Organ Preservation in Muscle-Invasive Bladder Cancer

While organ preservation with nonextirpative surgery, radiotherapy, and frequently, chemotherapy has become a favored strategy in the treatment of many cancers, bladder preservation for patients with invasive disease remains controversial. The standard treatment for muscle-invasive bladder cancer in the United States is still radical cystectomy with pelvic lymph node dissection. An alternative to cystectomy is multimodality bladder preservation with thorough transurethral resection, chemotherapy, and radiation therapy. This review will address issues raised by a multimodality approach for the treatment of invasive bladder cancer.

Organ preservation with nonextirpative surgery, radiotherapy, and frequently, chemotherapy has become a favored strategy in the treatment of cancers of the larynx, esophagus, breast, soft-tissue extremity sarcomas, and anal canal. Bladder cancer is a more controversial organ-preservation site due, in part, to the biology of the tumor. Bladder cancer can be multifocal, arising from several areas of urothelium in both the bladder and upper urinary system. Herr et al reported a 21% rate of upper urinary tract tumors in patients with recurrent carcinoma in situ and T1 bladder cancer treated with transurethral resection of the bladder tumor (TURBT) and bacillus Calmette-Gurin (BCG) immunotherapy.[1] In addition, there are concerns that superficial recurrence after bladder preservation may result in subsequent invasive neoplasms and decreased survival. The standard treatment for muscle-invasive bladder cancer in the United States is radical cystectomy with a pelvic lymph node dissection. The local control rate is excellent at 90%, but due to the development of nonregional metastatic disease, the 5-year overall survival rate is only about 50%.[2] An alternative approach is multimodality bladder preservation, which in modern series includes thorough TURBT, chemotherapy, and radiation therapy. This approach has been developed to improve quality of life for patients who want to maintain urinary function without a diversion, and also for patients who are not candidates for surgery. Overall survival results from large centers using the multimodality conservative approach are similar to those for radical cystectomy.[3-6] This review will address issues raised in a multimodality approach to the treatment of invasive bladder cancer including transurethral surgery, neoadjuvant or adjuvant chemotherapy, and radiation therapy.

