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CURRENT INDICATIONS AND NEW POSSIBILITIES FOR ORGAN PRESERVATION IN CARCINOMA OF THE BLADDER

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ABSTRACT

Objective: To assess the efficacy of bladder-sparing strategies in the treatment of muscle-invasive bladder cancer.

Patient and Methods: This overview discusses the evolving role of transurethral resection of bladder tumors, radiation therapy, systemic chemotherapy, and combination therapy in the treatment of invasive bladder cancer. The pertinent literature was reviewed and the specific aspects of each modality were analyzed. The results of bladder-sparing strategies were compared with radical cystectomy.

Results: The bladder preservation strategies that are currently available are capable of eradicating invasive bladder tumors in some patients, but most patients are unlikely to be durably cured by any of these regimens. Tumor recurrence occurs in approximately 40% to 60% of patients participating in bladder-sparing regimens. Approximately half of these recurrences are muscle invasive, placing the patients at risk for metastasis. Pelvic recurrence rates after radical cystectomy range between 10% and 30%. The disease specific five-year survival rates in pathological stages T1/T2 are close to 70% to 80%; less than 50% for pathological stages T3b/T4. Decreasing morbidity post radical cystectomy and the advent of the orthotopic neobladder technique using either the small or the large bowel is capable of restoring urinary function, which lessens the qualitative benefits of any organ-sparing modality currently available.

Conclusion: While radical cystectomy with neobladders remains the preferred therapy for invasive bladder cancer, research into improved bladder preservation strategies, possibly using biomarkers to predict responsiveness to treatment, should continue.

Key words: bladder, carcinoma, invasive, organ preservation, radiotherapy, chemotherapy
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INTRODUCTION

Management of high-grade urothelial carcinoma of the bladder is one of the most challenging problems facing urologists today. Radical cystectomy is currently accepted as the most effective treatment for muscle invasive disease based on the fact that it provides excellent local control in the pelvis with a low perioperative mortality rate. Nevertheless, the morbidity related to this procedure is significant and issues of impotence and urinary incontinence remain. The negative impact on the quality of life of patients undergoing radical cystectomy fosters a search for alternative ways to treat invasive bladder cancer that would allow a patient to retain the natural organ. Alternative therapies would have to provide fewer complications without compromising control of the primary tumor or survival. Several options tested in clinical practice attempt to preserve the urinary bladder in patients with invasive bladder cancer using a combination of chemotherapy and radiation or bladder-sparing surgery.

The aim of this article is to review the existing bladder preservation strategies. It is our view that current bladder-sparing techniques are less effective than radical cystectomy for cancer control, and thus reserved for highly selected patients.

RATIONAL FOR BLADDER PRESERVATION

Eradication of a tumor without removal of the affected organ is the ideal treatment for any cancer. Therefore, for bladder cancer, the best treatment is the one capable of providing control of the primary tumor without compromising survival, thus avoiding the morbidity and adverse effect in quality of life associated with radical cystectomy. Several options have been tested in clinical practice, from transurethral resection alone to a combination of multiple therapies.

TRANSURETHRAL RESECTION OF BLADDER TUMOR (TURBT)

Transurethral resection is the mainstay of treatment for noninvasive (Ta) or minimally invasive (T1) bladder cancer. It is apparent that TURBT may also effectively cure some patients with higher stage disease (T2a). This is supported by 2 pieces of evidence: 1)- TURBT yields a prolonged disease-free survival in selected patients with T2 disease; and 2)- no residual tumor is found in the radical cystectomy specimens in approximately 10% of patients (pathological stage T0), indicating that the TURBT effectively removed the tumor (1-4). Early studies have shown that TURBT alone can provide a five-year survival rate close to 50% in selected patients, which is not substantially different from that of some large cystectomy series (1-4).

