Commentary (Malkowicz): Organ Preservation in Muscle-Invasive Bladder Cancer

March 01, 2005
By S. Bruce Malkowicz, MD [1]

The most effective form of therapy for muscle-invasive bladder cancer is radical surgery and urinary diversion. Numerous clinical series demonstrate stage-for-stage 5- and 10-year survival data that are better than that seen for other treatment modalities.[1] The widespread application of continent urinary diversion over the past 2 decades has furthered the acceptance of radical surgery, as it provides for the lost function of volitional storage and emptying of urine. Even patients who undergo a standard ileal loop diversion generally tolerate it well and adapt to the altered body image.[2]

Single-modality therapy for invasive bladder cancer (such as externalbeam radiation therapy, chemotherapy alone, or transurethral resection alone) all demonstrate some impact on survival, so the concept of an integrated, dynamic, multimodal approach to the treatment of muscle-invasive disease with the additional aim of organ preservation has been an appropriate outgrowth from these observations. The report in this issue by Fernando and Sandler demonstrates the rational evolution and current status of this approach in the treatment of muscleinvasive bladder cancer.

Clinical Data
Single-institution studies and multiinstitutional trials demonstrate the feasibility and reasonable efficacy of multimodality, organ-sparing therapy. A review of the trials suggests that a 5-year survival of approximately 45% can be obtained with these techniques, which can be further consolidated to over 50% with the use of salvage cystectomy.[ 3,4] The general impression is that, stage for stage, these outcomes approach but do not match or exceed those obtained with cystectomy. Direct comparison studies have not been performed, however, nor are any randomized trials of surgery compared to multimodal organ preservation in progress. Nevertheless, the aggregate data demonstrate that organ-sparing techniques can work in well-selected patients. These positive findings need to be examined with respect to patient morbidity, surgical suitability of the patient, and the predictable responsiveness of a particular tumor to multimodal therapy. A summary of the clinical data suggests that well-administered bladder irradiation can be generally well tolerated, and that severe bladder dysfunction due to contraction or persistent hemorrhage is uncommon.[3] The degree of mild-to-moderate bladder dysfunction causing distress or the need for anticholinergic medications is less well documented in the literature. It is important that patients be aware of these less severe yet still pertinent potential alterations in bladder function.

Patient Selection
The suitability of patients for complex surgery such as cystectomy and urinary diversion is based on several factors. The overall level of comorbidities in a patient can be documented and have an impact on therapeutic choices and surgical outcomes.[5] A large body of literature attests to our ability to perform such surgery in older patients with excellent results.[6] While age alone should not be used as a discriminating factor in choosing the form of therapy for invasive bladder cancer, a reasonable proportion of older patients are disinclined to consider radical surgery as the only alternative to treating their disease. For these patients, the aggregate data on multimodal therapy cannot be ignored or dismissed and must be discussed among the alternatives to definitive surgery. Accurate clinical staging and the predictive response to a particular therapy are the most vexing issues in appropriately counseling patients with regard to treatment options. Largevolume, higher-stage disease-often reflected in upper urinary tract obstruction- is less likely to respond to more conservative therapy and best treated with neoadjuvant chemotherapy and surgery. The data on transuretheral resection alone are compelling but represent a select group of patients.
with moderate tumor burdens are probably best suited to surgical extirpation and urinary reconstruction, all things being equal. The potential curative benefit of an extended pelvic lymph node dissection probably adds to the overall benefit.[7] **Future Directions**
The molecular characteristics associated with therapeutic response are slowly being unraveled. Obvious candidates such as the cell-cycle components p53, p21<sup>WAF1/CIP1</sup>, and pRb have demonstrated predictive value regarding surgical outcomes retrospectively, and in the case of p53, are being tested prospectively.[8] Retrospective analysis of these proteins have also been performed on tumors treated with multimodal therapy, providing some hypothesis-generating data.[9] Future tumor phenotyping with more sophisticated RNA and protein arrays may allow us to better categorize tumor response and provide more informed counseling regarding the appropriateness of less than radical exenteration as the most effective mode of therapy. Although no data currently exist to suggest that multimodal organ-preservation strategies are equivalent to radical cystectomy and urinary diversion for the treatment of muscle-invasive bladder cancer, sustained curative responses are noted in many patients. Patients should be made aware of this alternative treatment modality. Those most likely to benefit from organ preservation include individuals with significant medical comorbidity and small-to-moderate local tumor burdens who are also compelled by age or the utility value of avoiding the morbidity of major surgery to seek other treatment. Greater precision in tumor phenotype clinical response may broaden the indications for this proven therapy.

**Disclosures:**
The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**