SELECTIVE BLADDER PRESERVATION BY COMBINED MODALITY PROTOCOL TREATMENT: LONG-TERM OUTCOMES OF 190 PATIENTS WITH INVASIVE BLADDER CANCER


ABSTRACT

Objectives. To evaluate the outcomes of patients with muscle-invasive Stage T2-4a bladder carcinoma managed by transurethral surgery and concurrent chemoradiation.

Methods. A total of 190 patients were treated on institutional prospective protocols using concurrent cisplatin-containing chemotherapy and radiotherapy after rigorous transurethral resection of the bladder tumor. Patients were re-evaluated by repeated biopsy and urine cytologic analysis after 40 Gy, with the initial tumor response guiding subsequent therapy. One hundred twenty-one patients with a complete response by cytologic and histologic examination and those medically unfit for cystectomy received boost chemoradiation to 64 to 65 Gy. Those patients without a complete response were advised to undergo radical cystectomy. A total of 66 patients (35%) ultimately underwent radical cystectomy: 41 for less than a complete response and an additional 25 for recurrent invasive tumors. The median follow-up was 6.7 years for all surviving patients.

Results. The 5 and 10-year actuarial overall survival rate was 54% and 36%, respectively (Stage T2, 62% and 41%; Stage T3-T4a, 47% and 31%, respectively). The 5 and 10-year disease-specific survival rate was 63% and 59% (Stage T2, 74% and 66%; Stage T3-T4a, 53% and 52%), respectively. The 5 and 10-year disease-specific survival rate for patients with an intact bladder was 46% and 45% (Stage T2, 57% and 50%; Stage T3-T4a, 35% and 34%), respectively. The pelvic failure rate was 8.4%. No patient required cystectomy because of bladder morbidity.

Conclusions. The 10-year overall survival and disease-specific survival rates are comparable with the results reported for contemporary radical cystectomy for patients of similar clinical and pathologic stage. One third of patients treated on protocol with the goal of bladder sparing ultimately required a cystectomy. A trimodality approach with bladder preservation based on the initial tumor response is, therefore, safe, with most long-term survivors retaining functional bladders.

Although radical cystectomy remains the standard of care for patients in the United States with muscle-invasive bladder cancer, several groups have explored therapeutic strategies that aim at bladder preservation. Early approaches at bladder preservation consisted of either aggressive transurethral resection alone done selectively only for patients with small tumors, which represented less than 20% of all muscle-invasive tumors seen by these centers, or for all patients with muscle-invasive tumors referred for external beam radiotherapy. Local failure rates with conventional radiotherapy alone were disappointingly high, and this approach as monotherapy has largely been abandoned. Substantial improvements in local control have more recently been seen with combined modality therapy: transurethral resection of the bladder tumor (TURBT) for debulking followed by radiotherapy with concurrent tumor-sensitizing cisplatin-based chemotherapy. Combining TURBT with only MVAC (methotrexate,
vinblastine, adriamycin, cisplatin) chemotherapy as reported by the Memorial Sloan-Kettering group and other internation series resulted in lower rates of bladder preservation.12

Despite promising results, reluctance to accept “trimodality therapy” (TMT) as an alternative to cystectomy remains widespread. This is, in part, because of improvements in urinary diversion for patients undergoing cystectomy and, in part, because of a widely held concern among urologists that the bladder is never free of the risk of recurrence, either superficial or invasive, and that any recurrence may increase the risk of death from cancer13 or that cystectomy and continent diversions may be more difficult after chemoradiation.14 When reporting the results of combined modality therapy, it is therefore important to report the outcomes of all patients by their intention-to-treat and to have long follow-up. The current report provides long-term follow-up data on the conservative treatment of muscle-invasive bladder cancer and includes all patients entered, regardless of whether bladder preservation was possible.