Treatment selection is clearly important. In a series of patients adversely selected by advanced age and poor surgical risk that underwent TURBT alone for muscle-invasive bladder cancer, the five-year survival was 14% (5). Although capable of controlling the cancer in some cases, TURBT alone will fail to cure most patients with high stage bladder cancer. TURBT as a primary treatment is more likely to be successful in patients with small volume tumors, who likely may have an even greater chance of cure by cystectomy. Circumstantial evidence to support this observation has also been reported. The five-year survival rate for patients with smaller T2 tumors, who underwent radical cystectomy, ranges from 60% to 80% as compared to the 50% rate observed after TUR alone (6-9). However, TURBT is an invaluable tool for evaluating bladder cancer therapy and staging after other modalities of bladder preservation (10). Patients who achieve a clinical T0 status on a transurethral resection of the primary tumor site are likely to respond better to further therapy (chemical or radiation) than those who do not achieve this condition (4).

PARTIAL CYSTECTOMY

Resection of only the cancerous portion of the bladder has some theoretical advantages over either TURBT or cystectomy in the management of invasive bladder cancer. It allows full-thickness resection of the bladder wall and more certain removal of the tumor confined to that segment compared to TURBT. It also preserves the patient's bladder and sexual function. The trade off is the risk of remaining or new cancer in the bladder, since the urothelium remains exposed to the same predisposing factors to bladder carcinoma. Approximately 50% to 70% of the patients who undergo partial cystectomy develop later tumors in the bladder; some of which will be muscle invasive and potentially lethal. The commonly reported five-year survival rates for partial cystectomy is approximately 50%, which is similar to TURBT alone (11). It ranges from 70% for early stages (T2 tumors) to 17% for more advances tumors (T3b and T4 tumors). Patient selection remains critical. Ideal patients for partial cystectomy have: 1)- a single tumor in space and time (no previous history of bladder cancer); 2)- the tumor located in a site favorable to resection (dome or high posterior wall of the bladder); and 3)- no carcinoma in situ (CIS). Patients with a urachal tumor or occasionally a tumor in a bladder diverticulum may be reasonable candidates for partial cystectomy. The number of patients meeting these criteria is extremely low, much less than 5% of the patients with stage T2a or higher disease. Good functional results with radical cystectomy and ileal neobladder formation have diminished considerably the role of partial cystectomy in patients with invasive bladder cancer. When indicated, it should be performed removing the overlying peritoneum along with the involved bladder and a 2 cm margin of nor-

mal bladder around the entire circumference of the bladder tumor. Biopsies around the resected area and elsewhere in the bladder are necessary to exclude concomitant CIS. The ill-advised partial cystectomy commonly turns into a nightmare and diminishes later success even with total cystectomy.

EXTERNAL RADIATION THERAPY

Ionizing radiation therapy has been extensively used in the treatment of invasive bladder cancer, particularly in Europe. In the United States, its role remains limited. Results with external radiation therapy (RT) in the U.S.A. have been consistently less optimistic than those from Europe.

In a large randomized European trial comparing pre-operative pelvic RT and radical cystectomy versus RT only for patients with T2b and T3 bladder cancer, the survival rate was not statistically different between the two groups. A five-year survival rate of 38% was reported for those who underwent radical cystectomy, compared to 29% for those treated with RT only (12). Similar results were reported in a more recent study (13). For those patients that underwent immediate surgery, a five-year survival rate of 29% was reported, versus 23% for the RT only group. In one of the largest series of patients treated with primary radiation therapy alone (cystectomy was reserved as salvage treatment), the complete clinical response rate was 45% for clinical stages T1 to T4. Fifty percent of the patients had locally recurrent tumors, with an overall five-year local control rate of 25% for stages T1 through T3 tumors. Those with clinical stage T4 achieved a five-year local control rate of only 16%. Patients with persistent tumors underwent radical cystectomy, with an overall five-year survival rate following surgery of approximately 45%. In this series, the overall survival rate for patients with deeply invasive tumors was approximately 25%; 69% for those with more superficial tumors (14).

