



Sidi Bou Said, Tunisia, 1999. Courtesy of J. Bryan Murphy, MD, Clearwater, Florida.

Several alternatives to radical cystectomy for muscle-invasive bladder cancer have been studied. None, however, are reliably superior to operative treatment.

Bladder-Sparing Treatment of Invasive Bladder Cancer

Inoel Rivera, MD, and Zev Wajzman, MD

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.*

Introduction

In the United States, 50,000 new cases of bladder cancer are diagnosed every year. Approximately 25% of these patients will have muscle-invasive bladder cancer at the initial presentation. Of the remaining 75% who initially present with superficial disease, 10%-15% will progress to invasive disease.¹

The standard treatment of invasive bladder cancer has been radical cystectomy with pelvic lymph node dissection (PLND). Radiation therapy has been reserved primarily for patients who are unfit for cystectomy based on age, comorbid conditions, and extent of disease.²

A major advancement in the treatment of invasive bladder cancer occurred with the advent of effective chemotherapy with the M-VAC protocol, consisting of methotrexate, vinblastine, doxorubicin, and cisplatin. A complete response rate of 25% and a partial response rate of 48% has been observed with this regimen.³ However, the role of systemic chemotherapy, as either an adjuvant or a neoadjuvant treatment, continues to evolve, and its impact on survival remains investigational. Many alternative

From the Division of Urology at the University of Florida College of Medicine, Gainesville, Fla.

Address reprint requests to Dr. Inoel Rivera, Division of Urology, University of Florida College of Medicine, PO Box 100247, Gainesville, FL 32610-0247.

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

Due to copyright restrictions, this table has been removed from this online article.
Please refer to the printed version found in *Cancer Control Journal*, V7, N4, to view this table.

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.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).^{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.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.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%.¹⁹ Selection criteria for primary radiotherapy include papillary tumors, complete TUR prior to radiotherapy, tumor size less than 5 cm, and low-stage tumors.¹³

Holmang et al²⁰ 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.²¹ A Canadian study reported that 104 patients achieved 90% complete clinical response when treated with radiation therapy and concurrent intra-arterial cisplatin.²² These results have not been reproduced in the United States.

Combining interstitial iridium-192 (¹⁹²Ir) 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 al²³ included 66 patients with solitary clinical T3a bladder tumors of less than 5 cm in size. TUR and EBRT followed by ¹⁹²Ir 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.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.²⁵⁻²⁸ In a 1995 study by Scattoni et al²⁹ 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 al³⁰ 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

TURBT, 15 patients underwent partial cystectomy, and 17 patients underwent radical cystectomy. No patient received radiation. Of these 60 patients, 38 (63%) had presented with T2 disease and 22 (37%) with T3 disease. Patients with clinical T3 disease were disproportionately selected for radical cystectomy over bladder-sparing surgery by 45% vs 18%. The overall survival at 10-year follow-up was 70% in the bladder-sparing treatment arm and 65% in the radical cystectomy arm. These good results were obtained without the use of radiation therapy. When tumor p53 status was assessed on the group undergoing bladder-sparing surgery, the 10-year survival for p53-negative patients was 92% compared with 47% for p53-positive patients. Of the group undergoing radical cystectomy, the 10-year survival for p53-negative patients was 71% compared with 60% for p53-positive patients, with no statistical difference. Fifty-six percent of patients in the bladder-sparing surgery arm were alive with their native bladder. Recurrent bladder tumors were found in 56% of patients, and more than half of these recurrences were invasive. This recurrence rate suggests that the chemotherapy-maximum transurethral resection approach should be considered experimental.

Recent data on new chemotherapeutic agents show promising results. In phase I and phase II trials of cisplatin and gemcitabine,³¹ the objective response rate was 66% in patients with metastatic disease without prior systemic chemotherapy. Other ongoing trials (eg, paclitaxel plus carboplatin, 3-day combinations of paclitaxel, carboplatin, and gemcitabine) appear to show comparable efficacy to the M-VAC regimen with less toxicity.^{21,32}

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.