MATERIAL AND METHODS

Between 1986 and 1997, 190 patients with invasive bladder cancer (clinical Stage T2-4-a) were entered on successive prospective protocols evaluating modifications for improved patient tolerance in the chemotherapy and radiotherapy schedules that have not differed significantly in survival rates.15 The initial patient evaluation included chest radiography, computed tomography (used for lymph node and liver staging, not for staging of the primary tumor), bone scan, and TURBT as thoroughly as possible. Clinical staging was by the American Joint Committee on Cancer system.16 Patients were ineligible for these protocols for the following reasons: evidence of distant spread of disease, including histologically or cytologically confirmed metastases to lymph nodes; a white blood cell count less than 4000/mL or platelet count less than 100,000/mL; serum creatinine level greater than 1.7 mg/mL or creatinine clearance less than 50 mL/min (this was changed in 1991 to less than 60 mL/min); evidence of hydrenephrosis (since 1993); or patient refusal to sign a consent form approved by the institutional review board after the nature of the procedures had been fully explained. Patients with severe irritative bladder symptoms were not candidates for the bladder-preserving protocols.

Protocol Designs

A common feature of all protocols was the selection of patients for bladder conservation on the basis of their initial response to TURBT combined with chemotherapy and radiotherapy (TMT). Bladder conservation was reserved for those who had a complete clinical response at a midpoint in therapy (after the induction phase, which was usually after a radiation dose of 40 Gy). These patients, approximately two thirds of the total, then received consolidation by additional concurrent chemotherapy and radiotherapy to a total tumor dose of 64 to 65 Gy and were followed up indefinitely with regular cystoscopic examinations. Patients with an incomplete response after induction TMT were advised to undergo radical cystectomy before their disease progressed and before they had received radiation doses that might make surgery, including continent diversion, more difficult. Patients whose invasive tumors persisted or recurred were advised to undergo prompt salvage cystectomy.

In these Phase II and III protocols, the scheduling of the chemoradiation or the drugs used was altered and/or the use of additional multidrug chemotherapy (first as neoadjuvant, then as adjuvant) was employed. For the first two protocols, which included 144 patients, the induction and consolidation TMT was as described previously.8,12 For patients with a complete response (CR), consolidation was a boost to the tumor volume to 64.8 Gy with an additional course of cisplatin. In 98 of these 144 patients, two courses of neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) preceded the chemoradiation (cisplatin and daily radiotherapy) on the Phase I/II protocol, and on one arm of a Phase III protocol as previously reported.15 The two subsequent Phase I/II protocols included 29 patients who received both cisplatin and 5-fluorouracil concurrent with accelerated twice daily irradiation schedules, as previously described.17,18 In the fifth protocol, 17 patients were treated with regimens of concurrent cisplatin with twice daily irradiation using conventional fractions (180 cGy and 160 cGy) followed by three cycles of adjuvant MCV chemotherapy.19

Criteria for Response and Follow-up Procedures

Patients underwent cystoscopy, biopsy of the tumor site, bimanual examination under anesthesia, and urinary cytologic examination every 3 months for 2 years. After 2 years, in patients with negative evaluations, the cold-cup biopsy was usually omitted if no worrisome endoscopic findings were present. Surveillance continued every 6 months for 3 more years and yearly thereafter. No patient was lost to follow-up. The response of the primary tumor was considered a clinically CR if no tumor was visible on cystoscopy and both a tumor-site cold cup biopsy and urinary cytologic findings were negative. The upper tracts were evaluated by serial computed tomography and ureteral cytologic analysis and endoscopy when indicated.

Statistical Analysis

Survival probabilities were estimated using the Kaplan-Meier method.20 The probability of time to invasive local failure and distant metastases was estimated using the cumulative incidence method.20,21 The patient characteristics for the two treatments were compared by the chi-square test. The comparison for various endpoints was performed using the log-rank test.22,23 Intervals of significance were represented by P values derived from two-sided tests. The median follow-up for all surviving patients was 6.7 years (range 2 to 13.4); 81 patients were followed up for 5 years or more and 28 patients for 10 or more years.