Transurethral Resection of Bladder Tumor Several studies have examined the role of TURBT as a single modality in the treatment of invasive bladder cancer. A series of 308 patients by Solsona et al reported a 5-year survival rate of 83% and a bladder preservation rate of 73%.[7] In a carefully selected group of patients, Herr et al reported a similar bladder preservation of 65% with an overall survival rate of 70% in patients with T2 bladder cancers. The majority of patients in this trial required a repeat TURBT.[8] Although survival rates are acceptable, local control with TURBT alone may be compromised. Complete TURBT is also the initial step in the multimodality approach to invasive bladder cancer. An aggressive resection is a crucial factor in controlling local recurrence for patients undergoing an organ-sparing approach. In a University of Erlangen series, patients were classified by completeness of TURBT, with R0 indicating no evidence of microscopic tumor, R1 indicating a macroscopically complete procedure with evidence of microscopic disease, and R2 indicating a macroscopically incomplete TURBT.[9] Multivariate analysis showed that R classification was the only prognostic factor for both local control and survival. Patients who had macroscopic disease after TURBT had a 5-year survival of 31%, compared to 81% survival in patients who had no evidence of microscopic disease after TURBT. The feasibility of a complete resection is also dependent on the biology of the tumor. A well circumscribed, superficial tumor would likely be fully resected, unlike a deeply invasive or widely extensive bladder tumor.[10] Chemotherapy as a Single Modality Several studies have shown that systemic chemotherapy alone has an inferior local control rate, compared to cystectomy, TURBT, and definitive radiation therapy. Roberts et al published a phase II study in locally advanced bladder cancer treated with cisplatin and methotrexate as primary therapy.[11] Response was seen in less than half of patients, with partial response in 34% and complete response in only 11%. A study by Scher et al showed that clinical response to chemotherapy did not correspond to pathologic response.[12] While 56% of patients achieved complete clinical response with neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin
[Adriamycin], cisplatin), residual tumor was seen in 61% of cystectomy specimens on pathology review. Another study found a pathologic complete response rate of 8.3% in 69 patients who received CMV (cisplatin, methotrexate, vinblastine) as primary therapy.[13] With such results, chemotherapy is not currently used as a single modality but instead as part of a multimodality approach. Chemotherapy can work synergistically with radiation to increase cell kill. The direct cytotoxic effect of chemotherapy is also important since up to 50% of patients with muscle-invasive bladder cancer have occult metastasis. **Radiation as a Single Modality** There are no randomized trials directly comparing cystectomy to definitive radiation therapy, but external-beam irradiation has been used as an alternative to cystectomy. Most historical series of definitive radiation therapy for muscle-invasive bladder cancer included patients who were medically unfit for cystectomy. Gospodarowicz et al reported a 32% overall survival at 5 years in 121 consecutive patients who received definitive radiation therapy.[14] The initial pelvic field received 35-40 Gy followed by an additional 15-20 Gy to the bladder. The cause-specific survival in this study was 45%, with 27% of patients maintaining functional bladders. In a larger series of 963 patients treated with radical photon radiotherapy and 58 patients treated with radical neutron radiotherapy reported by Duncan and Quilty, 5-year overall survival was similar at 36%.[15] Shipley et al found several positive prognostic factors for choosing patients for primary external-beam therapy including clinical stage, no evidence of hydronephrosis or obstruction, complete TURBT, complete response to radiotherapy at repeat cystoscopy, and adequate radiation dose.[16] In this study, patients received 50.4 Gy in the bladder and regional lymph nodes, followed by a bladder boost to 14-18 Gy. **Survival Comparisons** Several studies have compared immediate cystectomy to definitive external-beam radiation therapy with cystectomy only for incomplete response or failure. The only study to report a survival advantage with immediate cystectomy is a small series from M. D. Anderson.[17] The 35 patients randomized to immediate cystectomy had a 5-year survival of 45%, whereas survival in delayed cystectomy patients was decreased to 22% at 5 years. Other studies have shown no difference in survival for delayed cystectomy, including the Urologic Cooperative Group study.[18] In this series of 187 patients, 5- and 10-year survival rates in the cystectomy arm were 39% and 19%, compared to 28% and 15% for patients who had primary radiation therapy with cystectomy for incomplete response. The Danish National Bladder Cancer Group trial of 183 patients showed a statistically higher rate of pelvic recurrence in the radiation arm vs immediate cystectomy arm (35% vs 7%).[19] However, these investigators found no difference in 5-year overall survival. **Toxicity** Radiation therapy for bladder cancer has been associated with treatment toxicity. During treatment, approximately half of patients will report dysuria and urinary frequency, which resolves several weeks after radiation in most patients. Acute bowel toxicity occurs less frequently and is reported in approximately 15% of patients. The incidence of late bladder toxicity such as contracture was up to 45% in earlier series that used intravesical chemotherapy.[20] With the current fraction size of 2 Gy or less and a total dose of 60 Gy to the bladder, late bladder toxicity occurs much less often. Shipley et al have reported less than a 1% rate of salvage cystectomy for bladder contraction or radiation cystitis.[5] **Multimodality Approach for Organ Preservation** Several multimodality protocols have been conducted in the United States, with large series from Massachusetts General Hospital and cooperative groups such as the Radiation Therapy Oncology Group (RTOG). Most protocols start with TURBT of the bladder, with complete resection if possible. Then patients undergo concurrent radiation with chemotherapy. Certain chemotherapeutic agents, such as cisplatin and fluorouracil (5-FU), work as both cytotoxic agents and radiosensitizers. Several weeks after the induction phase, patients who are surgical candidates undergo a repeat cystoscopy with biopsy and cytology to determine response. Patients who have had a complete response undergo consolidation therapy with a combination of radiation and chemotherapy. Cystectomy is recommended for patients who have had an incomplete response.
Early Trials

Initial evidence for the use of concurrent chemotherapy and irradiation came from precystectomy studies. A National Cancer Institute of Canada trial randomized patients to radiation alone vs radiation and cisplatin prior to planned cystectomy or planned definitive radiation.[21] Investigators found a statistically higher rate of pelvic control in the patients who received chemotherapy at 58% vs 40% in the radiation-alone arm but no difference in distant metastasis or overall survival between the two groups. In a University of Paris study, patients underwent TURBT followed by radiation therapy to 24 Gy with concurrent cisplatin and 5-FU.[3] Reevaluation with cystoscopy and biopsy revealed a 74% complete response rate. Patients with a complete response were randomized to cystectomy vs accelerated radiation and 5-FU and cisplatin. There was no difference in the survival of complete responders who had surgery vs continued chemotherapy and irradiation. However, disease-free survival at 3 years was significantly better in the responders (77%) vs nonresponders (23%). A study from Germany reported similar response and survival rates with induction therapy alone.[4] The 184 patients in this study received platin-based chemotherapy with external-beam radiation to 45-54 Gy. Using cystoscopic evaluation, the complete response rate was 85% in patients receiving cisplatin and 70% in those receiving carboplatin (Paraplatin). The overall 5-year survival rate was 56%, with 41% survival in those with an intact bladder.

