Bladder-Sparing Treatment of Invasive Bladder Cancer

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Background: Radical cystectomy with pelvic lymph node dissection is the standard treatment for patients with invasive bladder cancer. However, many alternative techniques to spare the bladder have been investigated.

Methods: We review the experience reported in the literature on bladder-sparing techniques, including transurethral resection, chemotherapy, and radiation for muscle-invasive disease.

Results: Most comparative studies indicate that local recurrence and survival outcomes for bladder-sparing approaches are inferior to those from radical cystectomy to control muscle-invasive bladder cancer.

Conclusions: Although molecular biologic techniques may have the capacity to identify a subgroup who may benefit from a bladder-sparing approach, cystectomy is normally required for optimal results.
treatments to radical cystectomy, alone or in combination, have been tried.4

We review the alternatives to radical cystectomy for muscle-invasive bladder cancer in terms of organ preservation and survival, and we compare these results with the most recent data on radical cystectomy.

Transurethral Resection

Transurethral resection (TUR) is used primarily in muscle-invasive bladder cancer to establish the diagnosis and local extent of the disease. The use of TUR for definitive treatment of muscle-invasive bladder cancer is predicated on tumor volume, multifocality, and associated carcinoma in situ (CIS). Understaging of the depth of tumor involvement occurs in up to 40% of cases.5 Nevertheless, several series have shown that TUR provides disease control, particularly in patients with lower clinical disease stages.6-8

In a prospective study, Solsona et al9 reported on 133 candidates for conservative treatment. The inclusion criteria for this group were histological confirmation of muscular infiltration, endoscopic radical TUR, disappearance of hardened areas on the bladder wall after resection on bimanual examination, and negative biopsies of the depth and periphery of the tumor bed.8 The control group consisted of 76 patients with invasive pathologic stage pT2-3a, N0-3 bladder cancer treated with cystectomy and followed for more than 5 years. After 5 years, 61 patients (45.9%) in the TUR group relapsed, 35 (26.3%) had disease recurrence, and 37 (27.8%) had disease progression. Of the original 133 patients, 59 were followed for a median of 10 years, and there was no significant statistical difference in survival in the two groups vs the control group. At 5 and 10 years, the cause-specific survival rates were 80.5% and 79.5% and bladder preservation rates were 82.7% and 79.0%, respectively, in each group. This was not a randomized study; selection bias toward cystectomy and TUR could be present. Evidence of CIS was the only significant statistical variable to predict progression. Other series in the literature present overall survival from 31%-68% as follows: stage T2 at 57%-70%, stage T3a at 14%-57%, and stage T3b at 2%-7%.6,7 In the previous publication of Solsona et al,8 overall survival was reported at 83%.

A recent series by Memorial Sloan-Kettering evaluated 170 consecutive patients who underwent recent TUR for bladder tumors by a referring physician.10 A total of 150 patients had repeat TUR, with 114 (76%) having residual tumor on repeat TUR. In patients with superficial (Ta, Tis, T1) bladder tumors, 72 (75%) had residual tumor and 28 (29%) were upstaged to muscle-invasive disease. Only 12 (22%) of patients with an initial T2 pathologic stage had no residual tumor with repeat TUR. These data stress the importance of a repeat TUR on patients considered for bladder-sparing protocols and suggest that bladder preservation be used in controlled protocol studies and not as a standard treatment.

Recent data show only a 9% incidence of nodal metastasis in patients with pathologic stage T2 on radical cystectomy specimen compared with 37% of pathologic stage T3 patients.2 This suggests that a tumor amenable to complete resection by TUR will have a low incidence of nodal metastasis. We can conclude that patients with completely resected tumor may not need to undergo a cystectomy.

As suggested by the literature reviewed above, the ideal candidate for radical TUR has a primary, solitary, or papillary tumor that is 3 cm or less in size, and the patient must be amenable to follow-up.9,12

Partial Cystectomy

Partial cystectomy is not a commonly used technique by the urologist and remains an incompletely evaluated surgical option in the treatment of bladder cancer.12 Partial cystectomy permits complete pathologic staging of the tumor and pelvic lymph nodes while preserving bladder and sexual functions. No randomized trials have been conducted to compare this
surgical treatment, by stage, with other treatment modalities. Partial cystectomy as a treatment for muscle-invasive bladder cancer may be considered in patients with a tumor that is primary, solitary, and amenable to removal with 2-cm surgical margins. A biopsy must be performed on the remaining urothelium to ensure that it is normal.\textsuperscript{13}

