



Michael Mahany. *Trumpeter Swans on Byer's Lake*. Photograph. Denali National Park, Alaska.

*Bladder-preserving therapy is a safe and effective alternative to cystectomy for carefully selected patients with bladder cancer.*

# Bladder Preservation Protocols in the Treatment of Muscle-Invasive Bladder Cancer

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**Background:** Over the last 3 decades, we have seen a paradigm shift in our approach to the treatment of malignancy. During that time, organ conservation protocols have become standard in the treatment of breast cancer, laryngeal cancer, esophageal cancer, anal cancer and soft tissue sarcomas.

**Methods:** Data from reports of bladder preservation protocols were reviewed to evaluate organ preservation approaches in muscle-invasive bladder cancer.

**Results:** These trials have shown equivalent disease control rates when compared to radical surgery, with the advantage of organ function preservation. In spite of this, organ preservation efforts in muscle-invasive bladder cancer have lagged behind this overall trend in clinical oncology. However, efforts by several investigators over the last 2 decades have shown that for a number of selected patients with muscle-invasive bladder cancer, bladder preservation is feasible without an apparent compromise of overall survival.

**Conclusions:** Bladder preservation therapy with a trimodality approach for a carefully selected patient population is safe and effective. Formal randomized trials comparing radical cystectomy and trimodality bladder-sparing therapy are justified.

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Abbreviations used in this paper: TURBT = transurethral resection of the bladder tumor, CR = complete response, OS = overall survival, MCV = methotrexate, cisplatin, and vinblastine, M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin.

## Bladder Preservation

### Clinical Trials of the Radiation Therapy Oncology Group

Over the last 3 decades, the Radiation Therapy Oncology Group (RTOG) has conducted six prospective clinical trials in patients with muscle-invasive bladder cancer (Table 1) who were otherwise candidates for cystectomy.<sup>1</sup> The basic approach is similar in all six trials: patients received an initial maximal transurethral resection of the bladder tumor (TURBT), followed by radiation therapy to the bladder with concurrent cisplatin-containing chemotherapy.

**Table 1. — Bladder Preservation Studies: Radiation Therapy Oncology Group (RTOG)**

RTOG Study	Radiation Therapy	Radiosensitizing Chemotherapy	No. of Patients	5-Year Survival (%)
85-12 <sup>3</sup>	Daily (64.8 Gy)	Cisplatin	42	52
88-02 <sup>5</sup>	Daily (64.8 Gy)	Cisplatin	91	62
89-03 <sup>6</sup>	Daily (64.8 Gy)	Cisplatin	123	49
95-06 <sup>7</sup>	Hypofractionated	Cisplatin and 5-fluorouracil	34	N/A
97-06 <sup>8</sup>	Hyperfractionated	Cisplatin	52	N/A
99-06	Hyperfractionated	Cisplatin and paclitaxel	84	N/A

All patients received an initial course (generally referred to as induction) in which approximately two thirds of the total radiation dose was delivered (details vary depending on the trial). At the completion of induction radiochemotherapy, all patients underwent a cystoscopic evaluation with biopsies in order to select those who are more likely to preserve their bladder and to avoid delaying radical cystectomy in patients not responding to radiochemotherapy. Only those with a complete response (CR) to induction radiochemotherapy (ie, no tumor on biopsy) went on to receive the second phase of radiochemotherapy (consolidation), whereas patients with positive tumor on biopsy underwent early radical cystectomy. It should be noted that only those with a CR continued with bladder-preserving therapy. All patients are included when endpoint results (eg, overall survival [OS] rate, bladder preservation rate) are presented.

RTOG 85-12 was the first trial on bladder preservation designed by the RTOG for patients with muscle-invasive bladder cancer who were otherwise candidates for radical cystectomy. The rationale for this trial was based on the encouraging experience reported by the National Bladder Cancer Group in patients who were medically inoperable and were treated with concurrent radiochemotherapy.<sup>2</sup> This trial enrolled 42 patients, and a 5-year OS rate of 52% was reported. T stage was a prognostic factor, with patients with T2 disease experiencing 4-year survival rates of 64%, while patients with T3-T4 disease had a 24% 4-year OS rate.<sup>3</sup>

The next RTOG protocol (88-02) incorporated 2 cycles of neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) chemotherapy following TURBT but prior to radiochemotherapy. This was based on the success of a similar protocol at the Massachusetts General Hospital (discussed below).<sup>4</sup> A total of 91 patients were enrolled and a 5-year OS rate of 51% was reported.<sup>5</sup>