RTOG Studies

The RTOG has been actively involved in bladder preservation protocols for patients with T2-4 tumors since 1985. A recent overview of these trials was published by Shipley et al (Table 1).[22] The initial trial (RTOG 85-12) established the standard approach for subsequent trials. Patients received an induction radiotherapy dose of 40 Gy, with concurrent cisplatin.[23] Patients who had a complete response, based upon cystoscopy, rebiopsy, and urine cytology, received an additional radiation dose to the bladder with further chemotherapy. The overall 4-year survival rate was 64%. RTOG 95-06 evaluated an accelerated radiation treatment with concurrent 5-FU and cisplatin,[24] similar to the University of Paris regimen.[3] This RTOG study included 34 patients who had a 67% complete response rate with induction therapy. The overall survival rate at 3 years was 83%. Current RTOG protocols are investigating the role of newer agents. RTOG 02-33 is a phase II study that randomizes patients to either cisplatin and 5-FU or cisplatin and paclitaxel with twice-daily radiation. After the complete responders have finished local therapy, all patients received adjuvant systemic therapy with gemcitabine (Gemzar), cisplatin, and paclitaxel. Other studies have looked at the role of neoadjuvant chemotherapy in the multimodality approach. RTOG 88-02 was the pilot study of two cycles of MCV (methotrexate, cisplatin, vinblastine) prior to concurrent chemotherapy and irradiation. The response rate was 75%, and 5-year survival rate was 51%.[25] This led to the phase III trial RTOG 89-03, in which patients received either two cycles of neoadjuvant therapy with MCV followed by cisplatin and radiotherapy, or cisplatin and radiotherapy without the neoadjuvant MCV.

<table>
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<th>Protocol</th>
<th>Induction Treatment</th>
<th>Number of Patients</th>
<th>Complete Response</th>
<th>5-yr Survival</th>
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<tr>
<td>85-12</td>
<td>TURBT, XRT + Cis</td>
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<tr>
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<td>TURBT, XRT (BID) + Cis + adj MCV</td>
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<td>TURBT, Tax, XRT + Cis; adj Cis + Gem</td>
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<td>NA</td>
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</table>

Table 1: Radiation Therapy Oncology Group Protocols for Invasive Bladder Cancer (1985–2001)

Adapted from Shipley et al.[22]
Due to hematologic toxicities such as leukopenia and sepsis, this trial was stopped before the accrual goal was reached; nevertheless, 123 patients were accrued. There were no differences in overall survival, response rate, or rate of metastatic disease when the neoadjuvant group was compared to the standard-induction group.\textsuperscript{[5]} Meta-analysis

A meta-analysis of almost 2,700 patients from 10 randomized trials showed a small advantage in survival with neoadjuvant chemotherapy, although the difference was not statistically significant when compared to other platinum-based chemotherapy regimens.\textsuperscript{[26]} The overall hazard ratio for patients receiving neoadjuvant chemotherapy was 0.91; i.e., there is a 9% relative reduction in risk of death associated with neoadjuvant chemotherapy. Overall survival increased from 45% to 48% in this group, but the difference was not significant ($P = .08$). Patients who received platinum-based combination chemotherapy showed a 13% decrease in risk of death and a statistically significant improvement in overall survival (from 45% to 50%). This improvement was present regardless of whether local treatment consisted of cystectomy, radiation therapy, or both. Quality of Life With Organ Preservation

One of the main goals of bladder preservation is to improve quality of life by preserving a functional bladder and avoiding the need for a urinary diversion. Multimodality therapy can affect organs beyond the bladder including the rectum, small bowel, anal sphincter, and the nerves and vessels that control sexual functioning. A series by Henningson et al reported the results from 71 patients in Stockholm treated with radiation therapy between 1977 and 1995.\textsuperscript{[27]} The radiation dose ranged from 58-63 Gy. These patients were compared to 460 age-matched controls as well as 250 patients who underwent cystectomy. Through anonymous questionnaires, 74% of irradiated patients reported little or no distress from urinary symptoms and 68% were free of moderate or severe gastrointestinal symptoms. Compared to cystectomy patients, more irradiated patients retained sexual function. Based on the survey, 38% of irradiated patients had intercourse in the previous month compared to 13% of cystectomy patients. The 75% of patients who retained a functioning urinary bladder after radiotherapy in this series is similar to findings in other multimodality series (Table 2).\textsuperscript{[28]} Rates of salvage cystectomy for bladder contracture or radiation cystitis from recent multimodality protocols are 1% or less.\textsuperscript{[5]} Two recent abstracts addressing quality of life after organ preservation for muscle-invasive bladder cancer were presented at American Society for Therapeutic Radiation and Oncology (ASTRO) meeting. The first is a French study that assessed 53 patients treated with concurrent chemotherapy and radiation therapy between 1999 and 2001. With a median follow-up of 2 years, 82% of patients had preserved bladders. Approximately 67% of patients with a preserved bladder reported satisfactory urinary function at 2 years.\textsuperscript{[29]} Zietman et al presented bladder preservation results from Massachusetts General Hospital using both quality-of-life questionnaires and formal urodynamic studies. On urodynamic evaluation, 80% of patients (19/26) had normal bladder function. The quality-of-life questionnaire revealed no significant urinary symptoms in over 80% of patients. The incidence of bowel dysfunction was low, and 55% of men reported sufficient erection for intercourse within the month prior to the survey.\textsuperscript{[30]} Superficial Recurrence in Organ Preservation

