bowel reactions, and in four patients for hematologic toxicity. There was one late grade 4 event due to hematologic, renal and small bowel toxicity. All but one of the late grade 3 toxicities have

resolved with subsequent treatment and follow-up. In one patient, a grade 3 bladder reaction persists.

Table 4 shows the complete response rates of the primary tumor following induction therapy and following consolidation therapy. Twenty-two of 33 evaluable patients were complete responders (67%) after induction chemoradiation therapy. In the seven patients who had persistent tumor and who were evaluated for response, none exhibited tumor progression. In the six patients who underwent cystectomy for an incomplete response, cancer was found in the cystectomy specimens of all patients. Ileal conduit urinary diversions were performed on all of the patients undergoing radical cystectomy.

The median follow-up was 29 months. Nine of the 20 patients who were clinical complete responders following induction CFI and completed consolidation CFI have developed a bladder recurrence. Three of these nine have had an invasive recurrence and have undergone a cystectomy; the remainder were superficial tumors and have been treated, so far, successfully with conservative methods. Of the five incompletely responding patients who underwent consolidation by chemoradiation (as a protocol violation), three have suffered a local recurrence. Metastases have developed in 9 of 34 patients. Six patients have died with disease. Three of these patients received further cisplatin-based chemotherapy. The overall actuarial survival is 83% at three years, and 66% are alive without a cystectomy at three years (Fig. 3).

The morbidity of this protocol was documented. Six patients required modification of the induction or consolidation

chemotherapy doses due to acute toxicity (neutropenia in two). One of the 34 patients experienced urinary frequency during induction therapy but it was not sufficient to interrupt therapy or to discontinue the protocol. There have been four reported cases of hematuria and one patient has reported some incontinence. No patient has required a cystectomy for a bladder complication.

DISCUSSION

This study evaluated only a relatively small number of patients. It did not include those with advanced T4 tumors nor those with hydronephrosis, and so it is difficult to compare these results with other published bladder-sparing results. A completion rate of 97% for the induction phase indicates that this is clinically feasible. The overall three-year survival rate of 83% compares favorably with the prior RTOG protocol 89-03 (59% for the 99 patients without hydronephrosis) [7] and is similar to that reported by one single institution pilot using these three agents but with different radiation fractionation and different dose schedules (83%) [8]. The likelihood of being alive at three years with a functioning treated bladder (66%) is encouraging relative to the 46% for the 99 patients without hydronephrosis entered on RTOG 89-03 at three years [7] and similar to that reported

Table 4. Clinical complete response rates by urologic re-evaluation

RTOG 95-06	
Following induction	22/33 (67%)
Following consolidation (patients correctly assigned and received consolidation)	18/20 (90%)
Following consolidation (all patients receiving protocol consolidation)	21/24 (88%)

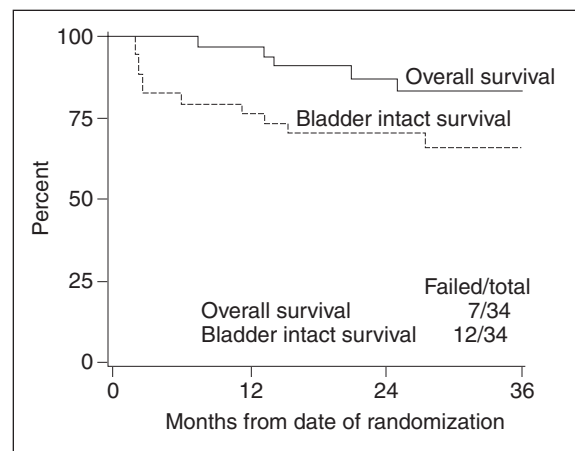


Figure 3. Estimates of overall survival and bladder intact survival rates for patients entered on RTOG 95-06.

from an institutional pilot at the Massachusetts General Hospital using a different dose schedule (78%) [8].

Of concern is that within 29 months of median follow-up, 9 of the 20 complete responding patients who completed the protocol have had local recurrence (three invasive, six superficial). This is higher than had been reported recently by the Paris group on whose results this protocol was modeled. In an update that includes 120 patients, Housset and colleagues [11] report a bladder recurrence rate of only 17% (12 of 71 complete responding patients). Clearly these comparisons are subject to unknown biases, and the follow-up on these series is too short for any substantive conclusions. However, until longer follow-up for local bladder tumor recurrence of the patients on this protocol is available for comparison to those from early RTOG studies that may be lower, we are evaluating the feasibility and efficacy of more conventional twice-a-

day radiation fractionation (1.8 Gy and 1.6 Gy) with concurrent cisplatin followed by three cycles of adjuvant chemotherapy. Also of concern is that 7 of the 34 patients (21%) developed grade 3 or 4 hematologic toxicity in conjunction with this treatment, which may make this combination a less than optimal one to combine with newer adjuvant chemotherapy regimens as are now being tested [8, 12, 13].

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