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Collaborative Review – Bladder Cancer

Critical Analysis of Bladder Sparing with Trimodal Therapy in Muscle-invasive Bladder Cancer: A Systematic Review

Guillaume Ploussard[a,b], *Siamak Daneshmand*[j], *Jason A. Efstathiou*[c], *Harry W. Herr*[d], *Nicholas D. James*[h], *Claus M. Rödel*[f], *Shahrokh F. Shariat*[e], *William U. Shipley*[c], *Cora N. Sternberg*[g], *George N. Thalmann*[i], *Wassim Kassouf*[a,*]

[a] *Department of Surgery, Division of Urology, McGill University, Montreal, Quebec, Canada;* [b] *Department of Urology, Saint-Louis Hospital, Assistance Publique Hôpitaux de Paris, Paris, France;* [c] *Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;* [d] *Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [e] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [f] *Department of Radiotherapy and Oncology, University of Frankfurt, Frankfurt, Germany;* [g] *Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy;* [h] *University of Birmingham, School of Cancer Sciences, Edgbaston, Birmingham, UK;* [i] *Department of Urology, University of Berne, Berne, Switzerland;* [j] *University of Southern California Institute of Urology, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA, USA*

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Abstract

Context: Aims of bladder preservation in muscle-invasive bladder cancer (MIBC) are to offer a quality-of-life advantage and avoid potential morbidity or mortality of radical cystectomy (RC) without compromising oncologic outcomes. Because of the lack of a completed randomised controlled trial, oncologic equivalence of bladder preservation modality treatments compared with RC remains unknown.
Objective: This systematic review sought to assess the modern bladder-preservation treatment modalities, focusing on trimodal therapy (TMT) in MIBC.
Evidence acquisition: A systematic literature search in the PubMed and Cochrane databases was performed from 1980 to July 2013.
Evidence synthesis: Optimal bladder-preservation treatment includes a safe transurethral resection of the bladder tumour as complete as possible followed by radiation therapy (RT) with concurrent radiosensitising chemotherapy. A standard radiation schedule includes external-beam RT to the bladder and limited pelvic lymph nodes to an initial dose of 40 Gy, with a boost to the whole bladder to 54 Gy and a further tumour boost to a total dose of 64–65 Gy. Radiosensitising chemotherapy with phase 3 trial evidence in support exists for cisplatin and mitomycin C plus 5-fluorouracil. A cystoscopic assessment with systematic rebiopsy should be performed at TMT completion or early after TMT induction. Thus, nonresponders are identified early to promptly offer salvage RC. The 5-yr cancer-specific survival and overall survival rates range from 50% to 82% and from 36% to 74%, respectively, with salvage cystectomy rates of 25–30%. There are no definitive data to support the benefit of using of neoadjuvant or adjuvant chemotherapy. Critical to good outcomes is proper patient selection. The best cancers eligible for bladder preservation are those with low-volume T2 disease without hydronephrosis or extensive carcinoma in situ.
Conclusions: A growing body of accumulated data suggests that bladder preservation with TMT leads to acceptable outcomes and therefore may be considered a reasonable treatment option in well-selected patients.
Patient summary: Treatment based on a combination of resection, chemotherapy, and radiotherapy as bladder-sparing strategies may be considered as a reasonable treatment option in properly selected patients.

* Corresponding author. Department of Surgery, Division of Urology, McGill University Health Center, 1650 Cedar Avenue, Room L8-315, Montreal, Quebec H3G 1A4, Canada.
Tel. +1 514 934 8246; Fax: +1 514 934 8297.
E-mail address: wassim.kassouf@muhc.mcgill.ca (W. Kassouf).

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1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection remains widely accepted as the gold-standard treatment for muscle-invasive bladder cancer (MIBC) supported by a substantial body of evidence [1–3] with long-term follow-up. Nevertheless, removal of the bladder may lead to significant morbidity and affect patients' comfort and quality of life (QoL) [4,5]. Concerns about oncologic equivalence may in part explain differences in local utilisation rates of bladder preservation in eligible patients among different countries [6–9].

Several bladder-preservation options exist, including single-modality treatments such as transurethral resection (TUR) alone, partial cystectomy, radiation therapy (RT), or chemotherapy alone. Nevertheless, it is generally accepted that single-modality treatments result in inferior outcomes compared with RC. A trimodal therapy (TMT) approach, including maximal TUR followed by concurrent radiosensitising chemotherapy and RT, is the most-studied bladder-sparing strategy. The aim of this systematic review was to assess the modern bladder-preservation treatment modalities, focusing on TMT in MIBC.