As a single modality for the treatment of muscle invasive cancers, RT may provide local control in 30% to 50% of the cases at best, with a five-year overall survival rate ranging from 23% to 40% (15-18). Analyzing data from several trials of primary radiation therapy for T2 disease, an overall five-year survival rate of approximately 40% was reported, with a local control rate ranging between 40% and 50%. Primary recurrence was a serious concern in all studies (19-24). Patients with T3 disease had a five-year survival rate of only 20%, with 50% to 70% having local recurrence (19-24).

More recently, several drugs (radiosensitizers) have been investigated as a possible means of improving the efficacy of RT. Most interesting have been the studies investigating the concurrent use of RT and Cisplatin. One small randomized study that compared radiotherapy with and without the concurrent use of Cisplatin demonstrated a significant improvement in local control with the concurrent regimen, but it failed to show any benefit in terms of overall survival (25). A pilot trial is currently under way at the University of Michigan to evaluate the combination of gemcitabine and radiation therapy as a bladder preservation strategy. Gemcitabine is an antimetabolite that was initially synthesized as an antiviral drug. Further investigations demonstrate that the drug is a potent radiosensitizer and has significant activity against urothelial carcinoma as a single agent.

In summary, the results with RT for invasive bladder cancer in the U.S.A. have been systematically inferior to those of radical cystectomy, therefore RT is only exceptionally recommended as a primary option for invasive bladder cancer.

SYSTEMIC CHEMOTHERAPY

The search for an effective chemotherapy regimen for metastatic bladder cancer led to the evaluation of various cytotoxic agents in patients with disseminated disease. Cisplatin was found to be the most active single agent against urothelial cancer, but other agents such as 5-FU, methotrexate, vinblastine and doxorubicin have also been tested with partial success. Nevertheless, none of these agents was found to be solely effective. Combination regiments are more effective and capable of inducing a complete response in patients with metastatic bladder cancer (26). Several combination regiments were tested in clinical practice until the introduction of the MVAC

regiment (methotrexate, vinblastine, doxorubicin and cisplatin) at the Memorial Sloan Kettering Center. The first results of a phase-II trial were reported in 1985, and since then, MVAC has evolved into the preferred chemotherapy treatment for bladder cancer. An updated report from 1989 revealed that 121 patients had been enrolled in the clinical trial. An overall response rate of up to 70% was reported, but a durable disease-free survival was observed in only a small percentage of patients (27). The median survival duration for the entire group was 13.3 months; only 20% of the patients were long-term disease-free survivors. MVAC was subsequently compared to other systemic regiments and found to be the most effective. This relative success in treating metastatic disease led to the utilization of MVAC in bladder-sparing protocols at the same institution. In a series of patients treated with both TURBT and MVAC, 54% achieved an early T0 status (28). Unfortunately, additional studies revealed that only in a few patients was the response durable and complete (29). In addition, the toxicity of the regiment is substantial and another limitation. Even at a standard dosage, the side effects of MVAC were poorly tolerated by most patients.

The toxicity and limited efficacy of this regimen led to new investigational agents. Two of the most promising agents are paclitaxel and gemcitabine (30). Both have shown significant activity as single agents against urothelial carcinoma. In a one phase-II trial, 27% of the patients with metastatic bladder cancer that were treated with paclitaxel achieved a complete response (31). When combined with carboplatin, an overall response rate of 50% was achieved. This combination was well tolerated, with only moderate side effects (granulocytopenia and thrombocytopenia) (32,33).

The combination of gemcitabine and cisplatin also appears particularly promising. Longer follow-up and randomized trials are required to reveal if any of them will supplant MVAC as the standard therapy for metastatic urothelial carcinoma of the bladder. The diminished toxicity of these new regiments as compared to MVAC makes them attractive. Data on the efficacy on localized disease must be obtained to judge a role for this treatment for bladder preservation.

