REVIEW ARTICLE

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Bladder Preservation Strategies for Muscle-Invasive Urothelial Carcinoma of the Bladder

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ABSTRACT

The standard of care for muscle-invasive bladder cancer is radical cystectomy with bilateral pelvic lymph node dissection. However, nowadays there is a tendency for organ preservation in selected cases of muscle-invasive bladder cancer. The triple-combined therapy consisting of a transurethral resection followed by concomitant chemoradiotherapy results in comparable outcomes to radical cystectomy. Clinical criteria in determining patients for organ preservation includes: small tumor size (< 2 cm), absence of urethral obstruction, no evidence of pelvis lymph node metastases, and absence of carcinoma *in situ.* Bladder conservation therapy could be offered to selected patients as one alternative to radical cystectomy.
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INTRODUCTION

Bladder cancer (BC) is major global health challenge with an estimated 429,000 new cases resulting in 165,000 deaths per year[1]. The majority of BC are composed of urothelial carcinoma (90%)[2]. Twenty-five percent of the cases are diagnosed as muscle-invasive bladder cancer (MIBC)[2]. Radical cystectomy with bilateral pelvic lymph node dissection is the gold standard for the management of MIBC[3].

Currently, there is no established consensus on how to determine which patients are candidates for cystectomy[4]. Factors used to determine a patient's suitability for surgery have included age, functional status, nutritional status, cognitive status, and medical comorbidities[5,6]. Several bladder-sparing approaches have investigated transurethral resection of bladder tumor (TURBT) or partial cystectomy – alone or in combination with chemotherapy, radiation therapy and trimodality therapy[7]. Clinical criteria helpful in identifying patients for bladder preservation include such variables as small tumor size (≤ 5 cm), early tumor stage, a visibly and microscopically complete TURBT, absence of urethral obstruction, and no evidence of pelvic lymph node metastases[6,7].

TRANSURETHRAL RESECTION OF BLADDER TUMOR

Transurethral resection of bladder tumor is used primarily in muscle-invasive bladder cancer to establish the diagnosis and local extent of the disease. The use of TURBT for definitive treatment of muscle-invasive bladder cancer is recommended in patients with solitary tumors at the trigone, posterior or lateral walls with focal invasion into *muscularis propria,* small tumor size (≤ 3 cm) without surrounding carcinoma *in situ,* absence of metastatic lymphadenopathy, and no evidence of hydronephrosis. This approach has been associated with bladder preservation in 60-70% of patients and a cancer-specific survival rate of 76-82% at 10 years in this subgroup of selected patients[8,9] .

PARTIAL CYSTECTOMY

Candidates for a partial cystectomy should have solitary tumors with focal *muscularis propria* invasion located anteriorly or in the bladder dome, amenable to removal of a 2 cm margen[10]. Partial cystectomy is associated with bladder preservation rates of 50-75%, overall survival rates of 25-60%, and local overall recurrence rates of 40-78%. However, a review of the literature indicates that only 5-10% of patients with muscle-invasive bladder cancer are eligible for this procedure[11]. No randomized trials have compared partial cystectomy with other treatment modalities.

RADIOTHERAPY

Radiotherapy can be administered alone or in combination with chemotherapy, either sequentially or concurrently. External beam radiation therapy (EBRT) has been widely used as a bladder-sparing strategy in patients who are not otherwise candidates for cystectomy. However, outcomes appear clearly inferior to surgery, with five-year overall survival rates of 20-40% and local control rates of 50%[12,13]. Several trials of primary radiation therapy in patients with clinical stage T2 disease have shown an overall five-year survival rate of 40%, with local control rates of 40-50%. Distant metastases developed in 10% of the patients. For clinical stage T3 disease, the five-year survival rate is approximately 20%, and local recurrence rates are 50-70%. For clinical stage T4 disease, the five-year survival rate is 10%[14]. Selection criteria for primary radiotherapy include papillary tumors, complete transurethral resection prior to radiotherapy, tumor size < 5 cm, and low-stage tumors[13-15]. Primary cystectomy has not yet been

tested against combined-modality bladder-sparing treatment.

TRIMODALITY THERAPY

The trimodality approach consists of extensive TURBT followed by radiation (40-45 Gy to the pelvis) with concurrent radiosensitizing chemotherapy and an additional radiation boost to the bladder (20-25 Gy) if a complete response is documented on repeat biopsy. While TURBT, radiotherapy, 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. Radiotherapy and chemotherapy are combined to achieve improved local control based on their synergistic effect, while addressing micrometastases with systemic chemotherapy.

In 1987, Shipley, et al. found a 77% improved initial response and a 35% improved survival at four years for the combination of cisplatin and full EBRT over radiotherapy alone[15]. Since then, several studies have studied various multimodality approaches with the goal of bladder preservation, and the Radiation Therapy Oncology Group (RTOG) has conducted several prospective clinical trials. To date, three prospective randomized trials have demonstrated that concurrent chemoradiotherapy is superior to radiotherapy alone.