RESULTS

The pretreatment patient and tumor characteristics were as follows: 75% men and 25% women; 47% clinical Stage T2 and 53% clinical Stage T3-T4a; 14% with hydronephrosis and 86% without; and 52% received neoadjuvant MCV chemotherapy and 48% did not. A visibly complete TURBT was possible in 57% of the patients. Tumor invasion into or beyond the muscularis propria was present in all patients. The histologic findings were transitional cell carcinoma in 97%, with Grade II/III in 20% and Grade III/III in 80%. Sixty-six patients (35%) underwent radical cystectomy; 41 for
an incomplete initial response and 25 as a salvage cystectomy for recurrent invasive tumor occurring during the postoperative follow-up period. No patient required cystectomy for a radiation complication. Eighty-two percent of patients completed the protocols as planned or with only minor deviations. The reasons for noncompletion of the protocols in 34 patients included neutropenia and/or sepsis resulting from MCV neoadjuvant chemotherapy in 19 (of which 4 were lethal, as previously reported), the use of consolidation chemoradiation in 12 patients with an incomplete response, because 4 had become unsuitable for, and 8 had refused, radical cystectomy, and 3 patients who developed distant metastases and were treated palliatively.

The actuarial 5 and 10-year overall survival and disease-specific survival rates for all 190 entered patients and for some clinically important subgroups are shown in Table I. The clinical stage of the tumor (Figs. 1 and 2) significantly influenced overall survival (P = 0.02) and disease-specific survival (P = 0.01), as well as the CR rate (Stage T2, 71%; Stage T3-T4a, 57%; P = 0.04) and the rate of subsequent distant metastases (Stage T2, 22%; Stage T3-T4a, 37%; P = 0.03). We also found a significantly higher 5 and 10-year disease-specific survival rate for patients with an intact bladder and Stage T2 disease (57% and 50%, respectively), than for those with Stage T3-4a (35% and 24%, respectively, P = 0.008). Neither the tumor grade nor the use of neoadjuvant MCV chemotherapy significantly improved the CR, overall survival, disease-specific survival, or distant metastasis-free survival rates, as previously reported. The presence of hydronephrosis significantly reduced the CR rate (37% versus 68%, P = 0.002) and may reduce (P = 0.09) disease-specific survival.

The 5 and 10-year disease-specific survival rate for all 66 patients undergoing cystectomy was 48% and 41%, respectively, indicating the important contribution of this procedure for the cure of the 66 patients treated with this approach. The tumor stage did not influence the 5 and 10-year disease-specific survival in the 66 patients undergoing either immediate cystectomy or salvage cystectomy (Stage T2, 57% and 39%; Stage T3-T4a, 42% and 42%). One patient had a serious complication, a perforated duodenal ulcer. Two patients underwent continent diversion. The disease-specific survival for the cystectomy patients was similar for the 41 patients who underwent cystectomy because of an incomplete response compared with the 25 patients who underwent salvage cystectomy for recurrence of an invasive tumor.

Sixty percent of patients who had a CR after induction therapy developed no further bladder tumors, 24% subsequently developed only a superficial recurrence, and 16% developed an invasive tumor. As separately reported, 29 patients with su-

### Table I. Survival outcomes by patient and tumor characteristics

<table>
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<tr>
<th>Patient Group</th>
<th>n</th>
<th>Overall Survival (%)</th>
<th>Disease-Specific Survival (%)</th>
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<tr>
<td></td>
<td></td>
<td>5 yr</td>
<td>10 yr</td>
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<tr>
<td>All patients</td>
<td>190</td>
<td>54 ± 7.5*</td>
<td>36 ± 8.3*</td>
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<tr>
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<td>48</td>
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* 95% confidence interval.

![FIGURE 1. Estimates of overall survival according to clinical tumor stage.](UROLOGY 60 (1), 2002)
pericificial recurrence (Stage Ta, n = 6; Stage Tis, n = 21; and Stage T1, n = 2) were treated conservatively by transurethral resection and intravesical therapy. However, 7 of the 29 required subsequent cystectomy for additional superficial (4 patients) or invasive (3 patients) recurrence. For these patients, the overall survival was comparable to the 74 who had no failure (however, one third of these patients required salvage cystectomy). Sixteen (8.4%) of the 190 patients developed a pelvic recurrence. This includes 6 (14.6%) of the 41 patients who underwent immediate cystectomy for an incomplete response to induction therapy and 6.7% of the remainder, with a median follow-up of 7.3 years. No patient developed upper tract transitional cell carcinoma or a urethral recurrence.