Several publications of retrospective series, with the above criteria as well as less restrictive, resulted in the use of partial cystectomy in 5.8%-18.9% of all patients undergoing cystectomy for bladder cancer (Table).\textsuperscript{12,14-18} These studies show a 5-year overall survival rate of approximately 25%-60%, with local overall and recurrence rates ranging from 40%-78%. The recurrence rates according to stage were as follows: stage T2 was 29%-80%, stage T3 was 7%-33%, and stage T4 was 0%-20%. As with any bladder preservation technique, appropriate patient selection is important to achieve adequate survival rates. The suboptimal survival observed in many series of partial cystectomy may be attributed to loosely interpreted inclusion criteria. At the time of partial cystectomy, a frozen section is necessary for evaluation of the margins by a uropathologist.\textsuperscript{12}

**Radiation Therapy**

External-beam radiation therapy (EBRT) is the primary treatment for invasive bladder cancer in some European countries. In North America, EBRT appears inferior to cystectomy and thus is rarely recommended as a primary treatment.\textsuperscript{2}

Several trials of primary radiation therapy in patients with clinical stage T2 disease show an overall 5-year survival rate of 40%, with a local control rate of 40%-50%. Distant metastasis developed in 10% of the patients. For clinical stage T3 disease, the 5-year survival rate of these patients is approximately 20%, and the local recurrence rate ranges from 50%-70%. For clinical stage T4 disease, the 5-year survival rate is 10%.\textsuperscript{19} Selection criteria for primary radiotherapy include papillary tumors, complete TUR prior to radiotherapy, tumor size less than 5 cm, and low-stage tumors.\textsuperscript{13}

Holmang et al\textsuperscript{20} reported a series of 74 patients treated with radical radiotherapy for bladder cancer. Following treatment, 84% of these patients had persistent tumor, a local recurrence, or a contracted bladder. The median survival for stages T2 and T3 was 16 months, with a high toxicity rate. Seven patients (9.5%) died of early or late treatment-related complications, and 8 patients (10.8%) had long-term survival. The patient selection in this series defines the outcome of this group. The low survival rate directly related to the older population in this study (70 to 75 years of age in the Radiation Therapy Oncology Group). The high toxicity rate was due to the high radiation dose (65 Gy), and 6 of the 8 long-term survivors had a radical TUR before radiotherapy.

As previously noted, the results of radiation therapy as a primary treatment for muscle-invasive bladder cancer are similar to TUR alone. Montie reported that the use of radiation sensitizers (cisplatin) combined with radiation therapy improved local control in 10%-20% of patients compared with radiation alone.\textsuperscript{21} A Canadian study reported that 104 patients achieved 90% complete clinical response when treated with radiation therapy and concurrent intra-arterial cisplatin.\textsuperscript{22} These results have not been reproduced in the United States.

Combining interstitial iridium-192 (\textsuperscript{192}Ir) and external-beam radiation therapy provides a higher radiation dose to the tumor. This combination has been previously reported to modestly increase survival but substantially increase morbidity. A 1997 study by Wijnmaalen et al\textsuperscript{23} included 66 patients with solitary clinical T3a bladder tumors of less than 5 cm in size. TUR and EBRT followed by \textsuperscript{192}Ir provided a long-term bladder control rate of more than 60% and an overall survival rate of 61%.

As a primary treatment of muscle-invasive bladder cancer, radiation alone does not provide survival rates comparable to radical cystectomy, even when combined with salvage cystectomy. In patients who fail to respond, the survival rates are lower than those achieved with primary radical cystectomy.\textsuperscript{24}

**Systemic Chemotherapy**

The advent of M-VAC chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) as an effective treatment for bladder cancer provided new opportunities for bladder preservation protocols. Neoadjuvant chemotherapy has shown a response rate of 63%-79% on primary bladder lesions. However, when patients were pathologically staged, 30%-50% were understaged at the time of the postchemotherapy clinical restaging.\textsuperscript{25-28} In a 1995 study by Scattoni et al\textsuperscript{29} on 60 patients with incomplete TUR of the bladder tumor (TURBT) treated with cisplatin, methotrexate, and vinblastine (CMV) followed by cystectomy, only 5 patients (8.3%) achieved a pathologically complete response.

Herr et al\textsuperscript{30} recently reported on 111 patients with clinical T2-3, N0, M0 transitional cell carcinoma of the bladder who were treated with neoadjuvant M-VAC, after repeat maximum TURBT. Of 60 patients with complete responses, 28 refused definitive treatment beyond
patients treated with combined modality, using colleagues' recently updated their experience with 106 the goal of bladder preservation. Shipley and colleagues have reported several multimodality approaches with therapy alone at 4 years. Since then, many investigators optimal response and a 35% improved survival over radio- platin and full EBRT demonstrated a 77% improved ini- mproved local control based on the synergistic affect be effective in carefully selected patients. Radiation therapy and chemotherapy were combined to achieve improved local control based on the synergistic affect of radiation therapy and chemotherapy, while addressing micrometastases with systemic chemotherapy.

