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Review

Selective organ preservation in muscle-invasive bladder cancer: Review of the literature

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ABSTRACT

The standard of care for transitional-cell carcinoma of the bladder with invasion to the muscularis propria is radical cystectomy with bilateral pelvic lymph node dissection. However, currently there is a tendency for organ preservation in selected cases of muscle-invasive bladder cancer. Trimodality treatment, including transurethral resection of the bladder tumor (TURBT), radiation therapy and chemotherapy, has been shown to produce 5-year and 10-year overall survival rates comparable to those of radical cystectomy. The current 5-year overall survival rates range from 50 to 67% with trimodality treatment, and approximately 75% of the surviving patients maintains their bladder. After trimodality treatment complete response is obtained in more than 70% of patients with muscle-invasive bladder cancer. Clinical criteria helpful in determining patients for bladder preservation include such variables as small tumor size (<2 cm), early tumor stage (T2–T3 disease), a visibly and microscopically complete TURBT, absence of ureteral obstruction, no evidence of pelvic lymph node metastases, and absence of carcinoma in situ (Tis). The close collaboration of urologists, radiation oncologists and medical oncologists is of paramount importance in succeeding in bladder preservation.

Contents

Introduction

Bladder cancer is the ninth most frequent cancer worldwide, accounting for 2.1% of all cancer deaths [1]. In 2008 in Europe an estimated 110,500 new cases of bladder cancer were diagnosed, leading to 38,000 cancer deaths [2], and in the Unites States the estimated incidence of bladder cancer is approximately 70,500 new cases per year [3]. Bladder cancer is three times more common in men than in women in western countries. The crude incidence of muscle-invasive bladder cancer (MIBC) in the European Union is 19/100,000/year, and the mortality is 7.9/100,000/year. The median age at diagnosis is 65 years, and 70% of patients with bladder cancer are >60 years of age. Bladder cancers are rarely diagnosed in

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individuals younger than 40 years. Thus, medical comorbidities are a frequent consideration in patient management.

Pathological diagnosis should be made according to the World Health Organization classification from a biopsy obtained by transurethral resection of the bladder tumor (TURBT). Urothelial or transitional-cell carcinoma is the most common histologic subtype of bladder cancer, accounting for more than 90% of the cases. Other less common histologic subtypes of bladder cancer are squamous cell tumors (3%); adenocarcinomas (2%), small-cell tumors (1%), sarcomatoid tumors (<1%) and mixed subtypes [4].

Most of bladder cancer (65–70%) are superficial at presentation and are typically managed conservatively. Bladder cancers are staged according to the depth of invasion. The main distinction, in terms of treatment and prognosis, is whether the disease invades the muscular layer of the bladder wall. In general, non-infiltrating tumors are treated with TURBT plus intravesical instilled treatments (Bacille Calmette–Guérin or chemotherapy); while MIBC are treated in a more aggressive way.

The standard of care for transitional-cell carcinoma of the bladder with invasion to the muscularis propria is radical cystectomy with bilateral pelvic lymph node dissection. However, currently there is a tendency for organ preservation in selected cases of MIBC. Trimodality treatment, including TURBT, radiation therapy and chemotherapy, has been shown to produce 5-year and 10-year overall survival (OS) rates comparable to those of radical cystectomy. The current 5-year OS rates range from 50 to 67% with trimodality treatment, and approximately 75% of the surviving patients maintains their bladder. After trimodality treatment a complete response (CR) is obtained in more than 70% of patients with MIBC. These approach require close coordination among all disciplines involved (urologists, radiation and medical oncologists).

Materials and methods

Identification of eligible trials

We searched in the Cochrane Central Register of Controlled Trials and MEDLINE (last search on December 2010) using combinations of terms such as bladder carcinoma, trimodality therapy, organ preservation, radical cystectomy, chemotherapy, radiotherapy, TURBT, cisplatin and radiochemotherapy. We considered all controlled trials providing information about the efficacy and safety of trimodality therapy for selective organ preservation in urothelial cell carcinoma of the bladder as eligible.