Currently, systemic chemotherapy fails to produces results comparable to radical cystectomy, and the results may be no better than TURBT or partial cystectomy alone. Until more effective and less toxic regiments are fully investigated, it should not be recommended as a primary treatment for invasive bladder cancer. Data using adjuvant or neoadjuvant chemotherapy combined with radical cystectomy is sparse, and thus far, no conclusive improvement in survival has been shown.

COMBINATION THERAPY

Combined approaches using all 3 modalities of therapy (TURBT, RT and chemotherapy) have also been investigated in organ preservation approaches with more encouraging results. A combination of maximal TURBT with initial chemotherapy (cisplatin, methotrexate and vinblastine), followed by RT with concurrent cisplatin was tested in a series of patients at Massachusetts General Hospital (34,35). Patients were evaluated after 4,000cGy and those with complete response received an additional 2,480cGy. For those who did not reach complete response, total cystectomy was recommended. After a median follow-up of four years, 53% of the patients had achieved complete response; bladder function was adequately preserved in 89% (34,35). In a recent update from the same institution with the same regimen, a complete response was observed in 76 of 106 patients enrolled in the study (66%). Twenty-one of the 76 patients developed Ta or T1 recurrence. Recurrence was controlled with TURBR and intravesical therapy in 15 of these patients; 13 patients presented with an invasive recurrence. After a median follow-up of five years, 54% of the enrolled patients had no cancer found in the bladder at their most recent evaluation (36). In other trials similar results were reported, with five-year survival with an intact bladder ranging from 39% to 45% (37-41). However, in another study, a disappointingly low rate of disease-free bladder preservation with no definitive improvement in survival was reported; only 18% of the enrolled population was alive with an intact bladder at the end of the study. The five-year survival rate of patients who had a cystectomy at some point

in the study was 65%, compared to 40% for those who had their bladder spared (41). The data from these studies suggests that the combined regimen is capable of preserving the bladder in some patients with muscle invasive disease; however, a significant number will have an incomplete response or will develop recurrent disease within the bladder, including some of these invading muscle tissue. Therefore, until new agents or more effective approaches become apparent, combinations of all 3 modalities remain as a secondary alternative for the management of invasive bladder cancer.

IMPROVING PATIENT SELECTION FOR BLADDER PRESERVATION

Not all patients with muscle invasive disease require radical cystectomy to eliminate the cancer in their pelvis. The dilemma is how to select which patients are appropriate candidates for bladder-sparing strategy. Most of the studies addressing bladder-sparing strategies are retrospective, and although capable of providing helpful information and some estimate of the efficacy of the different regiments, they are not appropriate to compare results achieved with cystectomy or for patient selection.

Tumor markers capable of predicting responsiveness to bladder-sparing strategies would be beneficial. Recent studies have identified several molecular markers important in the progression of urothelial carcinoma. Most of the attention has been focused on the p53 (42). p53 is a tumor suppressor gene that plays a significant role in determining cellular responses to DNA damage, leading to both cell cycle arrest and programmed cell death (42). Mutations of this gene and accumulation of the p53 protein are associated with the transition to an invasive phenotype of transitional cell malignancies (43). The gene may also influence the response to chemotherapy treatment, since most antineoplastic drugs act by promoting DNA damage. Several studies have now examined the proportion of invasive bladder cancer that express an abnormal p53 protein and how this finding would impact prognosis (44-48). According to these studies, from 43% to 66% of the invasive tumors expressed an abnormal p53 protein; an over expression of p53 was associated with a high recurrence rate and reduced survival. Conversely, patients with a tumor lacking p53 expression were more likely to have long-term survival, especially those with organ-confined T2 tumors. However, the influence of p53 on the response to treatment remains controversial. There is some evidence that patients with abnormal p53 may benefit from adjuvant chemotherapy (49). A recent report from the Memorial Sloan-Kettering Center suggests that long-term bladder preservation (up to ten years) is feasible in patients with T2 tumors who lack p53 if they respond completely to neoadjuvant chemotherapy with MVAC. Patients with T3 disease or T2 p53 expressing tumors are best treated with radical cystectomy (50). To better address the clinical usefulness of p53, a multi-center clinical trial is underway. Patients with organ-confined but invasive urothelial carcinoma of the bladder (T1 and T2) after cystectomy are randomized on the basis of their p53 status to receive adjuvant chemotherapy (MVAC) or observation with later chemotherapy.