A 1987 study by the Shipley et al combining cis- platin and full EBRT demonstrated a 77% improved initial response and a 35% improved survival over radio-therapy alone at 4 years. Since then, many investigators have reported several multimodality approaches with the goal of bladder preservation. Shipley and colleagues recently updated their experience with 106 patients treated with combined modality, using com-

Combined Modality

Trimodality therapy combines TURBT, EBRT, and concurrent chemotherapy for bladder preservation in patients with invasive bladder cancer. While TURBT, radiation therapy, or chemotherapy used alone does not result in significant local control, clinical evidence suggests that a combination of all three treatments could be effective in carefully selected patients. Radiation therapy and chemotherapy were combined to achieve improved local control based on the synergistic affect of radiation therapy and chemotherapy, while addressing micrometastases with systemic chemotherapy.

Radical Cystectomy

Radical cystectomy and PLND provide excellent control of the primary tumor and are superior to either...
radiation therapy alone or organ-conserving surgery. Operative mortality is less than 2%. However, approximately 50% of all cystectomy candidates with high-grade tumors have unrecognized distant metastasis at the time of surgery, and they die of disseminated disease within 2 years of presentation. This questions the rationale for cystectomy in these patients.42

Pathologic staging of the primary tumor is directly associated with the curability of bladder cancer. This finding is important when comparing clinical and pathologic staging among bladder preservation protocols. The overall staging error for bladder cancer is 73%, with 20.3% of overstaging and 52.3% of understaging, making this comparison difficult.43

Contemporary results of radical cystectomy and PLND for primary bladder cancer in patients with negative lymph nodes show a 5-year survival by pathologic stage as follows: 96% for pTis, 92% for pT1, 82% for pT2, 71% for pT3a, 45% for pT3b, 74% for pT4a (ducts), 51% for pT4a (stroma), and 26% for pT4b. For patients with radical cystectomy and nodal involvement, the 5-year overall survival shows 52% for <pT3b, 17% for pT3b, 33% for N1, 22% for N2, and 0% for N3. The overall cure rate of node-positive bladder cancer after radical cystectomy and PLND is approximately 25%. The 10-year survival for bladder cancer, by stage, after radical cystectomy is 83% for pT1, 74.8% for pt2, and 64.7% for pT3a.4

Cheng et al44 reported on 64 patients who had a history of pT2 bladder cancer with long-term follow-up after radical cystectomy. They evaluated 11 variables to try to predict distant metastasis-free survival and cancer-specific survival. Lymph node metastasis and tumor size were independent predictors of distant metastasis-free survival and cancer-specific survival and were age-associated to recurrence-free survival and all-cause survival. The 10-year distant metastasis-free survival and cancer-specific survival rates were 100% and 94%, respectively, for tumors less than 3 cm in size and were 68% and 73%, respectively, for tumors of 3 cm or more. These differences continue to be significant after adjustment for lymph node status.

Urinary Tract Recurrences

In a recent retrospective series from Memorial Sloan-Kettering Cancer Center of 529 patients with bladder cancer treated with radical cystectomy, the incidence of upper urinary tract transitional cell carcinoma was 3%.45 This is consistent with other series from the Mayo Clinic,46 the University of South California School of Medicine,47 and the University of Texas-M.D. Anderson Cancer Center,48 where the upper tract recurrence incidence was 3.3%, 2.4%, and 2.6%, respectively. In 1996, Herr et al49 reported a study of 86 patients with recurrent stage T1 and diffuse stage Tis bladder cancer that was treated conservatively with TUR and intravesical bacille Calmette-Guérin (BCG). The 15-year incidence rate of upper urinary tract tumors was 21% (18 patients). From the patients who developed progression and required cystectomy, only 2 patients developed upper-tract tumors. These two series suggest that radical cystectomy provides a protective affect from upper tract tumors.

Herr et al50 also reported a cohort of 186 patients with a history of superficial bladder tumors and a follow-up of 15 years. Of these patients, 80% had Ta G2-3 tumors, 20% had T1G2-3 tumors, and 72% had associated diffuse CIS treated with maximum TUR and intravesical BCG. Prostatic urethral relapse at 15 years was 39%. Of these relapses, 62% were non-invasive and 38% were stromal invasions.