COMMENT

The 5-year overall survival rate of 54%, disease-specific survival rate of 63%, and 5-year survival rate with a preserved native bladder of 45% reported here are similar to the results of other recently reported combined modality series using transurethral surgery plus concurrent chemotherapy and radiotherapy. Our results are also similar to those reported in prospective cystectomy series for patients of similar age and tumors of similar clinical stage.

Comparing our results with those of contemporary radical cystectomy series is confounded by the discordance between clinical (TURBT) staging and pathologic (cystectomy) staging. A recent thorough prospective evaluation from Stockholm has clearly documented that clinical staging is more likely to under stage the extent of disease with regard to penetration into muscular propria or beyond than is pathologic staging. Thus, if any favorable outcome bias exists, it is in favor of the pathologically reported radical cystectomy series.

The University of Southern California recently reported on 633 patients undergoing contemporary radical cystectomy with pathologic Stage T2-4a, with an actuarial overall survival rate at 5 years of 48% and at 10 years of 32%. The Memorial Sloan-Kettering Cancer Center’s contemporary radical cystectomy series was also recently reported. In 184 patients with tumors of pathologic stage T2-4, they reported a 5-year overall survival rate of 36%. The actuarial 5-year survival rate of all 269 patients undergoing contemporary radical cystectomy with pathologic stages ranging from T0 to T4 in this series was 45%. The similarity in long-term survival between contemporary cystectomy series and contemporary selective bladder preserving series is likely due, in part, to the prompt use of salvage cystectomy when necessary—35% of all entered patients in our series. The disease-specific survival rate at 10 years for the 66 patients undergoing cystectomy either at the time of an incomplete response or for invasive recurrence was 40%. This underscores the need in selective bladder-preserving approaches for close cystoscopic evaluation and prompt removal of the bladder for an incomplete response or invasive recurrence.

From 1986 to 1993, we studied the question of neoadjuvant multidrug systemic chemotherapy to reduce the appearance of distant metastases and increase cure rates. However, the 5 and 10-year metastasis-free survival rates were not influenced in any patient subgroup by the addition of two cycles of neoadjuvant MCV chemotherapy. The lack of efficacy of neoadjuvant MCV was confirmed in a previously reported Phase III trial. Our current protocol, therefore, includes the combination of gemcitabine and cisplatin as adjuvant therapy.

It has been argued that TMT may represent excessive treatment for many patients with invasive bladder cancer and that comparable results could be obtained by TURBT, either alone or with chemotherapy. Herr recently reported on the outcome of 432 patients initially evaluated by repeated TURBT for muscle-invasive bladder tumors. In that series, 99 patients (23% of the original 432 patients) initially treated conservatively without immediate cystectomy had a 34% rate of progression with recurrent muscle-invasive tumor at 10 years. Among our 90 patients with Stage T2 disease after TURBT, which includes more advanced tumors, 16% had an incomplete response or developed invasive recurrence at a median follow-up of 7 years. Comparing approaches by TURBT plus MVAC chemotherapy alone with TURBT plus concurrent chemotherapy and radiotherapy (see Table 13 in Scher et al.), the 5-year survival rates with a preserved bladder for all patients entered ranges from 20% to 33% when radiotherapy was not used.

FIGURE 2. Estimates of disease-specific survival according to clinical tumor stage.
and from 41% to 45% when radiotherapy was used. Thus, the use of radiotherapy concurrent with chemotherapy after TURBT (trimodality therapy) increases the probability of surviving and having an intact bladder by 30% to 50% compared with TURBT and chemotherapy alone. These two series taken together demonstrate not only the value of transurethral surgery with or without chemotherapy but also the importance of this surgery being followed by both chemotherapy and radiotherapy concurrently when the intent is to maximize long-term survival without invasive tumor recurrence.

CONCLUSIONS

The 10-year overall survival and disease-specific survival rates are comparable to the results reported with contemporary radical cystectomy for patients of similar clinical and pathologic stage. One third of patients treated on protocol with the goal of bladder sparing ultimately required cystectomy. A trimodality approach with bladder preservation on the basis of the initial tumor response is, therefore, safe, with most long-term survivors retaining functional bladders. However, lifelong bladder surveillance is essential, because only prompt salvage therapy can prevent a focus of new or recurrent bladder cancer from disseminating.