A 1987 study by the Shipley et al³³ combining cisplatin and full EBRT demonstrated a 77% improved initial response and a 35% improved survival over radiotherapy alone at 4 years. Since then, many investigators have reported several multimodality approaches with the goal of bladder preservation. Shipley and colleagues² recently updated their experience with 106 patients treated with combined modality, using com-

plete TURBT followed by 2 cycles of neoadjuvant CMV, concurrent cisplatin, and radiation therapy. Immediate radical cystectomy was performed in 13 patients due to incomplete response and in 6 patients due to an inability to tolerate induction chemotherapy and radiation. The overall survival was 52%, with disease-specific survival of 60% at 5 years. The 5-year overall survival with an intact bladder was 43%. The authors reported that 20%-30% of patients cured from invasive bladder cancer will subsequently develop new superficial tumors that will demonstrate a good response to intravesical drugs.

We reported our multimodality bladder-sparing series in 94 patients at our institute,¹³ using initial TUR with 2 to 3 cycles of neoadjuvant M-VAC or CMV followed by full-dose radiation therapy with concurrent cisplatin. Overall survival was 49%, and 5-year survival was 84% for stage T2, 53% for T3, and 11% for T4. Of the 5-year survivors, the bladder was preserved in 41%, with stage T2 at 50%, T3 at 37%, and T4 at 0%. From the initial group, only 18% were alive with an intact bladder. The recurrence rate was 58% at 5 years, with 27% of the recurrences being invasive. A survival advantage of 65% was observed in patients who had a cystectomy at some point during the study compared with 40% in patients with bladder preservation. The analysis of our long-term data, resulted in an abandonment of a bladder preservation approach at our institution. This approach is limited to study protocols and is rarely used, with the exception of individual cases involving nonsurgical candidates.

Reported series in the literature³⁴⁻⁴¹ show a 5-year overall survival between 51% and 63%, with a 5-year survival with bladder preservation of 18%-43%. Among the patients with preserved bladders, 50%-60% developed bladder recurrences, with approximately half being muscle invasive. The data collected from these series lead some to believe that patients who had radiation therapy added to their treatment protocols had an increase in bladder preservation, and the complete response rate was improved in patients when chemotherapy was used. Neither had any impact on survival.

The Radiation Therapy Oncology Group (RTOG) has performed two separate pilot trials of multimodality bladder preservation including complete TUR (with or without CMV) and concurrent cisplatin and radiotherapy. There was no benefit in survival of 2 cycles of CMV neoadjuvant chemotherapy and only a 67% completion rate of the CMV arm due to toxicity.³⁴⁻³⁸

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 effect 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.^{2,53}

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

1. Wajsman Z, Klimberg IW. Treatment alternatives for invasive bladder cancer. *Semin Surg Oncol.* 1989;5:272-281.
2. Shipley WU, Kaufman DS, Heney NM, et al. An update of combined modality therapy for patients with muscle invading bladder cancer using selective bladder preservation or cystectomy. *J Urol.* 1999;162:445-451.
3. Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol.* 1985;133:403-407.
4. Gschwend JE, Vieweg J, Faiv WR. Contemporary results of radical cystectomy for primary bladder cancer. Lesson 13. *AUA Update Series.* 1999;18.