2. Evidence acquisition

A systematic literature search in the PubMed and Cochrane databases was performed to identify clinical and randomised controlled trials (RCTs) published from 1980 to July 2013 [10]. Various algorithms, including the following terms, were used: *bladder cancer, bladder preservation, trimodality treatment, radiotherapy, chemotherapy, chemoradiation, chemoradiotherapy, organ-sparing, bladder-sparing*, and *salvage cystectomy*. Inclusion criteria used were published full articles, clinical trials, retrospective series, and meta-analyses written in English. The following exclusion criteria were used: (1) articles reporting on bladder preservation only in non-MIBC (NMIBC) and only in non–urothelial bladder cancer (BCa) and (2) abstracts and congress communications. Each identified article was analysed and classified.

Primary outcomes included oncologic results after bladder preservation (response rates, cancer-specific survival [CSS], overall survival [OS]). Secondary outcomes included safety and tolerability, long-term bladder-preservation rate, QoL, need for salvage treatment, type of TMT regimens, and locoregional recurrence rate defined by recurrence in bladder or pelvic nodes. Selection of articles is shown in a flow diagram (Fig. 1). Original articles reporting clinical trials were separated into three categories: TMT, neoadjuvant chemotherapy plus TMT, and TMT plus adjuvant therapy. TMT articles were then separated between large- and small-sample-size (<50 patients) trials. Large-sample-size TMT trials were then separated into two categories: prospective phase 3 trials and phase 2 or retrospective studies (Table 1).

3. Evidence analysis

Overall, five prospective TMT phase 3 trials have been published, including two phase 3 RCTs. The remaining articles included in this review were large retrospective series (with heterogeneous treatment protocols) and phase 2 trials with small cohorts. Although use of conservative management for MIBC has yielded promising results and gained wider acceptance, most studies have small cohorts or limited follow-up, providing few data on long-term oncologic safety or late toxicity.

3.1. Description of optimal treatment courses

The basic strategy of TMT is to combine an aggressive but safe TUR of the tumour followed by concurrent chemotherapy and RT [11]. It also includes the need for prompt salvage RC in patients who do not respond completely or who develop invasive recurrence. Thus, the treatment is more an attempt at bladder preservation than definitive bladder preservation.

3.1.1. Split versus continuous course

Cystoscopic assessment with adequate biopsy of the previous tumour site and voided urine cytology should be performed at TMT completion (continuous course) and may be performed early after TMT induction (split course; Fig. 2). In case of incomplete response, patients are advised to undergo immediate RC. To date, no prospective study has compared both courses (continuous versus split) [12].

Induction therapy mainly consists of radiation to a dose of 40 Gy. Consolidation radiation is continued to a full dose of approximately 65 Gy in most trials [13]. In the continuous-course strategy, cystoscopic evaluation with biopsy is deferred up to 1–3 mo after the end of TMT [14].

3.1.2. Radiation regimens

Several studies have assessed the impact of radiation fractionation on oncologic outcomes in TMT trials. The advantage of accelerated hypofractionation has been advocated [15–17], but to date, radiation fractionation has not been reported as a prognostic factor when comparing twice- versus once-daily fractions [13,18]. The Radiation Therapy Oncology Group (RTOG) 0712 protocol is currently under assessment to evaluate a twice daily versus once daily radiation regimen.

Inclusion of pelvic nodal packets in the target volume varied among series [13,19]. One randomised trial that included 230 patients has highlighted that targeting only the bladder with 2-cm margins did not adversely affect survival and could minimise side effects compared with a whole-pelvis volume [20]. The BC2001 trial comparing RT with or without chemotherapy by mitomycin C (MMC) and 5-fluorouracil (5-FU) had a planning target volume of bladder plus 1.5 cm (2 cm around the visible tumour) but nonetheless reported only a nodal recurrence rate of around 5% [14]. Nevertheless, most planned radiation regimens included RT to a limited pelvic region (typically to the mid-sacroiliac region, with an upper limit of the common iliac artery bifurcation). The rationale for including a limited pelvic field is that regional nodal involvement is not uncommon in muscle-invasive disease; yet, by limiting the nodal fields in size and dose (40–45 Gy), the treatments are