ACKNOWLEDGMENT. To Karin A. Pearson and Wendy S. Shrais for assistance in manuscript preparation.

REFERENCES


EDITORIAL COMMENT
Selective bladder preservation is a controversial topic that commonly evokes an emotional response in urologic oncology circles. A debate about the risks and benefits of bladder preservation for muscle-invasive cancer is a frequent feature at the American Urological Association or Society of Urologic Oncology meetings. The intense discussions arise, as the findings of recent studies are not easy to interpret or apply and several endpoints may be considered important.

The authors of this study are to be credited for applying clinical judgment before and during the protocol. The study contained 190 patients with invasive bladder cancer. Patients with larger volume cancers, heralded by hydronephrosis or severe irritative symptoms, were largely excluded. After the initial phase of treatment, patients with an incomplete response were directed to immediate cystectomy. Disease progression or a negative impact on survival during this initial phase was not clearly evident.

Questions arise concerning the cancers that developed in the patients with a good initial response to treatment. The flow diagram (Fig. 1) attempts to describe the outcomes in the study. The data presented suggest that 23 patients developed invasive recurrence in the bladder after an initial CR in the bladder. Presumably, this was a “new” cancer that developed after the initial one was eliminated. Because survival in this group was stated to be the same as the overall group (approximately 54% at 5 years), one may estimate that 10 to 11 patients may have died of this “new” cancer, which they would not have developed had their bladder been removed initially. This is the negative side of bladder preservation for muscle-invasive cancer. However, to put this in perspective, the potential increase in the number of patients who may succumb to bladder cancer in this scenario is approximately 5% of the total number of patients in the study. This small increase in mortality would be extraordinarily difficult to detect in a prospective randomized trial, even if one could be done.

On the positive side, approximately 40% of the patients did not develop recurrence in the bladder and in general retained good bladder function. Is a 40% chance of a potentially better lifestyle by not selecting cystectomy as the initial treatment option worth a possible 5% or more worsening in survival chances? Good question.

Frankly, most urologists have not embraced bladder preservation as a viable treatment option, citing the possible risk of a greater number of deaths, extent of treatment needed, and improved rehabilitation that may be possible with neobladders and nerve-sparing cystectomies. Nevertheless, that some patients do remarkably well with a bladder preservation strategy challenges us to identify the patient and tumor characteristics associated with a high certainty of successful trimodality therapy. I believe the use of better radiation-sensitizing agents, such as gemcitabine, and better selection of patients with minimal or no carcinoma in situ, small-volume cancer, pure urothelial cell histologic features, no hydronephrosis, a favorable molecular phenotype, and patient motivation for follow-up will lead to such a good response that it will be hard to ignore. As we are repeatedly taught in oncology, one particular treatment does not have to be mandated for every patient. We do a disservice to our patients by failing to recognize the opportunities for potentially better tolerated treatment regimens. A pilot Phase I–II study at the University of Michigan of concurrent gemcitabine and radiotherapy after aggressive TURBT has surprised me with remarkably good patient tolerance, preserved bladder function, and apparently favorable results. The discussion of the risks and benefits of bladder preservation for muscle-invasive cancer should remain open.

James E. Montie, M.D.
University of Michigan School of Medicine
Ann Arbor, Michigan

P00090-4295(02)01651-5
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REPLY BY THE AUTHORS
We appreciate the thoughtful editorial comments on our report.

Although we agree that “selective bladder preservation is a controversial topic . . . in urologic oncology circles,” the results have now been so well documented in peer-reviewed scientific publications, that it is appropriate, we believe, for the “emotional response” to be set aside.

In response to Dr. Montie’s comments, we offer the following facts and clarification.

1. Selective bladder preservation is, and should be, very selective. Only those patients who achieve a CR should have the full treatment. All those with less than a CR should have a cystectomy.

2. It was stated that only 72 of the original 190 patients maintained a durable CR in the bladder. This, however, ignores the further 29 who developed subsequent noninvasive disease, 22 of whom had CRs to subsequent therapy and kept their bladders, with a median follow-up of 4.0 years. 1

3. No significant diminution in survival occurred for those patients who underwent radiotherapy and then required cystectomy.