5. Wajzman Z, Rifkin MN. Alternative therapies for muscle-invasive transitional cell carcinoma. *Probl Urol.* 1992;6:493-505.
6. Herr HW. Conservative management of muscle-infiltrating bladder cancer: prospective experience. *J Urol.* 1987;138:1162-1163.
7. Henry K, Miller J, Mori M, et al. Comparison of transurethral resection to radical therapies for stage B bladder tumors. *J Urol.* 1988;140:964-967.
8. Solsona E, Iborra I, Ricos JV, et al. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: prospective study. *J Urol.* 1992;147:1513-1515.
9. Solsona E, Iborra I, Ricos JV, et al. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term follow-up of a prospective study. *J Urol.* 1998;159:95-99.
10. Whitmore WF. Selection of treatment for muscle infiltrating transitional cell bladder cancer. *Arch Esp Urol.* 1990;43:219-222.
11. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol.* 1999;162:74-76.
12. Sweeney P, Kursh ED, Resnick MI. Partial cystectomy. *Urol Clin North Am.* 1992;19:701-711.
13. Given RE, Wajzman Z. Bladder sparing treatments for muscle invasive transitional cell carcinoma of the bladder. Lesson 6. *AUA Update Series.* 1997;16.
14. Novick AC, Steward BH. Partial cystectomy in the treatment of primary and secondary carcinoma of the bladder. *J Urol.* 1976;116:570-574.
15. Faysal MH, Freiha FS. Evaluation of partial cystectomy for bladder cancer. *Urology.* 1979;14:352.
16. Merrell RW, Brown HE, Rose JF. Bladder carcinoma treated by partial cystectomy: a review of 54 cases. *J Urol.* 1979;122:471-472.
17. Lindahl F, Jorgensen D, Egvad K. Partial cystectomy for transitional cell carcinoma of the bladder. *Scand J Nephrol.* 1984;18:125-129.
18. Kaneti J. Partial cystectomy in the management of bladder carcinoma. *Eur Urol.* 1986;12:249-252.
19. Wesson MF. Radiation therapy in regionally advanced bladder cancer. *Urol Clin North Am.* 1992;19:725-734.
20. Holmang S, Hedelin H, Borghede G, et al. Long-term followup of a bladder carcinoma cohort: questionable value of radical radiotherapy. *J Urol.* 1997;157:1642-1646.
21. Montie JE. Against bladder sparing: surgery. *J Urol.* 1999;162:452-457.
22. Eapen L, Stewart D, Crook J, et al. Intraarterial cisplatin (IAC) and concurrent pelvic radiation (PR) in the management of transitional bladder cancer: an organ preservation strategy. *Proc Annu Meet Am Soc Clin Oncol.* 1995;14:A625.
23. Wijnmaalen A, Helle PA, Koper PC, et al. Muscle invasive bladder cancer treated by transurethral resection followed by external beam radiation and interstitial iridium-192. *Int J Radiat Oncol Biol Phys.* 1997;39:1043-1052.
24. Miller LS. Bladder cancer: superiority of preoperative irradiation and cystectomy in clinical stages B2 and C. *Cancer.* 1977;39(2 suppl):973-980.
25. Scher HI, Yagoda A, Herr HW, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) affect on the primary bladder lesion. *J Urol.* 1987;139:470-474.
26. Herr HW, Scher HI. Neoadjuvant chemotherapy and partial cystectomy for invasive bladder cancer. *J Clin Oncol.* 1994;12:975-980.
27. Sternberg CN, Arena MG, Calabresi F, et al. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for infiltrating transitional cell carcinoma of the bladder. *Cancer.* 1993;72:1975-1982.
28. Hatcher PA, Hahn RG, Richardson RL, et al. Neoadjuvant chemotherapy for invasive bladder carcinoma: disease outcome and bladder preservation and relationship to local tumor response. *Eur Urol.* 1994;25:209-215.
29. Scattoni V, Da Pozzo L, Nava L, et al. Five-year results of neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy plus radical cystectomy in locally advanced bladder cancer. *Eur Urol.* 1995;28:102-107.
30. Herr HW, Bajorin DF, Scher HI, et al. Can p53 help select patients with invasive bladder cancer for bladder preservation? *J Urol.* 1999;161:20-23.
31. Sternberg CN. Gemcitabine in bladder cancer. *Semin Oncol.* 2000;27(1 suppl 2):31-39.