In the first study, 99 patients with T2 to T4b transitional cell bladder cancer were randomized to receive radiation to the whole pelvis at a dose of 40 Gy in 20 fractions, with or without intravenous cisplatin 100 mg/m^2 on days 1, 15, and 30. Patients who attained a response were immediately boosted to a dose of 20 Gy. Upon completion of the treatment, patients were evaluated for clinical response. Salvage cystectomy was performed if locally progressive disease was observed. The main drawbacks of this study were that it was too small and it was not powered to detect an improvement in survival[16].

The second study assessed the efficacy and toxicity of concurrent chemoradiotherapy using 5-fluorouracil/mitomycin in 360 patients who were randomized in a 2 x 2 factorial design to either chemoradiation versus radiation alone and standard volume radiation (given as 55 Gy over 20 fractions or 64 Gy over 32 fractions) versus reduced high-dose volume radiation to the tumor. The primary endpoint was loco-regional disease-free survival (LRDFS). Secondary endpoints included toxicity, quality of life, and overall survival. At a median follow up of 40 months, two-year LRDFS was 67% for patients receiving chemoradiation and 54% for those receiving radiation alone ($p = 0.02$). However, there was no significant difference in overall survival[17].

In the third study, 333 locally advanced bladder carcinoma patients were randomized to radiotherapy alone or radiotherapy plus carbogen/nicotinamide (CON). A schedule of either 55 Gy in 20 fractions over four weeks or 64 Gy in 32 fractions over 6.5 weeks was used. The primary endpoint was cystoscopic control at six months and secondary end points were overall survival, LRDFS, and urinary and rectal morbidity. Response rates were 76% in the radiotherapy arm compared to 81% in the radiotherapy plus CON arm. At three years, there was a 13% improvement in overall survival in favor of the combination arm, with a 14% lower risk of death[18] .

The need for induction chemotherapy for successful bladder conservation was directly tested in the RTOG 89-03 trial, a phase III clinical trial comparing the efficacy of initial neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone. One hundred and seventy-four patients were randomized to receive or not two cycles of cisplatin/methotrexate/vinblastine (CMV) followed by 39.6-Gy pelvic irradiation with concurrent cisplatin 100 mg/m^2 for two courses, three weeks apart. Patients who attained a complete response were treated with an additional 25.2 Gy to a total of 64.8 Gy and one

additional dose of cisplatin. Those with less than complete response underwent cystectomy. This study was stopped early due to an unexpectedly high rate of severe neutropenia and sepsis for patients receiving CMV. This trial showed that two cycles of induction CMV did not confer a survival or response benefit over concurrent chemoradiotherapy[19].

Another RTOG clinical trial examined the combination of cisplatin plus twice-daily accelerated irradiation after TURBT. The protocol required TURBT within six weeks of the initiation of induction therapy. Induction treatment involved 13 days of concomitant boost radiotherapy at 1.8 Gy to the pelvis in the morning followed by 1.6 Gy to the tumor 4-6 hours later. For sensitization, cisplatin (20 mg/m^2) was given on the first three days of each treatment week. Three to four weeks after induction, patients were evaluated cystoscopically for residual disease. Patients whose biopsies and cytological evaluations showed no disease completed consolidation chemoradiation. Patients with residual tumor went on to cystectomy. After either consolidation or cystectomy, patients were to complete three cycles of CMV chemotherapy. The complete response rate after induction therapy was 74%, similar to findings in other bladder-sparing trials. Grade 3 toxicity related to chemotherapy was observed in 11% of patients during both induction and consolidation and in 41% during adjuvant chemotherapy. Since only 45% of patients completed the three cycles of CMV, this form of adjuvant chemotherapy appears to be poorly tolerated[20].

The optimal regimen and combination of radiotherapy and chemotherapy thus has yet to be established.

CONCLUSIONS

- Radical cystectomy with bilateral lymph node dissection is the standard of care for the management of muscle-invasive bladder cancer.
- TURBT alone, though attractive in selected patients, is at present investigational and cannot be recommended as standard treatment (level of evidence II, grade of recommendation B).
- Partial cystectomy is also at present investigational and cannot be recommended as standard treatment (level of evidence II, grade of recommendation B).
- Radiotherapy alone cannot be recommended as standard treatment (level of evidence II, grade of recommendation B).
- Multimodality treatment is an alternative in well-informed and compliant patients for whom cystectomy is not considered due to clinical or personal reasons (level of evidence Ib, grade of recommendation A).
- Criteria for selection of patients for bladder preservation include such variables as small tumor size (≤ 5 cm), early tumor stage, a visibly and microscopically complete TURBT, absence of urethral obstruction, and no evidence of pelvic lymph node metastases (level of evidence Ib, grade of recommendation A).

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