VIEWPOINT

Rethinking Radical Cystectomy as the Best Choice for Most Patients With Muscle-Invasive Bladder Cancer

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Should radical cystectomy be considered an alternative treatment to bladder preservation trimodality therapy in patients with muscle-invasive bladder cancer?—Yes.

For the first time, the question is formulated correctly, and for the first time, based on new published evidence in 2015, bladder preservation trimodality therapy should be considered first for patients with muscle-invasive bladder cancer (MIBC), with cystectomy reserved for patients unable or unwilling to undergo bladder preservation or as a salvage option for local recurrences.

Organ Preservation Treatments of Solid Malignancies

Consider the major developments in clinical oncology over the past 40 years. Radical mastectomy was a standard treatment for patients with localized breast cancer until 6 randomized trials have shown equivalent overall survival rates with breast conservation surgery and adjuvant radiation therapy, despite a slightly higher risk of locoregional failure. The Veteran Affairs larynx randomized trial established chemoradiation therapy as a standard of care for patients with laryngeal cancer, with salvage laryngectomy reserved for patients with local relapses. Despite a higher rate of local recurrences in patients who were randomized to the limb-preserving arm of the National Cancer Institute randomized trial with adjuvant external beam radiation therapy, amputation is no longer an up-front treatment for most patients with extremity sarcomas because it does not lead to improved overall survival. Organ preservation approaches were not established through randomized trials for all solid malignancies. Merely 40 years ago anal cancer was treated with an abdomino-perineal resection, and all patients required lifelong colostomies. Dr Nigro changed the treatment paradigm based on clinical observation in 28 patients treated with chemoradiation, which is now the standard of care for patients with squamous cell cancer of the anal canal (despite a local failure rate of 10% to 50% depending on the original size of the primary tumor) and salvage surgery is reserved for local failures.

Survival of Patients Who Undergo Cystectomy or Trimodality Bladder Preservation

The UK randomized trial SPARE for patients with MIBC closed in 2007 owing to poor accrual, in part because patients did not want to be randomized to the surgical arm. Based on 45 randomized patients, the trial showed no difference in overall survival, a trend toward decreased post-treatment grade 3 and 4 adverse effects in the bladder preservation arm and a salvage cystectomy rate of 18% for patients with local recurrence following bladder preservation treatment. Similar 5-year and 10-year survival rates from large published cystectomy and bladder preservation treatment series made the NCCN Bladder Cancer Guidelines committee in 2013 accept trimodality bladder preservation therapy as an alternative treatment option for patients fit to undergo cystectomy.

In 2015 Italian physicians conducted a meta-analysis and compared the overall survival outcomes in over 3000 patients treated with bladder preservation on 29 published studies to outcomes in over 10 000 patients treated with cystectomy on 30 clinical series. The lower 5-year overall survival rates were associated with undergoing cystectomy. What could explain the observed inferiority of radical cystectomy? Radical cystectomy has a significant risk of postoperative mortality that increases as patients age. A large SEER database analysis of over 10 000 patients treated in the United States with radical cystectomy between 1984 and 2004 showed that at 90 days mortality is 1% for patients younger than 60 years, 6% between 69 and 83 years, and 14% for patients older than 89 years. If postoperative mortality could be reduced by limiting cystectomy to young and healthy patients, it could be hypothesized that cystectomy outcomes would be in line, or superior, to outcomes with trimodality bladder preservation treatment.

How Does Treatment of MIBC Differ From Treatment of High-Grade T1 Bladder Cancer?
The debate over the role of bladder preservation is central not only to patients with MIBC but also to patients with high-grade T1 (HGT1) bladder cancer, where long-term studies show disease progression rates of up to 50% and cancer specific death rates up to 30%. Some urologists argue that these rates call for aggressive treatment of patients with HGT1 disease with upfront radical cystectomy rather than the bladder preservation approach with tumor resection followed by intravesical therapies. In the absence of randomized clinical trials, the American Urological Association guidelines recommend bladder preservation treatment strategy as the standard of care for patients with HGT1 bladder cancer and cystectomy as alternative treatment or as a salvage treatment for local recurrences. There is no data to approach patients with HGT1 and MIBC differently.

Trimodality Bladder Preservation: Facts and Myths

The most common myth pertains to the overwhelming radiation-induced adverse effects and poor quality of life.
for patients who opt to keep their bladders. Among 157 patients who underwent trimodality therapy for MIBC on national clinical protocols with a median follow-up of 5.4 years, only 7% experienced late stage 3 genitourinary or gastrointestinal adverse effects. There were no late grade 4 adverse effects and no treatment-related deaths. No cystectomies were performed due to treatment-related adverse effects in any of the patients. In another study on quality of life of long-term survivors, 200 patients were followed with a median follow-up of 6 years and were asked to undergo urodynamics study (UDS) and fill out quality-of-life questionnaires. Overall, 75% of patients had normal functioning bladders by UDS. Reduced bladder compliance was seen in 22% of patients; however, only one-third of these patients experienced distressing bladder symptoms. Bowel symptoms occurred in 22% of patients and caused distress in 14% of patients; 36% of men reported normal erections and another 18% less firm erections but sufficient for intercourse. Of note, the median age of male patients in this study at the time of the questionnaire was 68 years.

The second myth is the inability to perform cystectomy for patients with local recurrences after chemoradiation therapy. The reconstructive options may be limited for patients owing to presence of irradiated bowel, which may be unacceptable for a continent reservoir or neobladder creation. However, perioperative morbidity and mortality rates in almost 100 patients who underwent salvage cystectomy at Massachusetts General Hospital were remarkably similar to rates for immediate cystectomies without radiation as reported by other centers specializing in treatment of bladder cancer. MIBC Management in the Future

The future of management of bladder cancer is exciting. There are now several clinical trials (NCT02621151, NCT02560636, NCT02662062) in various planning stages to test novel targeted and immunomodulatory agents in combination with chemoradiation therapy to decrease the 30% local recurrence rates. Even more intriguing are results from clinical studies that show that patients could be selected for bladder preservation or cystectomy based on tumor markers like MRE11.

In the future, tumors will likely be tested for an ever-growing number of markers. Patients with tumors sensitive to chemoradiation therapy will be offered bladder preservation treatment modalities, with radiation doses and chemotherapeutic and targeted agents selected based on genetic analyses, whereas patients with resistant tumors will be offered upfront surgical extirpation of their bladders.

Based on growing evidence in the literature, we can conclude that trimodality bladder preservation treatment is associated with similar or better outcomes to cystectomy for patients with MIBC. Quality of life in these patients is excellent. Similarly to other solid malignancies, local recurrence rate is significant, necessitating a thorough and frequent cystoscopic follow-up for patients after completion of trimodality bladder preservation. Overall, 30 percent of patients will require salvage cystectomy for local disease recurrence, usually identified within the first 3 years, and the morbidity and mortality from salvage cystectomy is no different than from up-front radical cystectomy.

### REFERENCES


### ARTICLE INFORMATION


Conflict of Interest Disclosures: None reported.