32. Kaufman D, Stadler W, Carducci M, et al. Gemcitabine (GEM) plus cisplatin (CDDP) in metastatic transitional cell carcinoma (TCC): final results of a phase II study. *Proc Annu Meet Am Soc Clin Oncol.* 1998;17:A1235.
33. Shipley WU, Prout GR Jr, Einstein AB, et al. Treatment of invasive bladder cancer by cisplatin and radiation in patients unsuited for surgery. *JAMA.* 1987;258:931-935.
34. Kachnic LA, Kaufman DS, Heney NM, et al. Bladder preservation by combined modality therapy for invasive bladder cancer. *J Clin Oncol.* 1997;15:1022-1029.
35. Given RW, Parsons JT, McCauley D, et al. Bladder-sparing multimodality treatment of muscle-invasive bladder cancer: a five-year follow-up. *Urology.* 1995;46:499-505.
36. Dunst J, Sauer R, Schrott KM, et al. Organ-sparing treatment of advanced bladder cancer: a 10-year experience. *Int J Radiat Oncol Biol Phys.* 1994;30:261-266.
37. Tester W, Porter A, Asbell S, et al. Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85-12. *Int J Radiat Oncol Biol Phys.* 1993;25:783-790.
38. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol.* 1998;16:3576-3583.
39. Houssett M, Dufour E, Maulard-Durdux C. Concomitant fluorouracil (5-FU)-cisplatin (CDDP) and bifractionated split course radiation therapy (BSCRT) for invasive bladder cancer. *Proc Annu Meet Am Soc Clin Oncol.* 1997;16:A1139.
40. Srougi M, Simon SD. Primary methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy and bladder preservation in locally invasive bladder cancer: a 5-year followup. *J Urol.* 1994;151:593-597.
41. Sternberg CN, Raghaven D, Ohi Y, et al. Neoadjuvant and adjuvant chemotherapy in advanced disease: what are the effects on survival and prognosis? *Int J Urol.* 1995;2(suppl 2):76-88.
42. Skinner DG, Lieskovsky G. Management of invasive and high-grade bladder cancer. In: Skinner DG, Lieskovsky G, eds. *Diagnosis and Management of Genitourinary Cancer.* Philadelphia, Pa: WB Saunders Co; 1988:295-312.
43. Gschwend JE, Vieweg J, Fair WR. Disease specific survival after radical cystectomy. *J Urol.* 1997;157:1662A.
44. Cheng L, Neumann RM, Scherer BG, et al. Tumor size predicts the survival of patients with pathologic stage T2 bladder carcinoma: a critical evaluation of the depth of muscle invasion. *Cancer.* 1999;85:2638-2647.
45. Balaji KC, McGuire M, Grotas J, et al. Upper tract recurrences following radical cystectomy: an analysis of prognostic factors, recurrence pattern and stage at presentation. *J Urol.* 1999;162:1603-1606.
46. Schwartz DB, Bekirov H, Melman A. Urothelial tumors of upper tract following treatment of primary bladder transitional cell carcinoma. *Urology.* 1992;40:509-511.
47. Malkowicz SB, Skinner DG. Development of upper tract carcinoma after cystectomy for bladder carcinoma. *Urology.* 2000;36:20-22.
48. Kenworthy P, Tanguay S, Dinney DP. The risk of upper tract recurrence following cystectomy in patients with transitional cell carcinoma involving the distal ureter. *J Urol.* 1996;155:501-503.
49. Herr HW, Cookson MS, Soloway SM. Upper tract tumors in patients with primary bladder cancer followed for 15 years. *J Urol.* 1996;156:1286-1287.
50. Herr HW, Donat SM. Prostatic tumor relapse in patients with superficial bladder tumors: 15-year outcome. *J Urol.* 1999;161:1854-1857.
51. Little FA, Howard GC. Sexual function following radical radiotherapy for bladder cancer. *Radiother Oncol.* 1998;49:157-161.
52. Hart S, Skinner EC, Meyerowitz BE, et al. Quality of life after radical cystectomy for bladder cancer in patients with an ileal conduit, cutaneous or urethral kock pouch. *J Urol.* 1999;162:77-81.
53. Lerner SP. A phase I/II trial of transurethral surgery combined with concurrent cisplatin 5-fluorouracil and twice daily radiation followed by selective bladder preservation in operable patients with muscle invading bladder cancer: editorial comment. *J Urol.* 1998;160:1677.