Based on the success of 85-12 and 88-02, the RTOG embarked on 89-03, a phase III trial to test whether 2 cycles of neoadjuvant chemotherapy following TURBT would improve survival and bladder preservation rates. A total of 123 patients were enrolled, short of its projected accrual of 174 patients. Patients with T2-T4a muscle-invasive disease who were candidates for radical cystectomy were eligible. All patients initially underwent a maximal TURBT followed by 2 cycles of MCV chemotherapy (only for patients

assigned to the neoadjuvant chemotherapy arm) and then induction radiotherapy (for all patients) with cisplatin chemosensitization. At the completion of 39.6 Gy, a cystoscopic evaluation with biopsies was performed. Only patients with a CR (no tumor on biopsy) continued on consolidation radiochemotherapy to a total dose of 64.8 Gy. Patients with residual disease were referred for early radical cystectomy. The trial was stopped short because of poor patient tolerability for the MCV regimen. Three toxic deaths were reported in the MCV arm. This trial failed to show any difference among the treatment arms. With a median follow-up of 60 months, the actuarial 5-year OS rates for the patients who received neoadjuvant MCV and those who did not were 48% and 49%, respectively. The incidence of distant metastases at 5 years was also similar in both arms: MCV was 33%, no MCV was 39%. Finally, the OS rates with a functioning bladder were similar in both arms: MCV was 36%, no MCV was 38%.<sup>6</sup>

Building on the experience discussed above, the RTOG began a series of protocols to evaluate whether different radiation fractionation schedules could improve the CR rate of induction radiochemotherapy and thus allow bladder preservation. The selection criteria also became more stringent. These protocols excluded patients who presented with hydronephrosis, which had been shown to correlate with a poor CR rate in the above trials. RTOG 95-06 was based on the French experience, which used hypofractionated radiotherapy and concurrent outpatient cisplatin and 5-fluorouracil (5-FU). Eligibility criteria were similar to other trials (T2-T4a disease) except that patients with hydronephrosis were ineligible. The treatment regimen in the induction radiochemotherapy phase delivered radiation therapy to the pelvis at 3 Gy b.i.d. on days 1, 3, 15, and 17. Chemotherapy (cisplatin 15 mg/m<sup>2</sup> and 5-FU 400 mg/m<sup>2</sup>) was delivered on days 1-3 and 15-17. The response was evaluated at week 8. As in previous trials, only patients with a CR went on to receive consolidation radiochemotherapy. This phase delivered 2.5 Gy to the bladder on days 1, 3, 15, and 17. Chemotherapy was delivered in the same way as in the induction phase. With a total of 34 evaluable patients, a 67% CR rate was reported for induction radiochemotherapy. However, 21% of patients developed grade 3 or 4 urinary complications.<sup>7</sup> Given this unacceptably high level of urinary complications, this approach was abandoned by the RTOG.

RTOG 97-06 was a phase I/II trial designed to determine the feasibility of hyperfractionated radiotherapy with concurrent cisplatin chemotherapy. Radiation was delivered twice a day — 1.8 Gy to the pelvis and 1.6 Gy to the tumor with a 4- to 6-hour interval. The chemotherapeutic regimen consisted of cisplatin 20 mg/m<sup>2</sup> twice weekly. This protocol was the first to add adjuvant chemotherapy, with patients receiving 3 cycles of MCV following consolidation radiochemotherapy or cystectomy. Initial findings on this study have been published, reporting a CR rate of 71% and an 11% incidence of grade 3 or 4 toxicity.<sup>8</sup> RTOG 99-06 also evaluated hyperfractionated radiotherapy with a slightly different schedule but incorporated paclitaxel as a radiosensitizer (50 mg/m<sup>2</sup> once a week). Cisplatin was given at 20 mg/m<sup>2</sup> twice a week during both induction and consolidation radiochemotherapy. All patients received adjuvant chemotherapy in the form of 4 cycles of cisplatin (70 mg/m<sup>2</sup>) and gemcitabine (1,000 mg/m<sup>2</sup>). No reports are currently available on this trial.