After undergoing bladder preservation, patients must undergo careful surveillance because they are at risk for developing both invasive and superficial recurrences. If a muscle-invasive recurrence develops, salvage cystectomy is recommended. However, there is more debate on how to manage superficial recurrences. Between 9% and 28% of patients who undergo bladder preservation will have a superficial relapse.\textsuperscript{[31]} While a conservative approach—i.e., resection with TURBT and intravesical therapy—can be taken, there is concern that aggressive lesions may become invasive. Several studies have looked at the prognosis of superficial recurrence and its impact on survival. Zietman et al studied 190 consecutive patients enrolled in bladder preservation protocols at Massachusetts General Hospital between 1986 and 1998.\textsuperscript{[32]} The complete response rate in this group was 64% when reevaluation cystoscopy was performed; those who did not have a complete response were advised to undergo a cystectomy. The 5-year disease-specific survival rate was 63% for the entire group. Thirty-two patients (26%) had a superficial recurrence with a median time to failure of 2.1 years, and 28 of these patients were managed conservatively with intravesical BCG, TURBT, or a combination of the two. Of these patients, 64% had no further recurrence. The majority (67%) of recurrences in this study were in the same region as the original tumor. There was no difference in 5-year survival between patients who had superficial recurrence (69%) and those who did not (68%). However, there was a statistically significant difference in survival with an intact bladder: Among patients without a recurrence, 61% were alive with an intact bladder vs 34% of patients with a recurrence. Another study that examined superficial relapses after bladder preservation was published by Pieras et al.\textsuperscript{[33]} A select group of 51 patients underwent a transurethral resection followed by three cycles of carboplatin and vinblastine; no radiation therapy was given. A total of 42
patients responded to treatment on cystoscopy 3 weeks after finishing treatment and proceeded with bladder preservation. Eighteen patients (43%) experienced superficial recurrences at a mean of 19 months; median follow-up in this study was 5 years. There was no statistically significant difference in cancer-specific survival among patients who were recurrence-free (89%) vs those with a superficial recurrence (94%). Unlike the prior study, 66% of recurrences were at a different site than that of the initial tumor. There was also no significant difference in rates of bladder preservation when comparing patients who had a superficial recurrence (83%) to those who did not (78%) in this study. The authors concluded that superficial recurrences could be treated conservatively without compromising survival. **Conclusions** Multimodality bladder preservation protocols have produced survival rates similar to those achieved with radical cystectomy. Survival rates are directly related to the clinical stage of the tumor. In a series of 190 patients enrolled in a bladder-preservation protocol, 66 underwent cystectomy for either incomplete response or recurrence.[6] The overall survival for patients with T2 tumors at 5 and 10 years was 62% and 41%. The 5- and 10-year survival rates dropped to 47% and 31% for patients with T3-T4a tumors. Survival with an intact bladder at 10 years also dropped with stage, from 50% in T2 patients to 34% in T3-4a patients. Given that many patients would be candidates for neobladder formation with continent diversions, quality-of-life issues are raised with multimodality therapy. Additional quality-of-life data are becoming available, but thus far, urinary, bowel, and sexual functioning after bladder preservation seem acceptable. Moreover, the rates of cystectomy for bladder contracture or cystitis after multimodality treatment are extremely low. After bladder preservation, patients are at risk for both superficial and invasive recurrence. The ideal candidate for this approach would be compliant with the frequent follow-up necessary to evaluate disease status. Evidence from multiple studies does not support decreased survival with immediate cystectomy vs delayed cystectomy for recurrence. Patients with superficial recurrence also have no difference in cancer-specific survival when compared to those who show no evidence of recurrence. However, there are conflicting data regarding survival with an intact bladder after superficial recurrence. When examining these issues on the basis of available data, bladder preservation with multimodality treatment is a viable option for patients with muscle-invasive bladder cancer. For patients who are alive at 5 years, 80% have an intact bladder.[28] Current protocols incorporate chemotherapeutic agents such as docetaxel (Taxotere) and gemcitabine to improve efficacy without increasing toxicity. Various radiation fractionation schedules such as hypofractionation and twice-daily treatments are also being evaluated in current protocols. Evidence supports careful selection of patients for bladder preservation including those who have a complete TURBT, no evidence of ureteral obstruction, complete response to induction chemotherapy and radiation therapy, and T2 tumors. Lastly, this approach requires dedicated multidisciplinary teams so that patients receive effective initial treatment and close follow-up.

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**References:**
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