Since not all muscle invasive cancer express p53, progression of the disease in the bladder must be regulated by pathways other than p53. Recent investigations have suggested that the retinoblastoma gene protein (pRb) may also play a role in this process (51-53). Studies have shown that deletion of the Rb gene is a negative prognostic factor for disease progression and overall survival. Whether or not Rb abnormalities affect response to chemotherapy in bladder cancer is yet to be determined. Several others tumor markers (histological and molecular markers) are currently under investigation (54). The development of molecular biomarkers will hopefully allow us to determine more appropriately which patients are suitable for bladder-sparing therapy.

CONCLUSION

It is clear that the strategies for bladder preservation currently available are capable of eradicating invasive bladder tumors in some patients, but most patients with muscle invasive bladder cancer are unlikely to be durably cured by any of these regimens.

Tumor recurrence occurs in approximately 60% of patients participating in bladder-sparing regimens, and approximately half of these recurrences are muscle invasive, placing the patients at a high risk for metastasis. Not all of these patients will be saved by salvage cystectomy. Patients with superficial recurrence require further treatment with intravesical treatment and long-term surveillance, since they are also at a high risk for progression of the disease. Bladder function is another concern, and may not be ideal in those receiving multiple TURBTs, intravesical therapy with BCG, and a high dose of RT. It is also evident that patients with high stage disease (T3 and T4), who are at highest risk for developing metastatic cancer, are the ones with the lowest chance for complete elimination of the local cancer. Twenty percent of these will have a complete response with bladder preservation therapy, a figure inferior to radical cystectomy that is capable of providing local control of the disease in 60% to 90% of the cases. Expanding the indications for organ preservation likely exposes a greater proportion of the patients to a higher risk of metastasis or local progression of the disease. Do the qualitative benefits warrant this risk?

In our opinion, radical cystectomy remains a preferred local therapy. The peri-operative mortality rate currently ranges between 1% and 3% (55). Under close monitoring and a good pre-operative evaluation, it can be performed safely on patients of all ages who are reasonably healthy (56). The therapeutic results of radical cystectomy are dependent on the clinical and pathological stage; most failures are due to distant metastasis. The pelvic recurrence rate after radical cystectomy ranges from 10% to 30%, with the higher rate for larger T3b tumors (palpable mass) (57,58). Disease-specific five-year survival rates in pathological stages T1/T2 are close to 70% to 80%, compared to less than 50% for pathological stages T3b/T4. High-grade cancers (as most invasive tumors are) tend to perform worse; lymph node involvement is also a strong predictor of relapse, but cure is possible with surgery alone even in the presence of positive lymph nodes (58,59).

Improved quality of life and decreasing morbidity post radical cystectomy are clearly evident in the last 5 to 10 years. Nerve-sparing cystoprostatectomy allows preservation of the autonomic innervation of the corpora cavernosa with preservation of erectile function in some patients. In a highly selected series, recovery of sexual function was seen in up to 62% of patients between 40 and 49 years of age, without compromising cancer control (60). Orthotopic neobladder, using either the small or large bowel, is capable of restoring urinary function, bringing it closer to that of a preserved bladder, and should be recommended as the first option for diversion in most of the patients undergoing radical cystectomy. External urinary diversion (ileal conduit) is recommended only for patients with poor general health, sedentary lifestyles, or decreased renal function.

Until better molecular tumor markers are available to predict patients that are likely to respond to either RT or chemotherapy, radical cystectomy with neobladders should remain as the preferred therapy for invasive bladder cancer.

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