### Other Series

Several institutions have published their experience with bladder-sparing approaches in patients with muscle-invasive bladder cancer (Table 2). Three institutions (Massachusetts General Hospital, University of Erlangen, and Hôpital Necker) used a trimodality approach including aggressive TURBT, radiation therapy, and chemotherapy.<sup>4,9-11</sup> One approach pioneered in Italy used resection and chemotherapy without radiation,<sup>12</sup> and Memorial Sloan-Kettering Cancer Center used TURBT alone.<sup>13</sup>

Kaufman et al<sup>4</sup> first reported the experience of the Massachusetts General Hospital (MGH) in 1993. Their approach was similar to the RTOG, only differing in that 2 cycles of MCV were given following the TURBT. A total of 53 patients with T2-T4a muscle-invasive bladder cancer were enrolled. A 5-year OS rate of 48% with a median follow-up of 48 months was initially reported. T stage was a significant prognostic factor, with T2 patients responding better than T3-T4 patients (68% for T2 vs 38% for T3-T4, *P*=.02). Furthermore, the presence of hydronephrosis was

a poor prognostic factor for this group. Five-year OS rates were 27% for hydronephrosis vs 63% for no hydronephrosis (*P*=.004). Shipley et al<sup>9</sup> updated this experience in 2002, including all patients at MGH who had been treated with a bladder preservation approach. This review included 190 patients with T2-T4a disease. The 5- and 10-year OS rates were 54% and 36%, respectively. More importantly, a 45% 10-year disease-specific survival rate with an intact bladder was reported, indicating that in the long term, the bladder was preserved in approximately half of the patients. Cystectomy was required in 66 patients due to either incomplete response to induction radiochemotherapy (41 patients) or subsequent recurrent invasive or superficial disease (25 patients). The 5- and 10-year OS rates for this subset of patients were 48% and 41%, respectively, which is comparable to most modern radical cystectomy series, thus suggesting that survival is not compromised in patients in whom the attempt to preserve their bladder was not successful.

Rödel et al<sup>10</sup> from the University of Erlangen in Germany reported the outcome of 415 patients with bladder cancer (89 patients with high-risk T1 disease and 326 patients with T2-T4 disease) treated with TURBT followed by radiation alone (126 patients) or radiochemotherapy (289 patients). Radiotherapy doses ranged from 45 to 69.4 Gy, with a median dose of 54 Gy, which is lower than the standard dose of 64.8 Gy used in the MGH/ROTG series. A total of 145 patients received cisplatin 25 mg/m<sup>2</sup> per day (30-minute infusion on 5 consecutive days) as a radiosensitizer, while 95 patients received carboplatin 65 mg/m<sup>2</sup> per day (30-minute infusion on 5 consecutive days). Those treated prior to October 1985 received radiation alone (126 patients). Patients treated after 1993 received a combination of cisplatin 20 mg/m<sup>2</sup> per day (30-minute infusion on 5 consecutive days) and 5-FU 600 mg/m<sup>2</sup> per day (120-hour continuous infusion) on weeks 1 and 5 of radiotherapy. Their approach also differed from the MGH/RTOG approach in that there was no planned second-look cystoscopic evaluation with biopsies prior to completion of radiochemotherapy, with early cystectomy

Table 2. — Bladder Preservation Studies: Other Series

Investigators	Stage	Treatment	No. of Patients	Survival With Intact Bladder
Shipley et al <sup>9</sup>	T2-T4a	TURBT + chemotherapy + radiation therapy	190	45% (10-yr DSS with intact bladder)
Rödel et al <sup>10</sup>	T1-T4	TURBT + chemotherapy + radiation therapy	415	42% (5-yr OS with intact bladder)
Housset et al <sup>11</sup>	T2-T4	TURBT + chemotherapy + radiation therapy	54	Not reported (62% 3-yr DSS)
Sternberg et al <sup>12</sup>	T2-T4	Neoadjuvant M-VAC + TURBT	104	44% (5-yr OS, with intact bladder)
Herr <sup>13</sup>	T2	TURBT alone	99	57% (10-yr with intact bladder; includes only patients selected for bladder sparing)

TURBT = transurethral resection of the bladder tumor  
M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin  
DSS = disease-specific survival  
OS = overall survival

for nonresponders. All patients completed the full course of radiotherapy or radiochemotherapy, at which point a cystoscopic evaluation was performed. Median follow-up for the cohort was 60 months (range 6 to 199 months). At the completion of radiation or radiochemotherapy, 288 patients (72%) had achieved a CR, with 186 patients (65%) continuously free of tumor in the bladder at last follow-up. Local failure occurred in 35% of patients. They experienced either a superficial recurrence (approximately 50% of all recurrences) or a muscle-invasive recurrence. The 5- and 10-year OS rates for the whole cohort were 51% and 31%, respectively. Importantly, the bladder was preserved in the majority of survivors. While the 5-year OS rate was 51%, the 5-year OS rate with preserved bladder was 42%. This observation continued at 10 years, with a 31% OS rate and a 27% OS rate with preserved bladder. These investigators evaluated a number of prognostic factors. On multivariate analysis, they found T stage ( $P=.02$ ) and a complete TURBT as the strongest prognostic factors for OS.