Quality of Life

Patients with a preserved bladder have a low incidence of incontinence or hematuria. Shipley et al2 reported that 71% of women and 50% of men undergoing selective bladder preservation had no reduction in satisfaction from sexual intercourse. From data on personal experience by Montie, he observed that 20% of patients after radical cystectomy are able to have intercourse without aids to sustain erection. Another 20% may be helped with sildenafil or other assists.3,21,51

In a retrospective study, Hart et al52 compared quality of life after radical cystectomy for bladder cancer in 224 patients, including those with ileal conduits, cutaneous continent diversions, and orthotopic continent diversions. They found good overall quality of life, little emotional distress, and few problems with social, physical, or functional activities. As expected, the most commonly reported problems were related to urinary diversion and sexual function, with improvement of sexual quality of life for patients with penile prostheses. Recent data on radiation therapy for prostate cancer emphasize the fact that the use of radiation therapy frequently presents quality of life issues, most of which are related to rectal incontinence and urinary tract problems.

Economic Issues

Currently, the estimated cost of EBRT is $25,000 on bladder preservation protocols. The cost of the neoadjuvant chemotherapy (3 cycles) is between $6,000 and $16,000, with a medical oncology reimbursement of
$5,000. Six cycles of BCG prophylaxis for recurrent superficial disease is $3,000. The costs of long-term surveillance cystoscopies and salvage cystectomy for approximately 36% of patients also need to be included. The cost of radical cystectomy is $25,000, plus the expense of adjuvant chemotherapy for patients with extravesical disease. Another cost factor to consider is that prolonged hospitalizations or reoperations occur in up to 25% of patients following radical cystectomy and urinary diversion.

Conclusions

The ideal candidate for bladder preservation has a low-volume, invasive tumor 3 cm or less in size that has been completely resected by TUR with no evidence of CIS. While TUR alone could achieve a survival rate in the 80% range with good bladder preservation without the need for chemotherapy or radiotherapy in this ideal patient, the high incidence of CIS and a high recurrence rate require consideration of BCG prophylaxis.

For tumors 5 cm in size, a combination modality could be used for bladder preservation in this group of patients with higher rates of nodal metastasis and disease control. The use of markers such as p53, p21, or Rb could assist in distinguishing between patients who will respond well to bladder preservation and those who will be better served with radical surgery. For high-stage tumors (T3b to T4), combined modality offers only 20% control. In this situation, even radical cystectomy has failed to achieve high cure rates, principally due to extravesical and nodal disease. The role of adjuvant chemotherapy for this patient population continues to be investigational.

Data regarding the value of each of the components of combined modality are inconsistent. Most agree that complete TUR is essential for bladder preservation. The roles of chemotherapy (with a 1%-4% mortality rate) and radiation therapy (with associated morbidity) remain unclear. With new chemotherapeutic agents that offer similar response rates to M-VAC but with less toxicity, it should be possible to offer this treatment to a broader selection of patients and possibly decrease the morbidity of bladder preservation.

Presence of an experienced uropathologist and cytologist is key to performing bladder preservation protocols successfully. The decisions made in a bladder preservation protocol regarding candidates and follow-up are affected by the expertise of the pathologist, urologist, and oncologist. This can be done only in major centers, and at the present time, bladder preservation cannot be performed routinely in the community.

When comparing all of the available alternatives for the treatment of invasive bladder cancer, it is fair to evaluate the most recent results with radical cystectomy and PLND. The 10-year cancer-specific survival for patients with a muscle-invasive tumor or less than 3 cm treated with radical cystectomy is over 90%. If this type of patient is considered to be ideal for bladder preservation, then there is no alternative treatment of radical cystectomy with an equal survival rate. Approximately 9% of these patients will be found with nodal involvement at the time of surgery. There is a survival advantage for these patients with radical surgery and PLND.

Continuous improvement in surgical techniques and perioperative care greatly reduced morbidity and late effects of surgery, including sexual dysfunction. Consequently, neobladder and continent diversions are being increasingly accepted by patients. Thus, bladder preservation, with all of its associated risks, currently is not a better alternative to cystectomy for the majority of patients. The following points further underline this rationale: (1) Muscle-invasive disease is associated with a high incidence of CIS, multifocal field disease, and a high recurrence rate that can be invasive and lethal. (2) The role of radiation therapy in bladder preservation needs further evaluation and remains experimental at this time. (3) Improvements are needed for chemotherapy to provide better results and reduce toxicity. (4) The incidence of upper tract tumors in patients who have not had a cystectomy is high. (5) The strict criteria for patient selection and the need of a specialized team of urologists and uropathologists make it difficult to recommend bladder preservation in a community setting. (6) Based on experience at our center, the long-term results of bladder preservation support the need for early cystectomy. (7) Salvage cystectomy compromises the option for neobladder formation.

In the future, new markers may allow us to more appropriately select patients for bladder preservation. Continued improvements in chemotherapy may permit a more aggressive approach in some patients, even those with micrometastases, and thus allow combined radical surgery and effective adjuvant chemotherapy.

References