Data extraction

We extracted information from each eligible trial. The data recorded included author's name, year of publication, treatment protocols, number of patients included in the trial, median time to progression, overall response and median survival.

Organ preservation in MIBC: series of combined-modality treatment

The standard of care for MIBC is radical cystectomy with urinary diversion. Even the construction of a neobladder cannot substitute for the patient's original bladder. Thus, the bladder-preserving strategy as an alternative to radical cystectomy had begun to be used by several centers in the late 1980s [21,6]. Such an approach involves the participation of several disciplines (urologists, radiation and medical oncologists). Attempts to obtain organ preservation are only justified when they have a high likelihood of achieving local cure with no compromise in survival rates. Adequate local control cannot be achieved with TURBT, chemotherapy, or radiotherapy, when used alone. In the trimodality strategy, initially the tumor is resected with maximal TURBT, followed by radiotherapy with chemotherapy, with salvage cystectomy being reserved for patients with incomplete response or local relapse.

The centers with the largest experience in trimodality therapy for organ preservation in MIBC are the Massachusetts General Hospital, the University of Erlangen and the University of Paris (Table 1). According to their studies, a CR to an initial treatment consisting of TURBT followed by irradiation plus chemotherapy selects patients whose tumor is likely to be controlled by a bladder-sparing approach. After 4–6 weeks of radiochemotherapy, a cystoscopy is performed to assess the response rate. If residual invasive disease remains, the intent of bladder preservation is aborted, and the patient is considered for a radical cystectomy. On the other hand, if a CR is achieved, then a consolidative phase of radiochemotherapy is carried out for few more weeks, for a full course of radiochemotherapy (Fig. 1).

Long-term outcomes of 190 patients with MIBC treated with the trimodality strategy in the Massachusetts General Hospital was reported by Shipley et al. [7] in 2002. In this study patients with stage T2–4a MIBC were managed by TURBT and concurrent chemoradiation (cisplatin). Patients were re-evaluated by repeated biopsy and urine cytologic analysis after 40 Gy, with the initial tumor response guiding subsequent therapy. One hundred twenty-one patients with a CR by cytologic and histologic examination received boost chemoradiation to 64–65 Gy. Sixty-six patients (35%) of this cohort had subsequently undergone cystectomy due to either incomplete response to induction chemoradiation (41 patients), or recurrent invasive disease (25 patients). With a median follow-up of 6.7 years for all surviving patients, the 5- and 10-year OS rate was 54% and 36%, respectively; and the 5- and 10-year disease-specific survival (DSS) rate for patients with an intact bladder was 46% and 45%, respectively, suggesting that in the long term the bladder was preserved in approximately half of the patients.

The experience of the University of Erlangen was reported by Rödel et al. [8]. In this study conducted between 1982 and 2000, 415 patients with bladder cancer (high-risk T1, $n = 89$; T2 to T4, $n = 326$) were treated with radiotherapy ($n = 126$) or chemoradiation ($n = 289$) after TURBT. The doses of radiotherapy ranged from 45 to 69.4 Gy with a median dose of 54 Gy. Chemotherapy was

Table 1
Organ-preservation strategy in muscle-invasive bladder cancer.

Center	*N*	T-stage	Protocol	Survival with integral bladder
Massachusetts General Hospital (Shipley et al. [7])	190	T2–T4a	TURBT + radiochemotherapy (cisplatin)	45% at 10 years
University of Erlangen (Rödel et al. [8])	415	T1–T4	TURBT + radiochemotherapy (cisplatin or carboplatin or cisplatin–fluorouracil)	42% at 5 years
Hôpital Necker (Housset et al. [9])	54	T2–T4	TURBT + radiochemotherapy (cisplatin–fluorouracil)	Not reported (3-year DSS of 62%).

TURBT: transurethral resection of the bladder tumors; DSS: disease-specific survival.