Trimodality Therapy in Bladder Cancer
Who, What, and When?

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KEYWORDS

• Radiation • Bladder preservation • Muscle-invasive bladder cancer • Chemoradiation • Urothelial carcinoma of the bladder

KEY POINTS

- Bladder preservation with maximal transurethral resection of the bladder tumor (TURBT), concurrent chemotherapy, and irradiation can result in approximately 75% of long-term survivors maintaining a functional bladder.
- The ideal patient for bladder preservation has a clinical T2 unifocal tumor, a visibly complete TURBT, no carcinoma in situ (CIS), and no tumor-related hydronephrosis, with good pretreatment bladder function.
- Participation in a bladder preservation approach requires a highly motivated patient who is a good candidate for irradiation and chemotherapy and is committed to long-term cystoscopic surveillance.

INTRODUCTION

An estimated 74,690 cases of urinary bladder cancer were diagnosed in the United States in 2014,[1] of which 30% will be muscle invasive. The current standard of care for the treatment of muscle-invasive bladder cancer (MIBC) is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) with pelvic lymph node dissection.[2] In appropriately selected patients, bladder preservation can be an effective alternative to RC. The term bladder preservation can include TURBT, limited surgery, chemotherapy, radiation therapy, or various combinations of one or more of these modalities; however, the best outcomes have consistently been seen with trimodality therapy (TMT) including maximal TURBT followed by concurrent chemoradiation. This review focuses on TMT for bladder preservation and does not detail other therapeutic combinations for bladder preservation.

Several prospective trials have been completed evaluating TMT as a means of bladder preservation. The purpose of these studies has been to define the rate of bladder preservation and survival with this approach and to improve the tolerability and efficacy of TMT regimens. This review

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provides an overview of modern TMT bladder-preservation strategies, focusing on important criteria for patient selection, the integration of novel radiation techniques, commonly used and new chemotherapies for TMT, and the role of chemoradiation for T1 disease.

DISCUSSION

Trimodality Therapy Treatment Approach

TMT includes the combination of maximal tumor debulking and concurrent chemoradiotherapy. The optimal radiation target volume, radiation fractionation, chemotherapy, and sequencing remain areas of active study. In general, the patient undergoes a maximal, preferably visually complete, TURBT, ideally with bladder mapping (Fig. 1), followed by the delivery of cisplatin-based chemoradiotherapy to a dose of approximately 40 to 45 Gy. If no evidence of disease or minimal residual disease is noted at cystoscopic reassessment, the final consolidative phase of chemoradiotherapy is initiated. If progressive or unresponsive disease is found, therapy proceeds to RC. After completion of therapy, patients are closely surveilled with cystoscopy and urine cytology.

Patient Selection

Patient selection is a key component of bladder preservation (Table 1). Most criteria used to select appropriate patients for TMT predict for a high rate of response or the ability to safely tolerate therapy. Factors predicting for increased rates of distant metastases are important for predicting overall survival (OS) after TMT.

A complete response (CR) to induction therapy with concurrent chemoradiation has typically been defined as negative results on urine cytologic analysis, as well as no visible tumor and negative results on biopsies at cystoscopy. Achieving a CR to induction therapy is required to avoid salvage cystectomy and has been associated with improved disease-free and overall survival after TMT. The CR rate for patients with T2-T4a disease treated with TMT is approximately 70%.[3] Factors that may affect the likelihood of achieving a CR after TMT and should be considered when selecting patients include completeness of TURBT, tumor stage, hydronephrosis, multifocality and CIS, and baseline bladder function. It is important to consider that the rate of response to induction therapy may not always be known, as many recent trials, such as bladder cancer 2001 (BC2001) and Radiation Therapy Oncology Group (RTOG) 0926, do not include cystoscopic reassessment after induction. For these studies, careful patient selection becomes increasingly important as a full radiotherapy (RT) dose is delivered before response to therapy is assessed.

Completeness of transurethral resection of the bladder tumor

A pooled analysis of 314 patients treated on 6 RTOG trials found that a visibly complete TURBT was associated with a significantly higher rate of CR to TMT on multivariate analysis.[3] Similarly, the Erlangen series showed that completeness of resection after initial TURBT was an independent predictor of CR.[4] Likewise, a series of 348 patients from Massachusetts General Hospital found that visibly complete TURBT was associated with higher CR rates (79% with visibly complete TURBT vs 57% without).[5] Thus, a visibly complete TURBT is ideal. A less-than-complete TURBT is not an absolute contraindication to bladder preservation, as several trials have demonstrated acceptable CR rates without a visibly complete TURBT.

Tumor stage

Most TMT trials include patients with clinical T2-T4a disease. In RTOG 85-12, RTOG 88-02, RTOG 97-06, and the Erlangen series, tumor stage was not significantly associated with the rate of CR to TMT on multivariate analysis.[4,6–8] A pooled analysis of 361 patients treated on RTOG trials confirmed that T stage did not predict for the likelihood of CR to TMT on multivariate analysis.[3] In contrast, increasing T stage is reproducibly associated with reduced long-term survival after TMT.[4,5,9]

In surgical series, the presence of prostate invasion by urothelial carcinoma is associated with a higher risk of lymph node metastases and reduced 5-year survival.[10] The decrement in survival is greatest for patients with prostatic stromal invasion or extraprostatic invasion compared with patients with more limited mucosal involvement. Patients with prostatic stromal invasion are excluded from many trials of TMT for bladder preservation; however, prostatic urethral invasion is not generally an exclusion criterion if it is amenable to visibly complete resection.

Few data exist regarding the treatment of patients with involved lymph nodes with TMT. These patients have in some cases been included in RTOG trials of TMT if the lymph nodes are located below the bifurcation of the iliac vessels. The presence of lymph node involvement is a poor prognostic indicator in regards to OS, and in general, these patients are counseled to undergo neoadjuvant chemotherapy and RC.

Hydronephrosis

Tumor-related hydronephrosis has been an exclusion criterion for several trials of TMT. RTOG 89-03