Housset et al<sup>11</sup> published the results of a prospective trial performed at the Hôpital Necker in Paris. Their approach was similar to the RTOG in that patients were initially treated with a TURBT followed by a course of induction radiochemotherapy. A second cystoscopic evaluation was then performed, with complete responders continuing on to consolidation chemoradiotherapy and nonresponders receiving early radical cystectomy. Their radiotherapy schedule was also somewhat different in that patients were treated with 3 Gy b.i.d. every other day to a total dose of 24 Gy. Cystoscopic evaluation was performed at 6 weeks, with complete responders receiving an additional 2.5 Gy b.i.d. to a total dose of 20 Gy. Chemotherapy consisted of cisplatin (15 mg/m<sup>2</sup> per day on days 1-3, days 15-17 induction) and 5-FU (400 mg/m<sup>2</sup> per day on days 1-3, days 15-17 induction). A total of 54 patients were treated in this fashion with a median follow-up of 27 months. This approach yielded a 74% CR rate and a 3-year disease-free survival rate of 62%. As in the MGH experience, there was no difference in OS between complete responders and nonresponders who received early cystectomy, suggesting that delaying radical cystectomy while attempting to preserve the bladder is safe.

Sternberg et al<sup>12</sup> pioneered an alternative approach using neoadjuvant chemotherapy in select patients for bladder-sparing therapy. In this approach, radiation therapy was not included as part of the treatment protocol. They utilized 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) in 104 consecutive patients with T2-T4 disease. Upon completion of chemotherapy, patients were clinically restaged with a CT scan of the pelvis and a cystoscopy with TURBT of the original site of tumor. Patients experiencing major responses underwent either a partial cystectomy or no further treatment. Patients who did not respond well to chemotherapy were referred for radical cystectomy. Of the 104 patients, 48 attained a CR after 3 cycles of M-VAC,

and an additional 4 patients had only Ta disease at the time of their second TURBT. No further therapy was given to these 52 patients, and the 5-year survival rate was 67%. Importantly, the majority of long-term survivors (74%) had an intact bladder, with an overall bladder preservation of 44% for the entire group. Response to neoadjuvant chemotherapy was a major predictor of outcome. Patients with a major response to chemotherapy who had their muscle-invasive disease downstaged to T0 or superficial disease had a median survival of 63 months and a 5-year survival rate of 69%. In contrast, patients with poor chemotherapy response had a median survival of 31 months and a 5-year OS rate of 20%.

Herr<sup>13</sup> reported the experience at Memorial Sloan-Kettering Cancer Center in managing muscle-invasive disease with TURBT alone without adjuvant radiation therapy or chemotherapy. A total of 432 patients with T2 disease who were referred to their center after an initial transurethral resection underwent a second aggressive TUR that attempted to visibly resect the tumor bed into normal-appearing muscle or fat and laterally to include 1 to 2 cm of normal-appearing bladder mucosa, including underlying lamina propria and bladder muscle. Additional recommendations were based on the pathologic findings of the second TUR. Patients with T0 or T1 disease were offered either radical cystectomy or observation with cystoscopic evaluation every 3 to 6 months. Cystectomy was recommended to patients with persistent muscle-invasive disease (T2). Patients were followed by minimum of 10 years or until death. Of the 432 patients, 151 had T0 or T1 disease at the time of the second TUR. Of these 151 patients, 99 (with 73 having T0 disease and 26 having T1 disease) were observed without any immediate additional treatment. The remaining 52 patients (23 with T0 disease and 29 with T1 disease) underwent immediate radical cystectomy. At 10 years, 57% of the patients treated with the bladder-sparing approach still had their bladders, with a 76% 10-year disease-specific survival rate. Patients treated with immediate cystectomy had a 71% 10-year disease-specific survival rate. This shows the importance of a complete TUR; the survival rate for the patients who had T0 disease after the first TUR and who elected no surveillance over radical cystectomy was 82% compared with 57% of the patients with residual T1 disease. It should be noted that this last figure includes only patients who elected to undergo conservative treatment and does not account for those who were offered bladder preservation but elected immediate surgery.

## Bladder-Preserving Protocols

### *Comparison With Radical Cystectomy Series*

The discussion above shows that in general, bladder preservation with trimodality therapy yields a 5-year OS rate of approximately 50%. Importantly, the bladder is

retained in the majority of the surviving patients. Several large surgical series that report outcomes after radical cystectomy have been recently published. However, comparisons between surgical series and bladder preservation protocols are hindered by the difference in pathologic staging (used in surgical series) and clinical staging (used in bladder preservation series). This bias would tend to favor surgical series, since clinical staging generally tends to understage patients. In contrast, bladder-sparing protocols were offered to carefully selected patients. Although initial protocols accepted patients with T2-T4 disease, few patients with T4 disease were included. More recent protocols accepted patients with only T2-T3 disease, and those with hydronephrosis (usually a marker of tumor bulk) were excluded from many of them. Therefore, it could be argued that the overall prognosis of the patients included in bladder conservation protocols was better to begin with compared to those treated with radical cystectomy.

Stein et al<sup>14</sup> recently published the outcomes of 1,054 patients treated with radical cystectomy at the University of Southern California. A 5-year OS rate of 48% was reported for the 633 patients with muscle-invasive disease (T2-T4). Dalbagni et al<sup>15</sup> reported the experience at Memorial Sloan-Kettering Cancer Center, in which the 5-year OS rate for patients with invasive disease (T2-T4) was 36%. Finally, a recent Intergroup study on neoadjuvant chemotherapy reported a 5-year OS rate of 50% in patients with muscle-invasive disease who were treated with radical cystectomy.<sup>16</sup>

Although results between bladder conservation approaches and modern radical cystectomy series for muscle-invasive bladder cancer appear comparable, no prospective randomized trial to compare both modalities has been performed. In our opinion, radical cystectomy continues to be the standard of care for muscle-invasive bladder cancer. However, we think that there are enough data to justify a formal prospective randomized trial to compare radical cystectomy vs trimodality bladder-conserving protocol in patients who would have been eligible for the RTOG protocols.

### **Local Recurrence and Quality of Life**

An argument against the use of bladder conservation therapy has been the potential long-term effects of radiation on bladder function. To address this concern, Zietman et al<sup>17</sup> reported on the urinary quality of life of patients who had been treated with bladder preservation at MGH. Participation in the study was offered to 71 patients who had retained their bladder and had at least 2 years of follow-up. A validated quality of life questionnaire was given to the 49 patients who chose to enter the study, and they underwent urodynamic evaluation. The median time from treatment to urodynamic evaluation was 6.3 years. Of the 49 enrolled patients, 32 underwent urodynamic evaluation and 24 had normal urinary function.

A concern inherent to bladder preservation protocols is the possibility of local recurrence of the same disease or new disease. In a series from MGH, 26% of patients experienced a local recurrence at a median of 2.1 years after definitive treatment.<sup>18</sup> Two thirds of the recurrences were carcinoma in situ, and the vast majority of patients were managed conservatively. The occurrence of local failure did not correlate with a poorer prognosis; the 10-year survival of patients who experienced a local recurrence was similar to patients who did not (54% vs 61%, respectively). However, patients with local recurrence were more likely to eventually lose their bladder due to either multiple superficial recurrences or invasive disease. Therefore, bladder preservation mandates lifelong cystoscopic surveillance.

## **Conclusions**

Bladder preservation therapy with a trimodality approach for a carefully selected number of patients is safe and effective. Overall survival rates appear to be comparable to modern radical cystectomy series, with the majority of survivors retaining their bladder. In general, most patients retain normal urinary function after the completion of high-dose radiation therapy to the bladder. However, no prospective randomized trial to compare both modalities has been performed, and thus no formal conclusions can be reached regarding their equivalence. Furthermore, the delivery of this treatment requires the close collaboration of the urologist, medical oncologist, and radiation oncologist, and it requires a reliable patient who will adhere to the close cystoscopic surveillance needed after the completion of therapy. Radical cystectomy continues to be the standard of care for muscle-invasive bladder cancer. However, we believe that there are sufficient data to justify a formal randomized trial to compare radical cystectomy vs trimodality bladder-sparing therapy in patients having disease and host characteristics that would have rendered them eligible for the RTOG protocols.

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